PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIVISIÓN DE NUEVAS CREACIONES

10-33947

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS DE 5-(4-(HALO-ALCOXI)-FENIL)-PIRIMIDIN-2-AMINA Y COMPOSICIONES 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 23 de Marzo de 2010

99/

P2010/000018

Con ✓
Fx 22-03-2010
No Exhibit

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-033947- -00000-0000
Fecha: 2010-03-23 17:01:15 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 370

PETITORIO - FORMULARIO
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000018**

SOLICITUD DE:

1

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

2 **SOLICITANTE (71)**	**Nombre:** IRM LLC **Dirección:** 131 Front Street, P.O. Box HM 2899, Hamilton HM LX, Bermuda **Nacionalidad o Domicilio:** Bermuda **Lugar de Constitución:** Bermuda **Teléfono:** **Fax:** **E-mail:**	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** **Número**
REPRESENTANTE O APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10 **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [X] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** **Número** 79782747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

5 **PCT (86)**

Solicitud Internacional No. PCT/US2008/073573 Fecha Agosto 19, 2008

Publicación Internacional No. WO 2009/026276 Fecha Febrero 26, 2009

6 **Título (54)** **COMPUESTOS DE 5-(4-(HALO-ALCOXI)-FENIL)-PIRIMIDIN-2-AMINA Y COMPOSICIONES COMO INHIBIDORES DE CINASA**

Clasificación Internacional (51) C07D 239/42, C07D 401/12, C07D 403/12, C07D 413/12, A61K 31/505, A61K 31/506, A61P 1/00, A61P 7/04, A61P 11/06

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Agosto 22, 2007	60/957.260

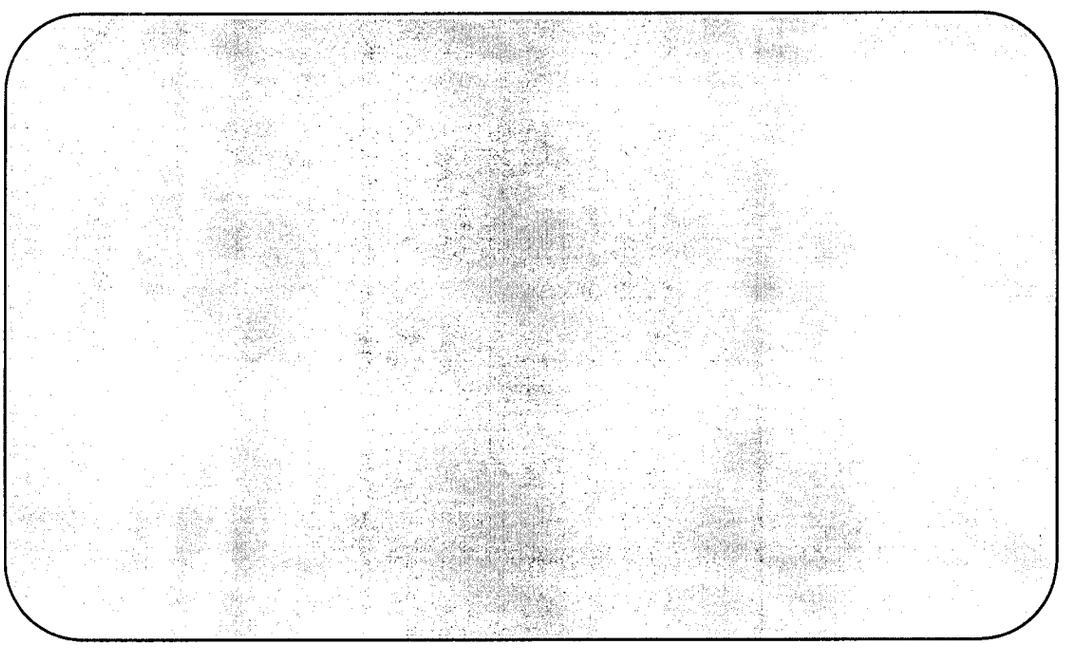
9 **Comprobante de pago No.** **Fecha** Marzo 23, 2010

(10) **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 Exp. Nº
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Bta T.P. 74.295

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

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4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 22,207
FECHA : MARZO 23 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-033947- -00000-0000
Fecha: 2010-03-23 17:01:15 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 370

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	174685910	23/03/2010	2,287,000.00

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

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

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

CERTIFICACIÓN

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

La autenticidad de las firmas se estableció por comparación.

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

(Firmado) M. Staehelin, Notario

Sello: Dr. M. Staehelin, Notario

Protocolo de Legalización No. 3253/2009

Apostilla:

Notaría Cuarenta y Seis del Círculo de Bogotá, como Notaría Cuarenta y Seis hago constar que esta copia coincide con documento original presentado para su autenticación. Bogotá, D.C. - República de Colombia

03 FEB 2010

Eugenia Rojas de Urueta

NOTARÍA CUARENTA Y SEIS

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

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

1. País:	Suiza
	El presente documento público
2. Ha sido firmado por:	Doctor en Jurisprudencia. M. Staehelin
3. Actuando en calidad de:	Notario Público
4. Lleva el sello/estampilla de:	El anteriormente mencionado
	Certificado
5. En:	Basilea.
6. El:	14 de diciembre de 2009
7. Por:	Cancillería municipal del Cantón de la ciudad de Basilea.
8. Bajo el No.:	8576/16899
9. Sello / estampilla:	Cancillería municipal · Ciudad de Basilea.
10. Firma:	Helena Schaffner

"FIN DE LA TRADUCCIÓN"

Certificación:
Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.
Documento: "IRM LLC – Certificación"
Fecha: 16 de enero de 2010.
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Traducción # 14-395

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JORGE E. SIERRA REYES
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MINISTERIO DE
RELACIONES EXTERIORES

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JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ASUME
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DEL TEXTO

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CUYA FIRMA APARECE EN EL
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OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

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, Mariana Fra

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Guillermo Ch
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Jacqueline Chap
Cruz E. de Moncale

Power of Attorney

The undersigned,
IRM LLC
a Delaware Limited Liability Company

domiciled in
131 Front Street
Hamilton HM 12
Bermuda

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

Poder

El suscrito,

domiciliado en

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

IRM LLC

Signature/Firma:

Biljana Colovic Dr. Georg von Sprecher
Authorized Signatories

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

Notaría Cuarenta y Seis del Circulo de Bogotá, como Notaría Cuarenta y Seis hago constar que esta copia coincide con documento original presentado para su autenticación. Bogotá, D.C. - República de Colombia
03 FEB 2010
Nohemy Eugenia Rojas de Urueta
NOTARIA CUARENTA Y SEIS

Attestation

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

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

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

M. Staehelin, Notar

Dr. M. Staehelin
Notar

Leg.Prot.Nr. 3253 /2009

APOSTILLE
(Hague Convention of October 5th, 1961)

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

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

STATE CHANCERY * BASLE-CITY *

Notaría Cuarenta y Seis del Círculo de Bogotá
Seis (46) como Notaria Cuarenta y Seis (46) del Círculo de Bogotá, hago constar que esta copia coincide con documento original presentado para su autenticación.
Bogotá, D.C. República de Colombia
05 FEB 2010
María Eugenia Rojas de Urueta
NOTARIA CUARENTA Y SEIS

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 February 2009 (26.02.2009)

PCT

(10) International Publication Number
WO 2009/026276 A1

(51) International Patent Classification:
C07D 239/42 (2006.01) *A61K 31/506* (2006.01)
C07D 401/12 (2006.01) *A61P 1/00* (2006.01)
C07D 403/12 (2006.01) *A61P 7/04* (2006.01)
C07D 413/12 (2006.01) *A61P 11/06* (2006.01)
A61K 31/505 (2006.01)

(21) International Application Number:
PCT/US2008/073573

(22) International Filing Date: 19 August 2008 (19.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/957,260 22 August 2007 (22.08.2007) US

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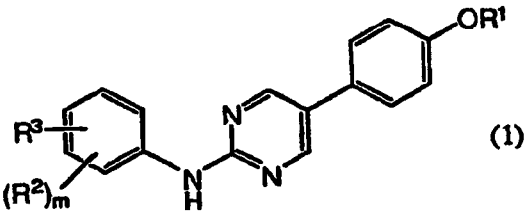
(74) Agents: **TONGCO WU, Emily** et al.; Genomics Institute of the NovartisResearch Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121 (US).

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

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

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(54) Title: 5- (4- (HALOALKOXY) PHENYL) PYRIMIDINE-2-AMINE COMPOUNDS AND COMPOSITIONS AS KINASE INHIBITORS



(1)

(57) Abstract: The invention provides compounds of formula (1) and pharmaceutical compositions thereof, which are useful as protein kinase inhibitors, as well as methods for using such compounds to treat, ameliorate or prevent a condition associated with abnormal or deregulated kinase activity. In some embodiments, the invention provides methods for using such compounds to treat, ameliorate or prevent diseases or disorders that involve abnormal activation of c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3. Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-rapor b-raf kinases.

WO 2009/026276 A1

5-(4-(HALOALKOXY)PHENYL)PYRIMIDINE-2-AMINE COMPOUNDS AND COMPOSITIONS AS KINASE INHIBITORS

Cross-Reference to Related Applications

[0001] This application claims the benefit of U.S. provisional application serial number 60/957,260, filed August 22, 2007, which is hereby incorporated by reference in its entirety.

Technical Field

[0002] The invention relates to protein kinase inhibitors, and methods of using such compounds. More particularly, the invention relates to c-kit and PDGFR inhibitors, and uses thereof for the treatment and prevention of c-kit and PDGFR mediated disorders.

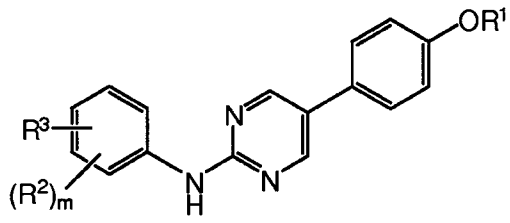
Background Art

[0003] The protein kinases represent a large family of proteins, which play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. A partial, non-limiting, list of these kinases include: receptor tyrosine kinases such as platelet-derived growth factor receptor kinase (PDGFR), the receptor kinase for stem cell factor, c-kit, the nerve growth factor receptor, trkB, and the fibroblast growth factor receptor, FGFR3; non-receptor tyrosine kinases such Abl and the fusion kinase BCR-Abl, Fes, Lck and Syk; and serine/threonine kinases such as b-RAF, MAP kinases (e.g., MKK6) and SAPK2β. Aberrant kinase activity has been observed in many disease states including benign and malignant proliferative disorders as well as diseases resulting from inappropriate activation of the immune and nervous systems.

Disclosure of the Invention

[0004] The invention provides compounds and pharmaceutical compositions thereof, which may be useful as protein kinase inhibitors.

[0005] In one aspect, the present invention provides compounds of Formula (1):



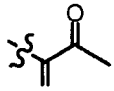
(1)

or a pharmaceutically acceptable salt thereof;

R^1 is a haloalkyl having 1-6 fluorine atoms;

R^2 is 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; halo, cyano, nitro, $(CR_2)_kOR^7$, $(CR_2)_kO(CR_2)_{1-4}R^7$, $(CR_2)_kSR^7$, $(CR_2)_kNR^9R^{10}$, $(CR_2)_kC(O)O_{0-1}R^7$, $OC(O)R^7$, $(CR_2)_kC(S)R^7$, $(CR_2)_kC(O)NR^9R^{10}$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^9R^{10}$, $(CR_2)_kS(O)_{1-2}R^8$, $(CR_2)_kNRS(O)_{1-2}R^8$ or $(CR_2)_kR^6$; or any two adjacent R^2 groups together may form an optionally substituted 5-8 membered carbocyclic, heterocyclic, aryl or heteroaryl ring;

R^3 is -L-NR^4R^5, -X-NR-C(O)R^8 or -X-NR-C(O)NR^4R^5 wherein L is –X-C(O), -X-



OC(O), $-(CR_2)_j$, $-SO_{0-2}(CR_2)_j$, $-O(CR_2)_{1-4}$, or ; and X is $(CR_2)_j$ or [C(R)(CR_2OR)];

R^4, R^5, R^9 and R^{10} are independently 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, alkoxy, cyano, carboxyl or R^6; $(CR_2)_kCN$, $(CR_2)_{1-6}NR^7R^7$, $(CR_2)_{1-6}OR^7$, $(CR_2)_kC(O)O_{0-1}R^7$, $(CR_2)_kC(O)NR^7R^7$ or $(CR_2)_k$-R^6;

R^6 is an optionally substituted C_{3-7} cycloalkyl, C_6 aryl, or a 5-6 membered heteroaryl or 5-7 membered heterocyclic ring;

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

alternatively, R^4 and R^5 together with N in each NR^4R^5, R^7 and R^7 together with N in NR^7R^7 or R^9 and R^{10} together with N in NR^9R^{10} may form a 4-7 membered heterocyclic ring optionally substituted with 1-3 R^{11} groups;

R^{11} is R^8, $(CR_2)_k$–OR^7, CO_2R^7, $(CR_2)_k$–C(O)-$(CR_2)_k$-R^8, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ or $(CR_2)_kNRS(O)_{1-2}R^8$;

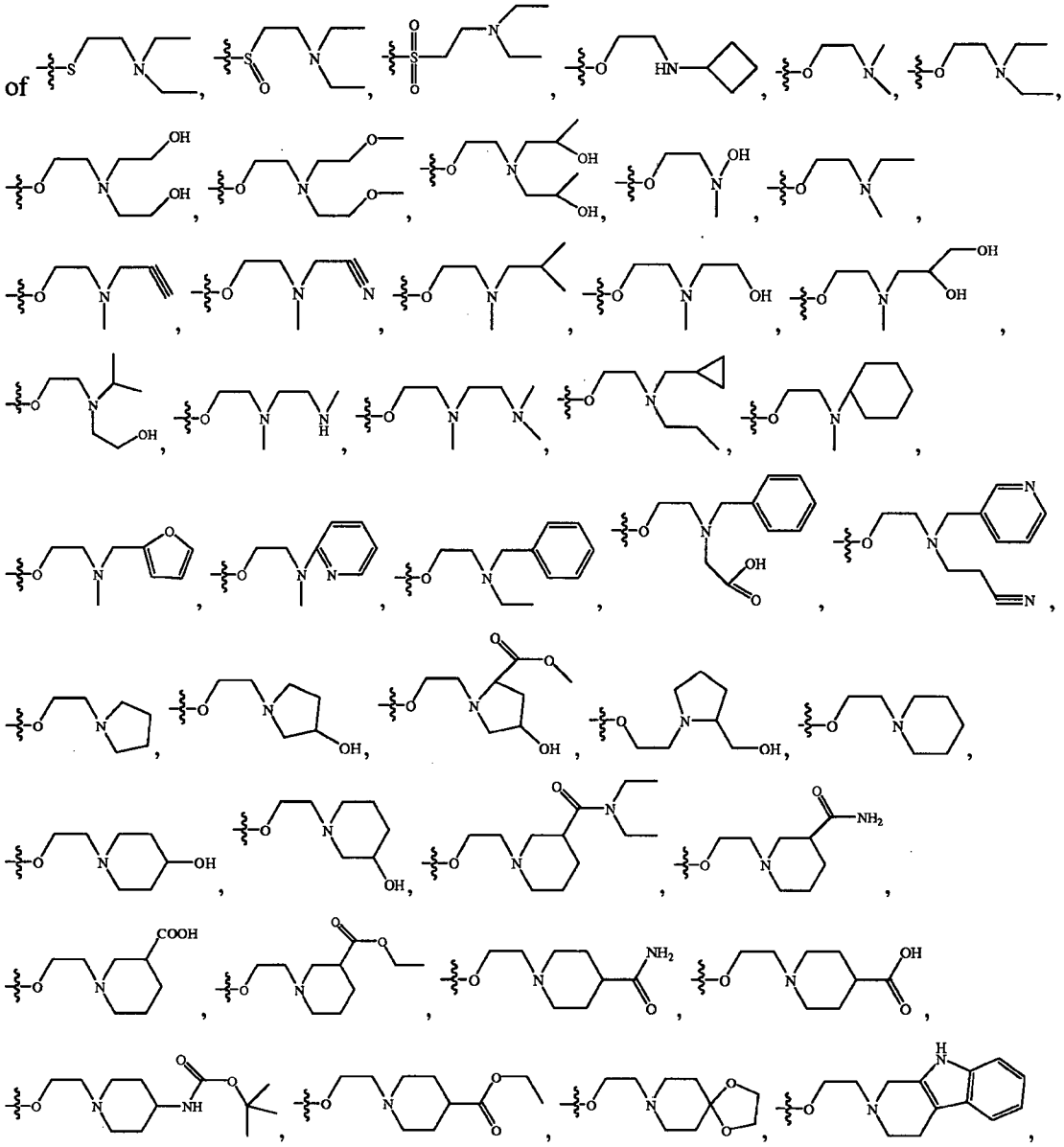
each R is H or C_{1-6}alkyl;

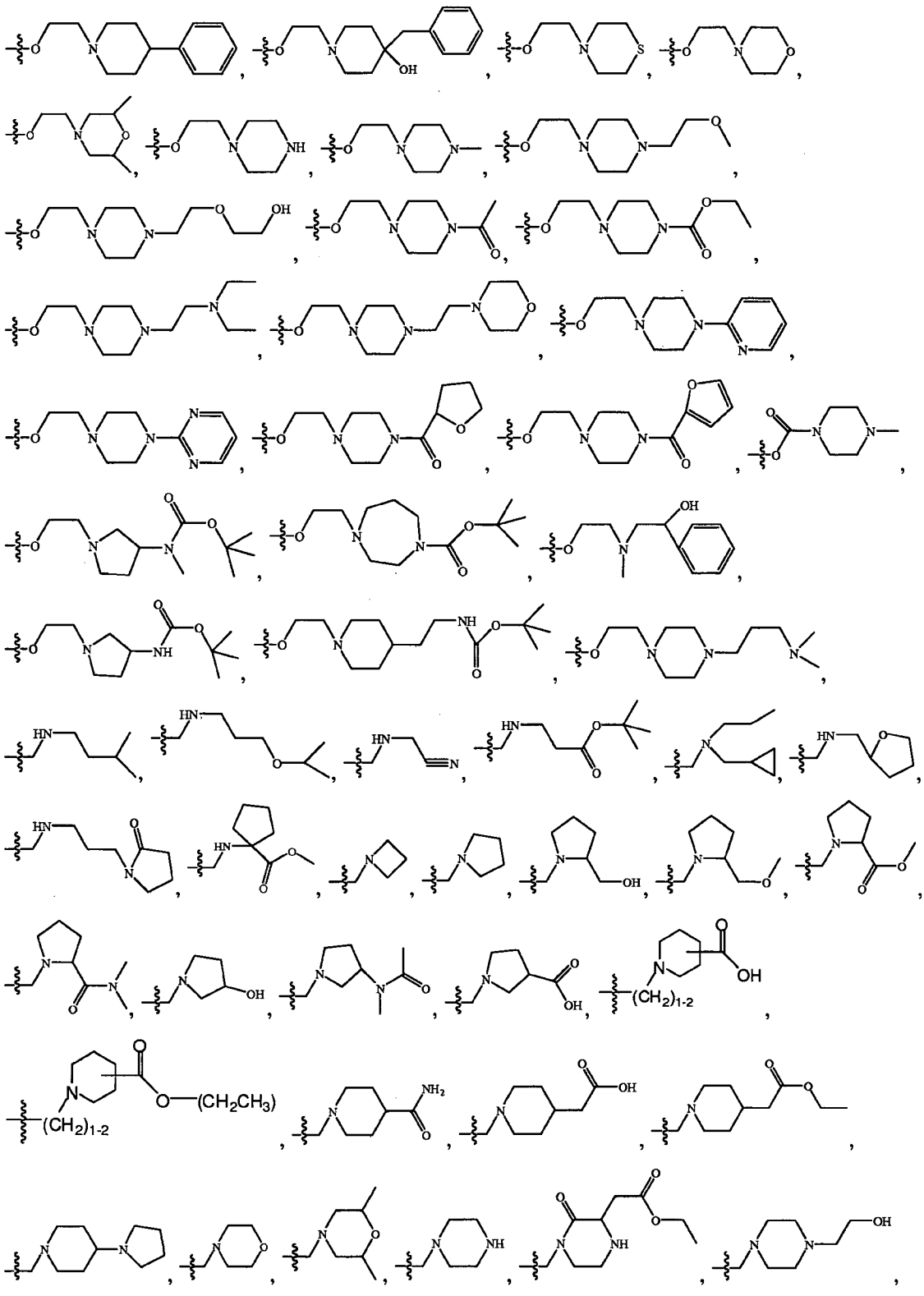
each k is 0-6; and

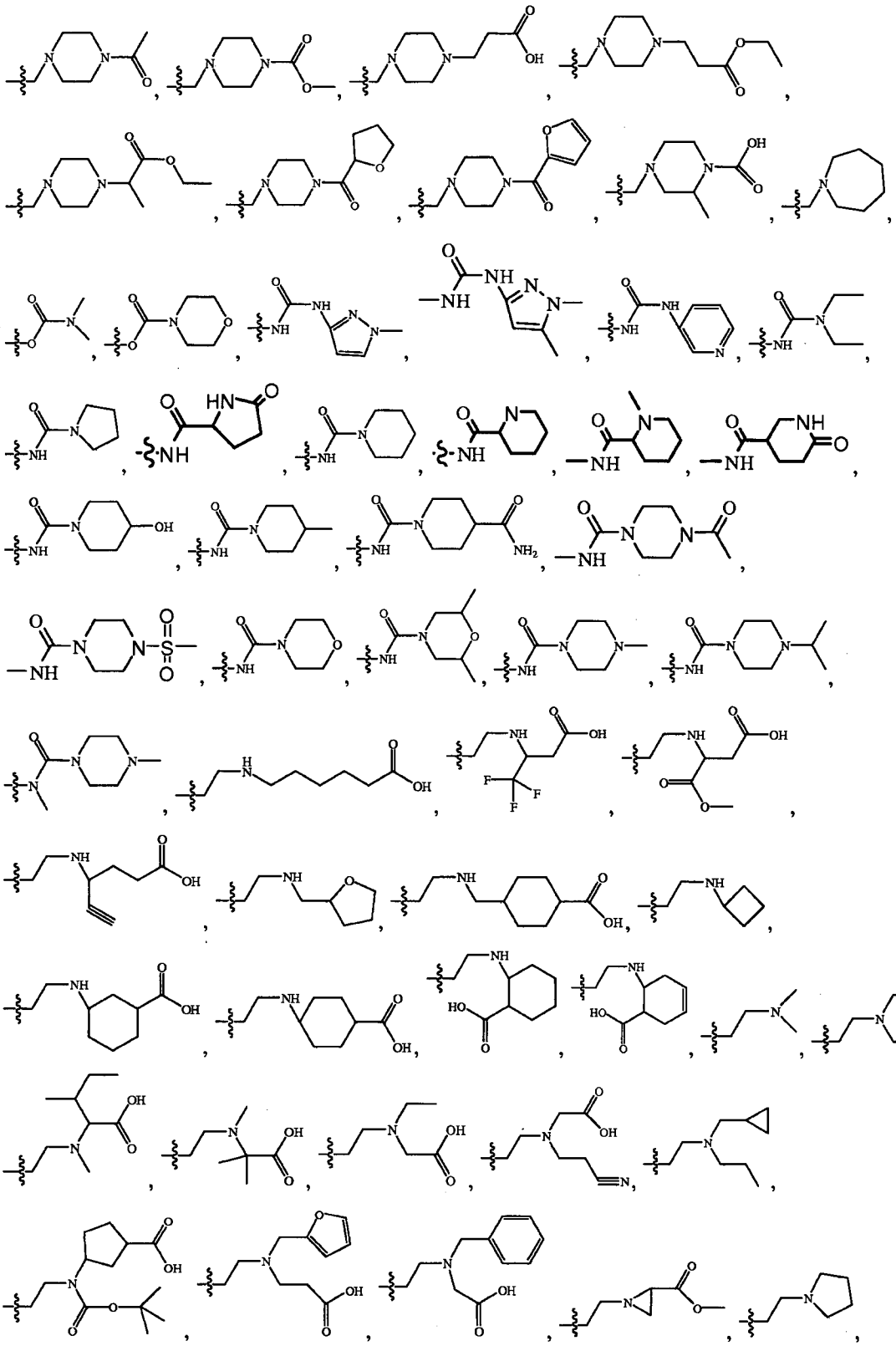
j and m are independently 0-4;

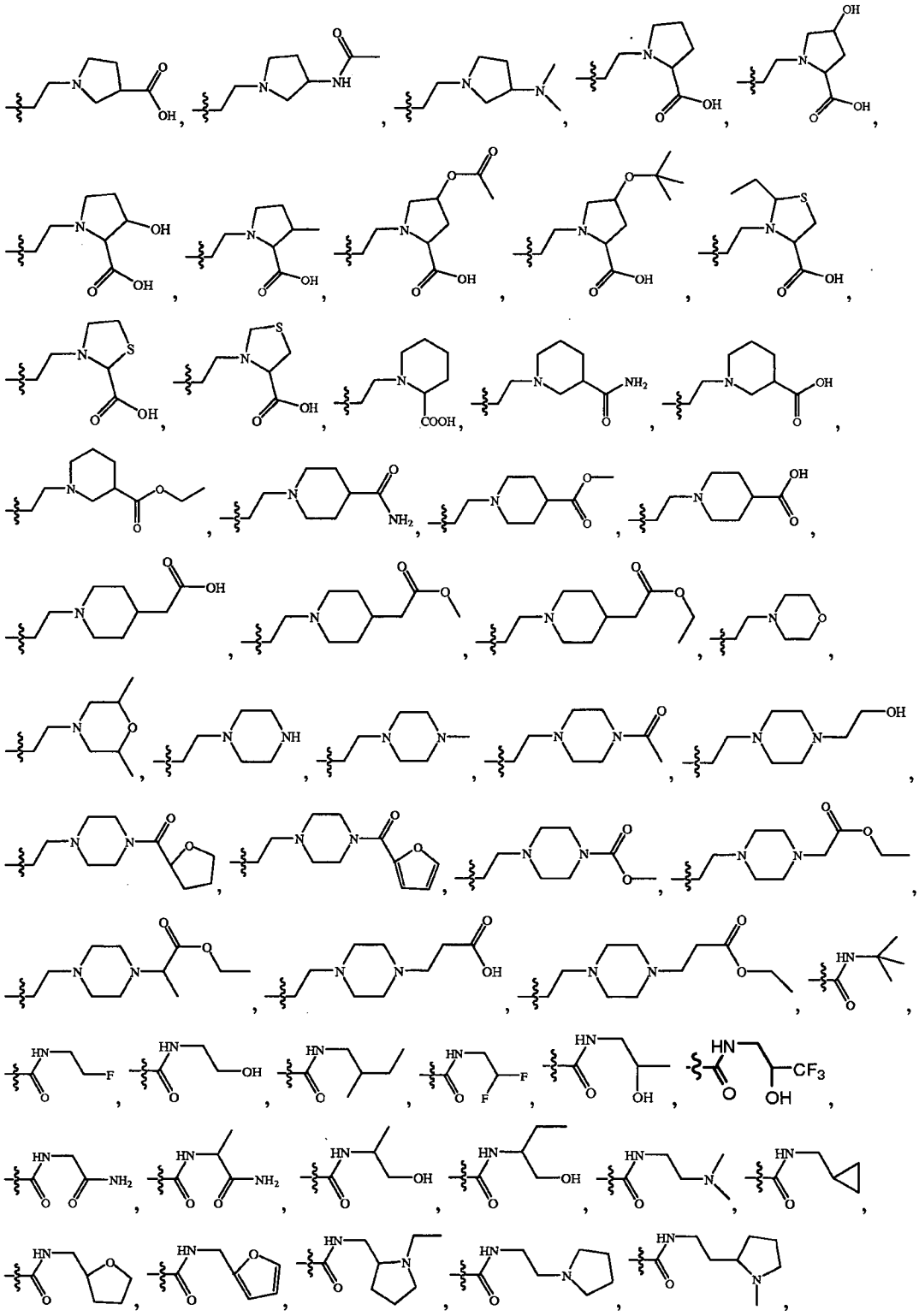
provided R^1 is not trifluoromethoxy when R^3 is $C(O)NH_2$, $C(O)NR^{12}R^{13}$ or $SO_2NH(CH_2)_{2-3}NR^{14}R^{15}$; wherein R^{12} and R^{13} together form piperazinyl and R^{14} and R^{15} together form morpholinyl.

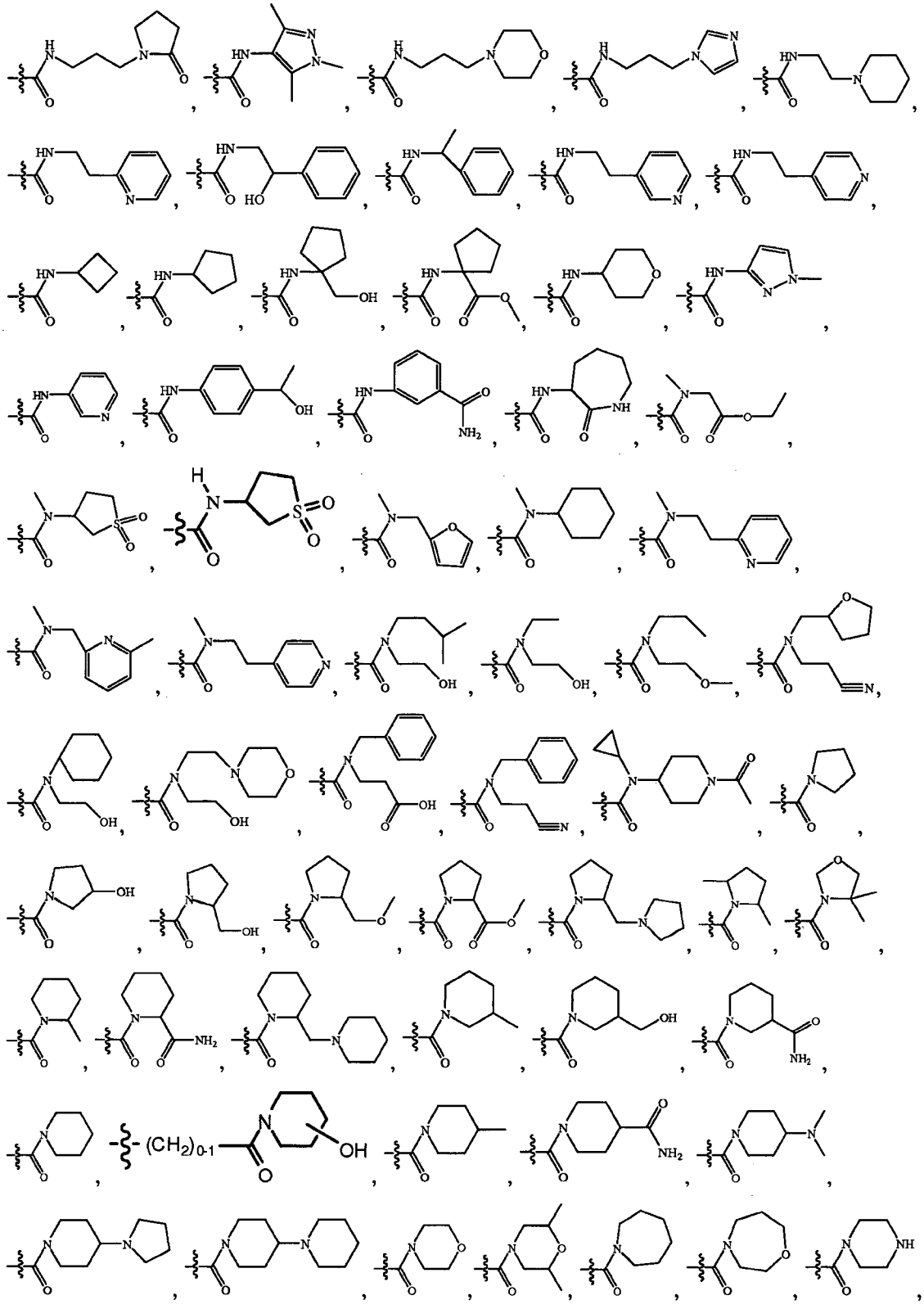
[0006] In the above Formula (1), R^1 may be $OCHF_2$, OCF_3, OCH_2CF_3, OCF_2CH_2 or OCH_2CF_3. In particular examples, R^1 is $OCHF_2$.

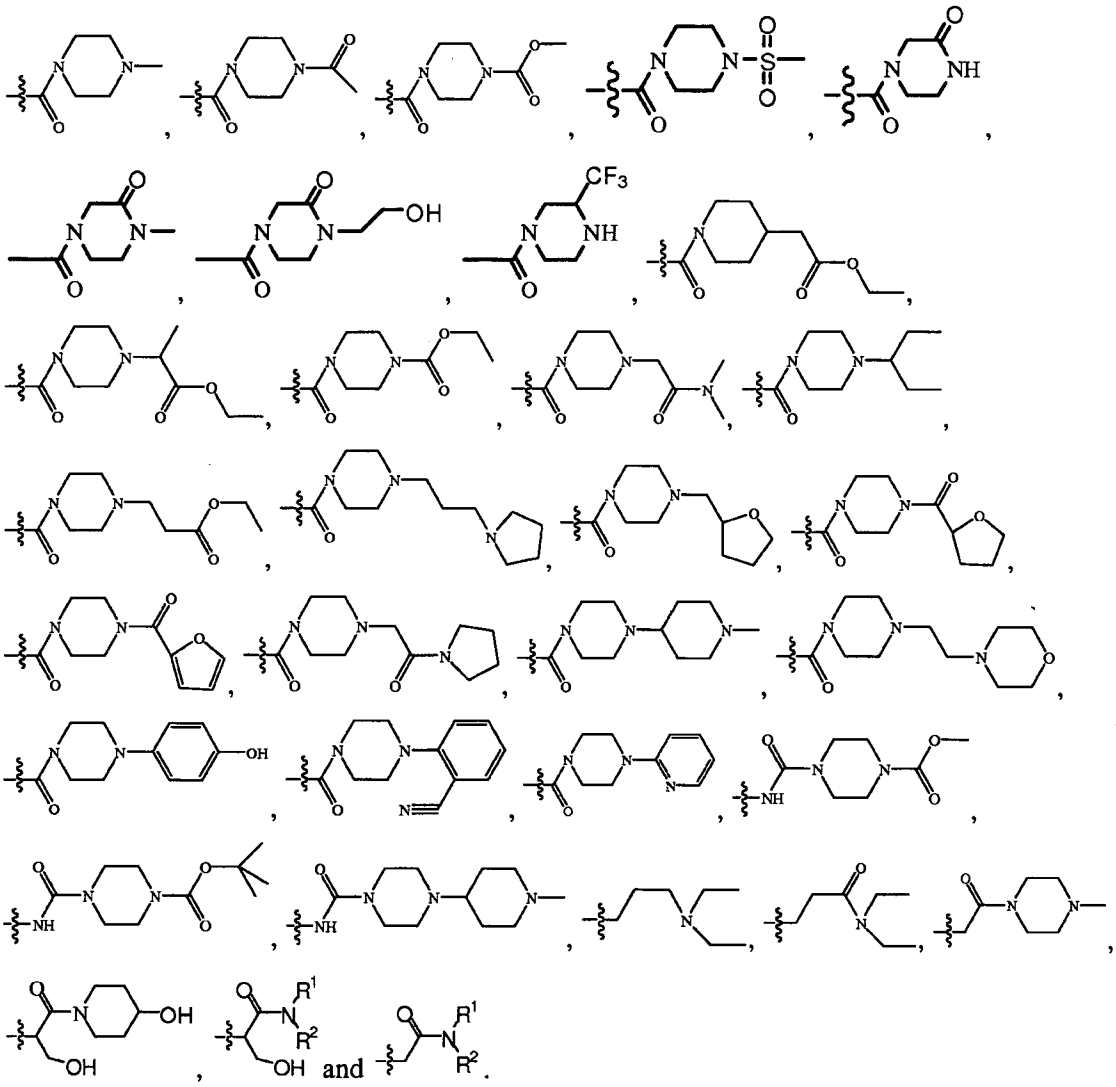
[0007] In some examples, R^3 in the above Formula (1) is selected from the group consisting of 



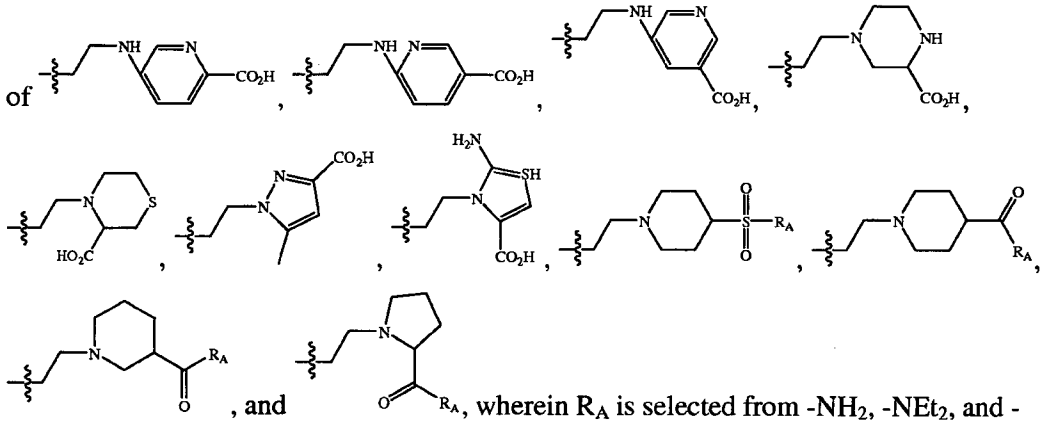








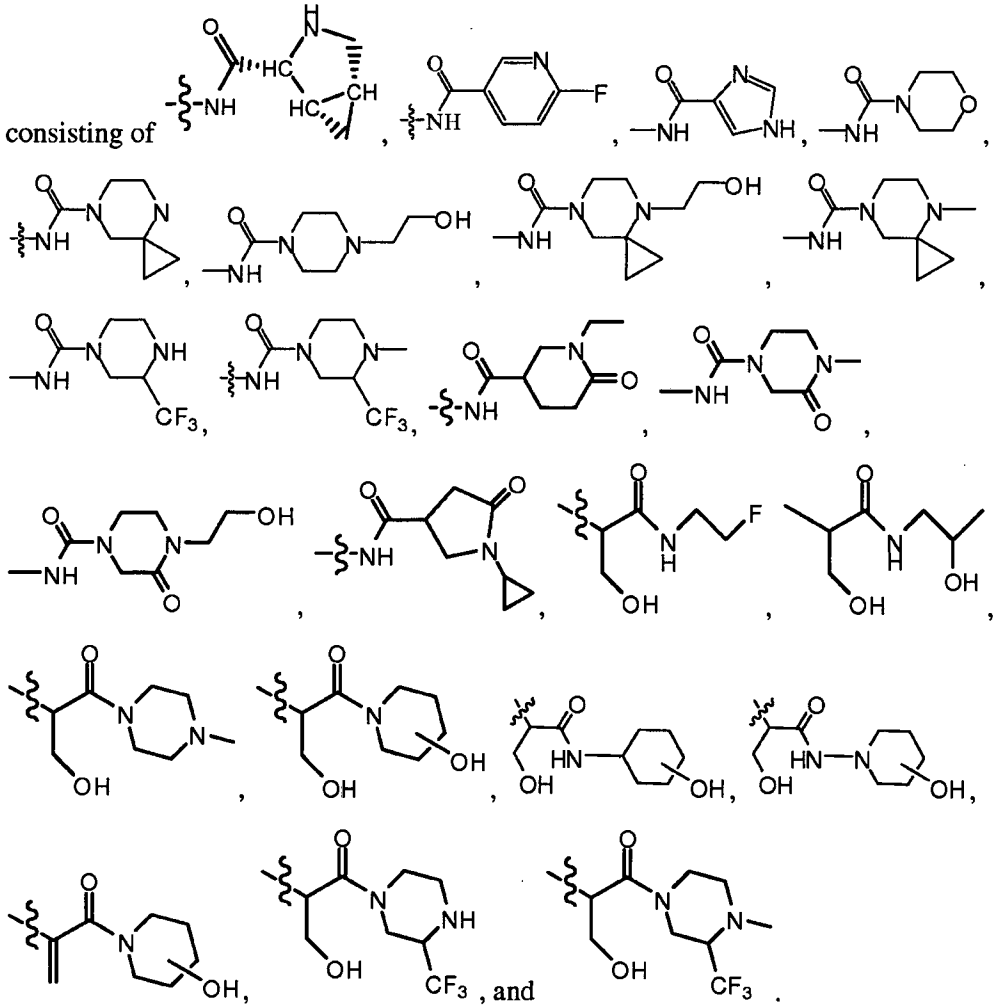
[0008] In other examples, R^3 in the above Formula (1) is selected from the group consisting of



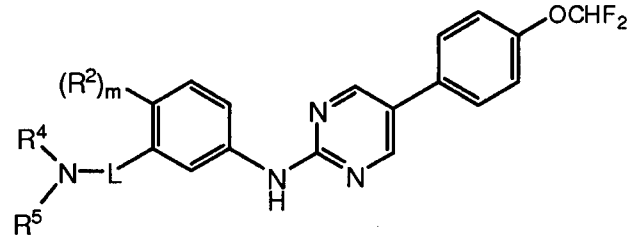
, and

, wherein R_A is selected from -NH_2, -NEt_2, and -

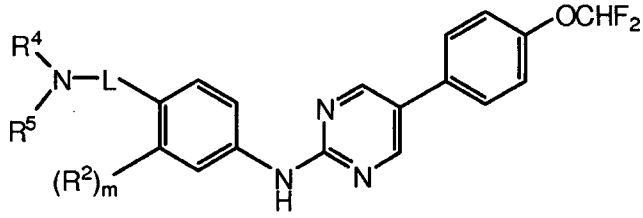
$NH(CH_2)_{1\text{-}6}OH$.

[0009] In yet other examples, R^3 in the above Formula (1) is selected from the group consisting of  , and .

[0010] In one embodiment, the compounds have Formula (2A) or (2B):



(2A)



(2B);

wherein R^4 and R^5 together with N form a 5-6 membered heterocyclic ring optionally containing NR^{16}, O, S, =O or a double bond; wherein said heterocyclic ring is optionally substituted with 1-2 R^{11} groups;

R^{16} is H, R^8, $-(CR_2)_{1-4}CO_2R^7$, $(CR_2)_k$–C(O)-$(CR_2)_k$-R^8, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_{1-4}NRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ or $(CR_2)_kNRS(O)_{1-2}R^8$; and

R^4, R^5, R^7, R^8, R^{11}, R and k are as defined in Formula (1).

[0011] In the above Formula (2A) or (2B), R^4 and R^5 together with N in NR^4R^5 may form an optionally substituted piperidinyl, piperazinyl or morpholinyl. In some examples, L is –X-C(O), $-(CR_2)_{1-4}$ or $-O(CR_2)_{1-4}$; wherein X is $(CR_2)_{0-1}$ or [C(R)(CR_2OR)]. In other examples, L is $(CR_2)_{1-2}$.

[0012] In the above Formula (1), (2A) or (2B), R^2 if present, is halo, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or CO_2R^7 and R^7 is H or C_{1-6} alkyl.

[0013] In one embodiment, the present invention provides a compound selected from the group consisting of:

N-(4-(2-(diethylamino)ethoxy)phenyl)-5-(4-(trifluoromethoxy)phenyl) pyrimidin-2-amine;

N-(4-(2-(diethylamino)ethoxy)phenyl)-5-(4-(difluoromethoxy)phenyl) pyrimidin-2-amine;

1-(2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy) ethyl)piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl) piperidine-4-carboxylic acid;

1-(4-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl) piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl) piperidine-4-carboxylic acid;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1-methylpiperidine-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2R,5R)-N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)piperidine-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-5-oxopyrrolidine-2-carboxamide;

(R)-N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-5-oxopyrrolidine-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-6-oxopiperidine-3-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-6-fluoropyridine-3-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1H-imidazole-5-carboxamide;

N-(2-methyl-5-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-5-oxopyrrolidine-2-carboxamide;

(S)-N-(2-methyl-5-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-5-oxopyrrolidine-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1-cyclopropyl-5-oxopyrrolidine-3-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1-ethyl-6-oxopiperidine-3-carboxamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-N-(2-fluoroethyl)-3-hydroxypropanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-(2-hydroxypropyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((R)-2-hydroxypropyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((R)-2-hydroxypropyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((S)-2-hydroxypropyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((S)-2-hydroxypropyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((S)-2-hydroxypropyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-(4-hydroxycyclohexyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1r,4r)-4-hydroxycyclohexyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1r,4R)-4-hydroxycyclohexyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1r,4R)-4-hydroxycyclohexyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1s,4S)-4-hydroxycyclohexyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1s,4S)-4-hydroxycyclohexyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1s,4s)-4-hydroxycyclohexyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(3-hydroxypiperidin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((S)-3-hydroxypiperidin-1-yl)propan-1-one;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((S)-3-hydroxypiperidin-1-yl)propan-1-one;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((S)-3-hydroxypiperidin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((R)-3-hydroxypiperidin-1-yl)propan-1-one;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((R)-3-hydroxypiperidin-1-yl)propan-1-one;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((R)-3-hydroxypiperidin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-(2-hydroxycyclopentyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1R,2R)-2-hydroxycyclopentyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2R)-2-hydroxycyclopentyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2S)-2-hydroxycyclopentyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1R,2R)-2-hydroxycyclopentyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2S)-2-hydroxycyclopentyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2R)-2-hydroxycyclopentyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2S)-2-hydroxycyclopentyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2R)-2-hydroxycyclopentyl)propanamide;

2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(4-hydroxypiperidin-1-yl)prop-2-en-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(4-hydroxypiperidin-1-yl)ethanone;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-methylpiperazin-1-yl)propan-1-one;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-methylpiperazin-1-yl)propan-1-one;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-methylpiperazin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(3-(trifluoromethyl)piperazin-1-yl)propan-1-one;

2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(3-(trifluoromethyl)-4-methylpiperazin-1-yl)-3-hydroxypropan-1-one;

N1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)piperidine-1,4-dicarboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methylpiperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methanesulfonyl-piperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-acetylpiperazine-1-carboxamide;

1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-(1,3-dimethyl-1H-pyrazol-5-yl)urea;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)morpholine-4-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-(2-hydroxyethyl)piperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4,7-diazaspiro[2.5]octane-7-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-4,7-diazaspiro[2.5]octane-7-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-(2-hydroxyethy)-4,7-diazaspiro[2.5]octane-7-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-(trifluoromethyl)piperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-3-(trifluoromethyl)piperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-3-oxopiperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-(2-hydroxyethyl)-3-oxopiperazine-1-carboxamide;

1-(2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy) ethyl)piperidine-4-carboxylic acid;

1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl) piperidine-4-carboxylic acid;

1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl) piperidine-4-carboxylic acid;

1-(2-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-fluorophenoxy)ethyl)piperidine-4-carboxylic acid;

1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenethyl)piperidine-4-carboxylic acid;

4-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-1-methylpiperazin-2-one;

4-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-1-(2-hydroxyethyl)piperazin-2-one;

4-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl) piperazin-2-one;

(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)(3-(trifluoromethyl)piperazin-1-yl)methanone;

Methyl 1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylate;

1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-hydroxyphenethyl)piperidine-4-carboxylic acid;

1-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)ethyl)piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylbenzyl)piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-fluorobenzyl)piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-hydroxybenzyl)piperidine-4-carboxylic acid;

4-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-1-(piperidin-4-yl)piperazin-2-one;

Isopropyl 4-(4-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-2-oxopiperazin-1-yl)piperidine-1-carboxylate;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)tetrahydro-2H-pyran-4-carboxamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-1-ethyl-6-oxopiperidine-3-carboxamide;

1-cyclopropyl-N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-5-oxopyrrolidine-3-carboxamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-3,5-dimethylisoxazole-4-carboxamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)isoxazole-5-carboxamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-2-(3-methylisoxazol-5-yl)acetamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-2-(tetrahydro-2H-pyran-4-yl)acetamide; and

N3-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)piperidine-1,3-dicarboxamide.

[0014] In another aspect, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of a compound having Formula (1), (2A) or (2B), and a pharmaceutically acceptable excipient.

[0015] In yet another aspect, the present invention provides methods for modulating kinase activity, comprising administering to a system or a subject in need thereof, a therapeutically effective amount of compound having Formula (1), (2A) or (2B), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby modulating said kinase activity.

[0016] In one embodiment, the invention provides methods for modulating c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-raf or b-raf kinases. In particular embodiments, the invention provides methods for modulating c-kit, PDGFRα or PDGFRβ; and more particularly, the invention provides methods wherein a compound having Formula (1), (2A) or (2B), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, may directly contact c-kit, PDGFRα or PDGFRβ *in vitro* or *in vivo*.

[0017] The present invention also provides methods for treating a disease or condition wherein modulation of kinase activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease or condition, comprising administering to a subject a therapeutically effective amount of a compound having Formula (1), (2A) or (2B), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, and optionally in combination with a second therapeutic agent. Examples of therapeutic agents which may be used in combination with a compound of the invention include but are not limited to an anti-fibrotic agent, pirfenidone, tacrolimus, an anti-inflammatory agent, a corticosteroid, a cromolyn, a leukotriene antagonist, an IgE blocker, a bronchodilator, a β_2-agonist, xanthines, an anticholinergic, or a chemotherapeutic agent. When administered with a second therapeutic agent, the compound of Formula (1), (2A) or (2B), or pharmaceutically acceptable salts or pharmaceutical compositions thereof may be administered prior to, simultaneously with, or after the second therapeutic agent.

[0018] In one embodiment, the invention provides methods for treating a disease or condition modulated by c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-raf or b-raf kinases. In particular examples, the invention

provides methods for treating a disease or condition modulated by PDGFRα, PDGFRβ or c-kit. In some examples, the invention provides methods for treating a disease or condition modulated by c-kit.

[0019] Examples of kinase mediated disease or conditions which may be mediated using the compounds and compositions of the invention include but are not limited to a mast-cell associated disease, an allergy disorder, irritable bowel syndrome (IBS), a fibrotic disease, a neoplastic disorder, an inflammatory disorder, an autoimmune disorder, a graft-versus-host disease, a metabolic syndrome, a CNS related disorder, a neurodegenerative disorder, a pain condition, a substance abuse disorder, a cancer, a cardiovascular disease, and a prion disease.

[0020] Examples of a mast cell associated disease which may be treated using compounds and compositions of the invention include but are not limited to allergic disorders (including asthma and atopic dermatitis), urticaria, acne and Propionibacterium acnes, Fibrodysplasia ossificans progressiva (FOP), inflammation and tissue destruction induced by exposure to chemical or biological weapons (such as anthrax and sulfur-mustard), cystic fibrosis; renal disease, inflammatory muscle disorders, HIV, type II diabetes, cerebral ischemia, mastocytosis, drug dependence and withdrawal symptoms, CNS disorders, preventing and minimizing hair loss, bacterial infections, interstitial cystitis, inflammatory bowel diseases (*e.g.*, Crohn's disease, ulcerative colitis, indeterminate colitis, and infectious colitis), tumor angiogenesis, autoimmune diseases, inflammatory diseases, multiple sclerosis (MS), and bone loss.

[0021] Examples of allergy disorders which may be treated using the compounds and compositions of the invention include but are not limited to asthma, atopic dermatitis, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, and blood sucking parasite infestation.

[0022] Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain and altered bowel habit. Pain is characteristically relieved by defecation and may be associated with increase or decrease in stool frequency, alterations in stool consistency, straining or urgency, a sensation of incomplete evacuation, passage of mucus or abdominal distention.

[0023] A fibrotic disease as used herein encompasses all conditions linked to or associated with the formation and deposition of extracellular matrix components, particularly in the internal organs, including the kidneys, heart, lungs, liver, skin and joints. Examples of fibrotic diseases

which may be treated using the compounds and compositions of the invention include but are not limited to scleroderma, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), primary pulmonary hypertension (e.g., pulmonary arterial hypertension (PPAH)), liver fibrosis, renal fibrosis, cardiac fibrosis, cirrhosis in liver, bone marrow fibrosis, hepatitis C (HCV) and nonalcoholic steatohepatitis (NASH).

[0024] Examples of neoplastic disorders which may be treated using the compounds and compositions of the invention include but are not limited to mastocytosis, gastrointestinal stromal tumor, small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodyplastic syndrome, chronic myelogenous leukemia, colorectal carcinoma, gastric carcinoma, testicular cancer, glioblastoma and astrocytoma.

[0025] Examples of inflammatory disorders which may be treated using the compounds and compositions of the invention include but are not limited to rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis and gouty arthritis.

[0026] Examples of autoimmune disorders which may be treated using the compounds and compositions of the invention include but are not limited to multiple sclerosis, psoriasis, intestine inflammatory disease, inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, rheumatoid arthritis, polyarthritis, local or systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosis, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy and proliferative glomerulonephritis.

[0027] Examples of graft-versus-host diseases which may be treated using the compounds and compositions of the invention include but are not limited to organ transplantation graft rejection, such as kidney transplantation, pancreas transplantation, liver transplantation, heart transplantation, lung transplantation, and bone marrow transplantation.

[0028] Examples of metabolic syndrome which may be treated using the compounds and compositions of the invention include but are not limited to type I diabetes, type II diabetes, and obesity.

[0029] Examples of CNS related disorders which may be treated using the compounds and compositions of the invention include but are not limited to depression, dysthymic disorder, cyclothymic disorder, anorexia, bulimia, premenstrual syndrome, post-menopause syndrome, mental slowing, loss of concentration, pessimistic worry, agitation, self-deprecation and decreased libido, an anxiety disorder, a psychiatric disorder and schizophrenia.

[0030] Examples of depression conditions which may be treated using the compounds and compositions of the invention include but are not limited to bipolar depression, severe or melancholic depression, atypical depression, refractory depression, and seasonal depression. Examples of anxiety disorders which may be treated using the compounds and compositions of the invention include but are not limited to anxiety associated with hyperventilation and cardiac arrhythmias, phobic disorders, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, and generalized anxiety disorder. Examples of psychiatric disorders which may be treated using the compounds and compositions of the invention include but are not limited to panic attacks, including psychosis, delusional disorders, conversion disorders, phobias, mania, delirium, dissociative episodes including dissociative amnesia, dissociative fugue and dissociative suicidal behavior, self-neglect, violent or aggressive behavior, trauma, borderline personality, and acute psychosis such as schizophrenia, including paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, and undifferentiated schizophrenia.

[0031] Examples of neurodegenerative disorder which may be treated using the compounds and compositions of the invention include but are not limited to osteoarthritis, Alzheimer's disease, Parkinson's disease, Huntington's disease, the prion diseases, Motor Neuron Disease (MND), and Amyotrophic Lateral Sclerosis (ALS).

[0032] Examples of pain conditions which may be treated using the compounds and compositions of the invention include but are not limited to acute pain, postoperative pain, chronic pain, nociceptive pain, cancer pain, neuropathic pain and psychogenic pain syndrome.

[0033] Examples of substance use disorders which may be treated using the compounds and compositions of the invention include but are not limited to drug addiction, drug abuse, drug habituation, drug dependence, withdrawal syndrome and overdose.

[0034] Examples of cancers which may be treated using the compounds and compositions of the invention include but are not limited to glioma, melanoma, gastrointestinal stromal tumor (GIST), small cell lung cancer, colorectal cancer, and other solid tumors.

[0035] Examples of cardiovascular diseases which may be treated using the compounds and compositions of the invention include but are not limited to angina pectoris, myocardial infarction, congestive heart failure, cardiomyopathy, hypertension, arterial stenosis, and venous stenosis.

[0036] More particularly, the compounds of the invention may be used for the treatment and

prevention of asthma, atopic dermatitis, urticaria, irritable bowel syndrome (IBS), or a fibrotic disease including but not limited to scleroderma, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), primary pulmonary hypertension (PPH), primary pulmonary arterial hypertension (PPAH), idiopathic arterial hypertension (IPAH), liver fibrosis, renal fibrosis and cardiac fibrosis.

[0037] Furthermore, the present invention provides for the use of a compound having Formula (1), (2A) or (2B), or a pharmaceutically composition thereof, and optionally in combination with a second therapeutic agent, for the manufacture of a medicament for treating a disease or condition modulated by c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-raf or b-raf kinases; and more particularly, for the manufacture of a medicament for treating a disease or condition modulated by PDGFRα, PDGFRβ or c-kit.

[0038] In the above methods for using the compounds of the invention, a compound having Formula (1), (2A) or (2B) may be administered to a system comprising cells or tissues. In other embodiments, a compound having Formula (1), (2A) or (2B) may be administered to a human or animal subject.

Definitions

[0039] "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).

[0040] "Aryl" refers to a monocyclic or fused bicyclic aromatic ring containing carbon atoms. For example, aryl may be phenyl or naphthyl. "Arylene" means a divalent radical derived from an aryl group.

[0041] "Heteroaryl" as used herein is as defined for aryl above, where one or more of the ring members is a heteroatom. Examples of heteroaryls include but are not limited to pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc.

[0042] 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.

[0043] A "heterocyclic ring" as used herein is as defined for a carbocyclic ring above, wherein one or more ring carbons is a heteroatom. For example, a heterocyclic ring may contain N, O, S, -N=, -S-, -S(O), -$S(O)_2$-, or -NR- wherein R may be hydrogen, C_{1-4}alkyl or a protecting group. Examples of heterocyclic rings include but are not limited to morpholino, pyrrolidinyl, pyrrolidinyl-2-one, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, etc.

[0044] 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.

[0045] Unless otherwise indicated, when a substituent is deemed to be "optionally substituted," it is meant that the substituent is a group that may be substituted with one or more group(s) individually and independently selected from, for example, an optionally halogenated alkyl, alkenyl, alkynyl, alkoxy, alkylamine, alkylthio, alkynyl, amide, amino, including mono- and di-substituted amino groups, aryl, aryloxy, arylthio, carbonyl, carbocyclic, cyano, cycloalkyl, halogen, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, heterocyclic, hydroxy, isocyanato, isothiocyanato, mercapto, nitro, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, perhaloalkyl, perfluoroalkyl, silyl, sulfonyl, thiocarbonyl, thiocyanato, trihalomethanesulfonyl, and the protected compounds thereof. The protecting groups that may form the protected compounds of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference in their entirety.

[0046] The terms "co-administration" or "combined administration" or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

[0047] 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.

[0048] The term "therapeutically effective amount" means the amount of the subject compound that will elicit a biological or medical response in a cell, tissue, organ, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

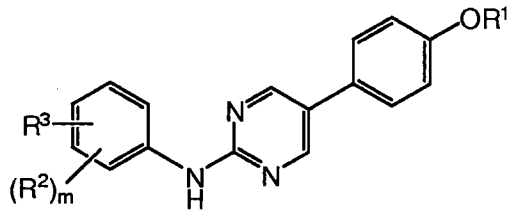
[0049] The term "administration" or "administering" of the subject compound means providing a compound of the invention and prodrugs thereof to a subject in need of treatment.

[0050] Unless otherwise stated for this invention, a kinase selected from c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-raf and b-raf refers to wild-type and mutant forms (i.e,. having single or multiple amino acid changes from the wild-type sequence).

Modes of Carrying Out the Invention

[0051] The present invention provides compounds and pharmaceutical compositions thereof, which may be useful as protein kinase inhibitors.

[0052] In one aspect, the present invention provides compounds of Formula (1):

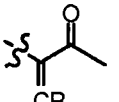


(1)

or a pharmaceutically acceptable salt thereof;

R^1 is a haloalkyl having 1-6 fluorine atoms;

R^2 is 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; halo, cyano, nitro, $(CR_2)_kOR^7$, $(CR_2)_kO(CR_2)_{1-4}R^7$, $(CR_2)_kSR^7$, $(CR_2)_kNR^9R^{10}$, $(CR_2)_kC(O)O_{0-1}R^7$, $OC(O)R^7$, $(CR_2)_kC(S)R^7$, $(CR_2)_kC(O)NR^9R^{10}$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^9R^{10}$, $(CR_2)_kS(O)_{1-2}R^8$, $(CR_2)_kNRS(O)_{1-2}R^8$ or $(CR_2)_kR^6$; or any two adjacent R^2 groups together may form an optionally substituted 5-8 membered carbocyclic, heterocyclic, aryl or heteroaryl ring;

R^3 is -L-NR^4R^5, -X-NR-C(O)R^8 or -X-NR-C(O)NR^4R^5 wherein L is –X-C(O), -X-OC(O), -$(CR_2)_j$, -$SO_{0-2}(CR_2)_j$, -$O(CR_2)_{1-4}$, or  ; and X is $(CR_2)_j$ or [C(R)(CR_2OR)];

R^4, R^5, R^9 and R^{10} are independently 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, alkoxy, cyano, carboxyl or R^6; $(CR_2)_kCN$, $(CR_2)_{1-6}NR^7R^7$, $(CR_2)_{1-6}OR^7$, $(CR_2)_kC(O)O_{0-1}R^7$, $(CR_2)_kC(O)NR^7R^7$ or $(CR_2)_k$-R^6;

R^6 is an optionally substituted C_{3-7} cycloalkyl, C_6 aryl, or a 5-6 membered heteroaryl or 5-7 membered heterocyclic ring;

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

alternatively, R^4 and R^5 together with N in each NR^4R^5, R^7 and R^7 together with N in NR^7R^7 or R^9 and R^{10} together with N in NR^9R^{10} may form a 4-7 membered heterocyclic ring optionally substituted with 1-3 R^{11} groups;

R^{11} is R^8, $(CR_2)_k$–OR^7, CO_2R^7, $(CR_2)_k$–C(O)-$(CR_2)_k$-R^8, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ or $(CR_2)_kNRS(O)_{1-2}R^8$;

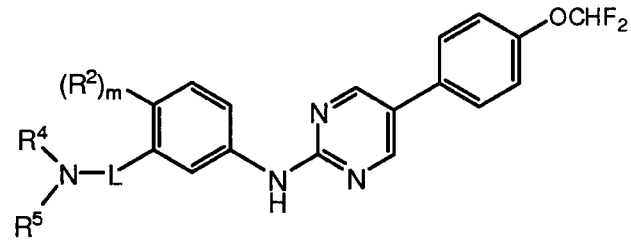
each R is H or C_{1-6}alkyl;

each k is 0-6; and

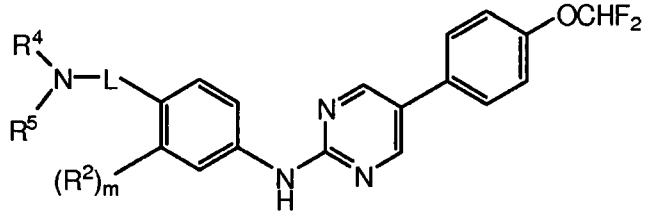
j and m are independently 0-4;

provided R^1 is not trifluoromethoxy when R^3 is $C(O)NH_2$, $C(O)NR^{12}R^{13}$ or $SO_2NH(CH_2)_{2-3}NR^{14}R^{15}$; wherein R^{12} and R^{13} together form piperazinyl and R^{14} and R^{15} together form morpholinyl.

[0053] In one embodiment, the compounds have Formula (2A) or (2B):



(2A)



(2B);

wherein R^4 and R^5 together with N form a 5-6 membered heterocyclic ring optionally containing NR^{16}, O, S, =O or a double bond; wherein said heterocyclic ring is optionally substituted with 1-2 R^{11} groups;

R^{16} is H, R^8, $-(CR_2)_{1-4}CO_2R^7$, $(CR_2)_k$–C(O)-$(CR_2)_k$-R^8, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_{1-4}NRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ or $(CR_2)_kNRS(O)_{1-2}R^8$; and

R^4, R^5, R^7, R^8, R^{11}, R and k are as defined in Formula (1).

[0054] 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.

[0055] The present invention also includes all suitable isotopic variations of the compounds of the invention, or pharmaceutically acceptable salts thereof. An isotopic variation of a compound of the invention or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that may be incorporated into the compounds of the invention and pharmaceutically acceptable salts thereof include but are not limited to isotopes of hydrogen, carbon, nitrogen and oxygen such as as ^2H, ^3H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F, ^{36}Cl and ^{123}I. Certain isotopic variations of the compounds of the invention and pharmaceutically acceptable salts thereof, for example, those in

which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies.

[0056] In particular examples, ^{2}H, ^{3}H and ^{14}C isotopes may be used for their ease of preparation and detectability. In other examples, substitution with isotopes such as ^{2}H may afford certain therapeutic advantages resulting from greater metabolic stability, such as increased in vivo half-life or reduced dosage requirements. Isotopic variations of the compounds of the invention or pharmaceutically acceptable salts thereof can generally be prepared by conventional procedures using appropriate isotopic variations of suitable reagents. Isotopic variations of the compounds have the potential to change a compound's metabolic fate and/or create small changes in physical properties such as hydrophobicity, and the like. Isotopic variation have the potential to enhance efficacy and safety, enhance bioavailability and half-life, alter protein binding, change biodistribution, increase the proportion of active metabolites and/or decrease the formation of reactive or toxic metabolites.

[0057] 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.

[0058] Compounds having Formula (1), (2A) or (2B) 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. The IC_{50} value in those experiments is given as that concentration of the test compound in question that results in a cell count that is 50 % lower than that obtained using the control without inhibitor. In 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. Formula (1), (2A) and (2B) may exhibit a percentage inhibition of greater than 50%, or in other embodiments, may exhibit a percentage inhibition greater than about 70%, against one or more of the following kinases at 10 μM: c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK,

JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-raf or b-raf kinases.

[0059] The compounds of the invention may also be used for the treatment of a kinase-mediated condition or disease, such as diseases mediated by c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-raf or b-raf kinases.
More particularly, the compounds of the invention may be used for the treatment and prevention of asthma, atopic dermatitis, urticaria, irritable bowel syndrome (IBS), or a fibrotic disease including but not limited to scleroderma, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), primary pulmonary hypertension (PPH), primary pulmonary arterial hypertension (PPAH), idiopathic arterial hypertension (IPAH), liver fibrosis, renal fibrosis and cardiac fibrosis.

Pharmacology and Utility

[0060] Compounds of the invention are screened against the kinase panel (wild type and/or mutation thereof) and may modulate the activity of at least one panel kinase panel member. As such, compounds of the invention may be useful for treating diseases or disorders in which kinases contribute to the pathology and/or symptomology of the disease. Examples of kinases that may be inhibited by the compounds and compositions described herein and against which the methods described herein may be useful include, but are not limited to c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-raf or b-raf kinases.

c-Kit

[0061] Mast cells are tissue elements derived from a particular subset of hematopoietic stem cells that express CD34, c-kit and CD13 antigens. Mast cells are characterized by their heterogeneity, not only regarding tissue location and structure but also at the functional and histochemical levels. Immature mast cell progenitors circulate in the bloodstream and differentiate into various tissues. These differentiation and proliferation processes are under the influence of cytokines, one of importance being Stem Cell Factor (SCF), also termed the Kit ligand, Steel factor or Mast Cell Growth Factor. The Stem Cell Factor receptor is encoded by the protooncogene, c-kit, which is expressed in hematopoietic progenitor cells, mast cells, germ

cells, interstitial cells of Cajal (ICC), and some human tumors, and is also expressed by non hematopoietic cells.

[0062] Tyrosine kinases are receptor type or non-receptor type proteins, which transfer the terminal phosphate of ATP to tyrosine residues of proteins thereby activating or inactivating signal transduction pathways. The Stem Cell Factor receptor, c-kit, is a Type III transmembrane receptor protein tyrosine kinase which initiates cell growth and proliferation signal transduction cascades in response to SCF binding. Ligation of c-kit receptor by SCF induces its dimerization followed by its transphorylation, leading to the recruitment and activation of various intracytoplasmic substrates. These activated substrates induce multiple intracellular signaling pathways responsible for cell proliferation and activation. These proteins are known to be involved in many cellular mechanisms, which in case of disruption, lead to disorders such as abnormal cell proliferation and migration, as well as inflammation. The compounds of the present invention may inhibit cellular processes involving SCF, such as inhibiting SCF receptor autophosphorylation and SCF-stimulated activation of MAPK kinase (mitogen-activated protein kinase).

[0063] The activity of the c-kit receptor protein tyrosine kinase is regulated in normal cells, and the normal functional activity of the c-kit gene product is important for the maintenance of normal hematopoeisis, melanogenesis, gametogenesis, and growth and differentiation of mast cells. In addition to its importance in normal cellular physiologic activities, c-kit plays a role in the biological aspects of certain human cancers, and unregulated c-kit kinase activity is implicated in the pathogenesis of human cancers, and in certain tumors types. Proliferation of tumor cell growth mediated by c-kit can occur by a specific mutation of the c-kit polypeptide that results in ligand independent activation or by autocrine stimulation of the receptor. In the former case, mutations that cause constitutive activation of c-kit kinase activity in the absence of SCF binding are implicated in malignant human cancers, including germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, neuroblastoma and mastocytosis.

[0064] Mast cells present in tissues of patients are implicated in or contribute to the genesis of diseases such as autoimmune diseases (multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases (IBD)), allergic diseases, tumor angiogenesis, inflammatory diseases, and interstitial cystitis. Allergic diseases include but are not limited to allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact

dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, and asthma. Asthma is characterized by airflow obstruction, bronchial hyper responsiveness and airway inflammation, and includes bronchial asthma and allergic asthma.

[0065] In these diseases, mast cells participate in the destruction of tissues by releasing a cocktail of different proteases and mediators such as histamine, neutral proteases, lipid-derived mediators (prostaglandins, thromboxanes and leucotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL- 6, IL-8, TNF-A, GM-CSF, MIP-LA, MIP-lb, MIP-2 and IFN-y). Mast cell activation induces diverse effector responses, such as secretion of allergic mediators, proteases, chemokines such as MCP-1 and RANTES, leukotrienes, prostaglandins, neurotrophins, induction of cytokine gene transcription (IL-4, IL-5, IL-6, IL-13, TNFA and GM-CSF). These mediators contribute to creating the asthmatic phenotype by their effects on endothelial cells, smooth muscle cells and fibroblasts and on extracellular matrix, and by recruiting other inflammatory cells.

[0066] Mast cells may play a role in asthma as suggested by the humanized anti-IgE monoclonal antibody treatment. The rationale of anti-IgE therapy is to specifically target IgE with the result of inactivating free anti-IgE and halting further IgE production. In addition, since IgE levels are a major regulator of the level of expression of IgE receptor FceRI, one aim of this therapy is to decrease FceRI expression on mast cells and basophils, and, as a consequence, to decrease the capacity of these cells to be activated. The capacity of the anti-IgE therapy to decrease FceRI expression has been demonstrated on basophils. The decrease in FceRI expression on basophils is associated with a decrease in the capacity of basophils to secrete mediators upon activation.

[0067] C-kit inhibitors may also be used in the treatment of non-insulin-dependent diabetes mellitus (NLDDM), also known as type II diabetes, a chronic disease appearing when insulin is inefficient in promoting glucose uptake by cells, resulting in increased levels of glucose in the blood. This disease affects about 100 million people world-wide, 75% of which are obese at the time of diagnosis. Over many years, the failure of the glucose uptake regulation leads to the development of Type II diabetes, and the blood glucose level needs to be regulated with medicinal products. Ultimately, unregulated blood glucose level is responsible for blood vessels, kidney and eye damages, as well as cardiovascular diseases. This tissue damages contribute to mortality in diabetics.

[0068] In addition, the activation of mast cells by different stimuli such as stress, trauma,

infection as well as neurotransmitters, may participate in the exacerbation of the chemical imbalance causing CNS disorders. More specifically, mast cell degranulation is stimulated by common neurotransmitters such as neurotensin, somatostatin, substance P and acetylcholine, by growth or survival factors, notably NGF, TGFßL Mast cells involved in the response to such stimulus can be brain mast cells but also other mast cells releasing the content of their granules in the blood stream that ultimately reach sensory, motor or brain neurons. Brain mast cells staining is CTMC staining-like but they show the secretory pattern of MMC, implying that they constitute a particular subset of mast cells presenting specificities.

[0069] Following mast cells activation, released granules liberate various factors capable of modulating and altering neurotransmission and neurons survival. Among such factors, serotonin is important since an increase of the level of free serotonin has been observed in depressed patients. Alternatively, the sudden burst of serotonin may be followed by a period of serotonin shortage, leading to pain and migraine. As a consequence, it is believed that mast cells exacerbate in autocrine or paracrine manner the deregulation of neurotransmission. For example, anxiety or stress-induced release of neurotransmitters such as serotonin activates mast cells, which in turn release the content of their granules, further contributing to the chemical imbalance in the brain leading to CNS disorders.

[0070] Other mediators released by mast cells can be categorized into vasoactive, nociceptive, proinflammatory and other neurotransmitters. Taken together, these factors are able to induce great disturbance in the activity of neurons, whether they are sensory, motor, or CNS neurons. In addition, patients afflicted with mastocytosis are more inclined to develop CNS disorders than the normal population. This can be explained by the presence of activating mutations in the c-kit receptor, which induce degranulation of mast cells and a burst of factors contributing to chemical imbalance and neurotransmission alteration.

[0071] In some cases, activated mast cells can also participate in the destruction of neuronal tissues by releasing a cocktail of different proteases and mediators categorized into three groups: preformed granule-associated mediators (histamine, proteoglycans, and neutral proteases), lipid-derived mediators (prostaglandins, thromboxanes and leucotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-A, GM-CSF, MIP-LA, MIP-lb, MIP-2 and IFN-y). The liberation by activated mast cells of mediators (TNF- A, histamine, leukotrienes, prostaglandins etc.) as well as proteases may i) induce inflammation and vasodilatation and ii) participate in the neuronal tissue destruction process. Inhibition of c-kit activity reduces cellular proliferation,

depleting the mast cells responsible for diseases and/or conditions, thereby suggesting a role for use of inhibitors of c-kit in the treatment of c-kit dependent diseases and/or conditions, such as CNS disorders.

[0072] Mast cells have also been identified to be involved in or to contribute to drug dependence and withdrawal symptoms. Drug dependence is the result of a phenomenon called tolerance, which is the need to increase the dose of the drug to maintain its full effect, and of physical dependence, which is the habituation of the body to a drug. When the intake of a drug is discontinued, individual may experience unpleasant withdrawal syndrome.

[0073] The activation of mast cells by different drugs, including, but not limited to, salicylic derivatives, morphine derivatives, opioids, heroin, amphetamines, alcohol, nicotine, analgesics, anesthetics, and anxyolitics results in the degranulation of mast cells, which participate in the exacerbation of the chemical imbalance responsible for drug habituation and withdrawal syndrome. Following mast cells activation, released granules liberate various factors capable of modulating and altering neurotransmission. Among such factors is morphine which is bound or stored in mast cells granules. Tobacco smoke also induces the release of mediators from canine mast cells and modulates prostaglandin production leading to asthma. In addition, patients afflicted with mastocytosis are more incline to develop substance use disorders than the normal population. This can be explained by the presence of activating mutations in the c-kit receptor, which induce degranulation of mast cells and a burst of factors contributing to chemical imbalance and neurotransmission alteration.

[0074] Presently, there is no available treatment that provides relief and help for individuals to withdraw from substance abuse disorders. C-kit inhibitors may be used for treating substance abuse disorders, particularly drug addiction, drug abuse, drug habituation, drug dependence, withdrawal syndrome and overdose, comprising administering a compound capable of depleting mast cells to a human in need of such treatment.

[0075] c-Kit has a substantial homology to the PDGF receptor and to the CSF-1 receptor (c-Fms). Investigations on various erythroid and myeloid cell lines indicate an expression of the c-Kit gene in early stages of differentiation (Andre et al., Oncogene 4 (1989), 1047-1049). Certain tumors such as glioblastoma cells likewise exhibit a pronounced expression of the c-Kit gene.

PDGF (Platelet-derived Growth Factor)

[0076] PDGF (Platelet-derived Growth Factor) plays an important role both in normal

growth and also in pathological cell proliferation. Compounds of the invention may inhibit PDGF receptor (PDGFR) activity, and may be used as an agent to treat non-malignant proliferative disorders, such as scleroderma and other fibrotic disorders, atherosclerosis, thrombosis or psoriasis. The compounds of the present invention may also be used as a tumor-inhibiting substance, for example in small cell lung cancer, gliomas, sarcomas, prostate tumors, and tumors of the colon, breast, and ovary.

[0077] In one embodiment, the compounds of the invention may be used for the treatment and prevention of a fibrotic disorder or disease, a condition linked to or associated with the formation and deposition of extracellular matrix components in the internal organs, including the kidneys, heart, lungs, liver, skin and joints. Various studies have implicated PDGFR as a central player in fibrotic responses to tissue injury, e.g.:

i) PDGF is upregulated in alveolar macrophages from patients with idiopathic pulmonary fibrosis (IPF);

ii) PDGFRβ is one of the first genes upregulated after activation of hepatic stellate cells to become myofibroblasts, a central step in development of fibrosis in the liver;

iii) PDGF and its receptors are significantly upregulated in scleroderma, and similarly upregulated in the process of renal fibrogenesis;

iv) PDGF is induced by injury and/or pro-inflammatory cytokines, or in an autocrine fashion on myofibroblasts driving their proliferation, differentiation, and migration. These myofibroblasts then secrete extracellular matrix proteins and collagen leading to scarring and progressive organ damage. TGFβ secretion also contributes significantly to the production of collagen during fibrogenesis;

v) A PDGF-C transgene induces the development of liver fibrosis in mice, while a soluble dominant-negative version of PDGFRβ prevents liver fibrosis in ratsl; and

vi) Administration of PDGF-B to the kidney promoted signs of renal fibrogenesis in rats.

[0078] Fibrotic disorders or diseases which may be treated using the compounds of the invention include fibrotic lung diseases such as pulmonary fibrosis (or interstitial lung disease or interstitial pulmonary fibrosis), idiopathic pulmonary fibrosis, primary pulmonary hypertension, idiopathic pulmonary arterial hypertension, the fibrotic element of pneumoconiosis (which is associated with exposure to environmental hazards such as smoking, asbestos, cotton lint, stone dust, mine dust and other particles), pulmonary sarcoidosis, fibrosing alveolitis, the fibrotic or

hypertrophic element of cystic fibrosis, chronic obstructive pulmonary disease, adult respiratory distress syndrome and emphysema. The compounds of the invention may also be used for the treatment and prevention of diseases that have as a manifestation fibrotic hypertrophy of the kidneys (renal fibrosis), liver (liver fibrosis), heart (cardiac fibrosis), prostate (e.g., benign prostatic hypertrophy (BPH)), pleura (e.g., pleurisy, pleural fibrosis), pancreas, and of the skin and/or muscle tissues such as scleroderma, eosinophilic fasciitis, discoid lesions associated with lupus or discoid lupus or surgical adhesions.

[0079] Other fibrotic disorders or diseases which may be treated using the compounds of the invention include but are not limited to systemic sclerosis, mixed connective tissue disease, fibrodysplasia, fibrocystic disease, sarcoidosis, myositis (e.g. polymyositis, primary idiopathic polymyositis, childhood polymyositis, dermatomyositis, childhood dermatomyositis, primary idiopathic dermatomyositis in adults, inclusion body myositis, polymyositis or dermatomyositis associated with malignant tumors); diseases that have as a manifestation fibrotic vascular intimal hypertrophy, such as vasculitis (including coronary artery vasculitis), polyarteritis nodosa or temporal arteritis; diseases that have as a manifestation fibrotic hypertrophy of nerve tissue such as cerebrosclerosis, annular sclerosis. diffuse sclerosis and lobar sclerosis; and diseases that have as a manifestation fibrotic hypertrophy or fibrosis of the bowel wall, such as inflammatory bowel disease, including Crohn's disease.

[0080] Furthermore, the compounds of the present invention may also be useful for the protection of stem cells, for example to combat the hemotoxic effect of chemotherapeutic agents, such as 5-fluorouracil; and may also be useful for the treatment of asthma and hypereosinophilia. Compounds of the invention may especially be used for the treatment of diseases which respond to an inhibition of the PDGF receptor kinase.

[0081] Compounds of the present invention may also exhibit useful effects in the treatment of disorders arising as a result of transplantation, for example, allogenic transplantation, especially tissue rejection, such as obliterative bronchiolitis (OB), i.e. a chronic rejection of allogenic lung transplants. In contrast to patients without OB, those with OB often show an elevated PDGF concentration in bronchoalveolar lavage fluids.

[0082] Compounds of the present invention may also be effective against diseases associated with vascular smooth-muscle cell migration and proliferation (where PDGF and PDGFR often also play a role), such as restenosis and atherosclerosis. These effects and the consequences thereof for the proliferation or migration of vascular smooth-muscle cells *in vitro* and *in vivo*

may be demonstrated by administration of the compounds of the present invention, and also by investigating its effect on the thickening of the vascular intima following mechanical injury *in vivo*.

CSF1R (FMS)

[0083] The protein encoded by this gene is the receptor for colony stimulating factor 1, a cytokine which controls the production, differentiation, and function of macrophages. CSFR1 mediates most if not all of the biological effects of this cytokine. The encoded protein is a tyrosine kinase transmembrane receptor and member of the CSF1/PDGF receptor family of tyrosine-protein kinases. Mutations in this gene have been associated with a predisposition to myeloid malignancy. (See e.g., Casas et al., Leuk. Lymphoma 2003 44:1935-41).

Abl, Trk, Syk, Ras, Raf, MAPK, TGFβ, FGFR3, c-Src, SAPK, Lck, Fes, Csk

[0084] Abelson tyrosine kinase (i.e. Abl, c-Abl) is involved in the regulation of the cell cycle, in the cellular response to genotoxic stress, and in the transmission of information about the cellular environment through integrin signaling. The Abl protein appears to serve a complex role as a cellular module that integrates signals from various extracellular and intracellular sources and that influences decisions in regard to cell cycle and apoptosis. Abelson tyrosine kinase includes sub-types derivatives such as the chimeric fusion (oncoprotein) BCR-Abl with deregulated tyrosine kinase activity or the v-Abl.

[0085] The fusion protein BCR-Abl is a result of a reciprocal translocation that fuses the Abl proto-oncogene with the Bcr gene. BCR-Abl is then capable of transforming B-cells through the increase of mitogenic activity. This increase results in a reduction of sensitivity to apoptosis, as well as altering the adhesion and homing of CML progenitor cells.

[0086] BCR-Abl is important in the pathogenesis of 95% of chronic myelogenous leukemia (CML) and 10% of acute lymphocytic leukemia. STI-571 (GLEEVEC®) is an inhibitor of the oncogenic BCR-Abl tyrosine kinase and is used for the treatment of chronic myeloid leukemia (CML). However, some patients in the blast crisis stage of CML are resistant to STI-571 due to mutations in the BCR-Abl kinase. Over 22 mutations have been reported to date, such as G250E, E255V, T315I, F317L and M351T.

[0087] Compounds of the present invention may inhibit abl kinase, for example, v-abl kinase. The compounds of the present invention may also inhibit wild-type BCR-Abl kinase and

mutations of BCR-Abl kinase, and thus may be suitable for the treatment of Bcr-abl-positive cancer and tumor diseases, such as leukemias (especially chronic myeloid leukemia and acute lymphoblastic leukemia, where especially apoptotic mechanisms of action are found). Compounds of the present invention may also be effective against leukemic stem cells, and may be potentially useful for the purification of these cells *in vitro* after removal of said cells (for example, bone marrow removal), and reimplantation of the cells once they have been cleared of cancer cells (for example, reimplantation of purified bone marrow cells).

[0088] The trk family of neurotrophin receptors (trkA, trkB, trkC) promotes the survival, growth and differentiation of the neuronal and non-neuronal tissues. The TrkB protein is expressed in neuroendocrine-type cells in the small intestine and colon, in the alpha cells of the pancreas, in the monocytes and macrophages of the lymph nodes and of the spleen, and in the granular layers of the epidermis (Shibayama and Koizumi, 1996). Expression of the TrkB protein has been associated with an unfavorable progression of Wilms tumors and of neuroblastomas. Moreover, TrkB is expressed in cancerous prostate cells but not in normal cells. The signaling pathway downstream of the trk receptors involves the cascade of MAPK activation through the Shc, activated Ras, ERK-1 and ERK-2 genes, and the PLC-gammal transduction pathway (Sugimoto et al., 2001).

[0089] Syk is a tyrosine kinase that plays an important role in mast cell degranulation and eosinophil activation. Accordingly, Syk kinase is implicated in various allergic disorders, particularly asthma. It has been shown that Syk binds to the phosphorylated gamma chain of the FcεR1 receptor via N-terminal SH2 domains and is important for downstream signaling.

[0090] The Ras-Raf-MEK-ERK signaling pathway mediates cellular response to growth signals. Ras is mutated to an oncogenic form in ~15% of human cancer. The Raf family belongs to the serine/threonine protein kinase and includes three members, A-Raf, B-Raf and c-Raf (or Raf-1). B-Raf may have a prominent role in the formation of certain tumors with no requirement for an activated Ras allele (*Nature* 417: 949 - 954 (2002)). B-Raf mutations have been detected in a large percentage of malignant melanomas.

[0091] Existing medical treatments for melanoma are limited in their effectiveness, especially for late stage melanomas. The compounds of the present invention also inhibit cellular processes involving b-Raf kinase, providing a new therapeutic opportunity for treatment of human cancers, especially for melanoma.

[0092] Mitogen-activated protein kinases (MAPKs) are members of conserved signal

transduction pathways that activate transcription factors, translation factors and other target molecules in response to a variety of extracellular signals. MAPKs are activated by phosphorylation at a dual phosphorylation motif having the sequence Thr-X-Tyr by mitogen-activated protein kinase kinases (MKKs). In higher eukaryotes, the physiological role of MAPK signaling has been correlated with cellular events such as proliferation, oncogenesis, development and differentiation. Accordingly, the ability to regulate signal transduction via these pathways (particularly via MKK4 and MKK6) could lead to the development of treatments and preventive therapies for human diseases associated with MAPK signaling, such as inflammatory diseases, autoimmune diseases and cancer.

[0093] Multiple forms of p38 MAPK (α, β, γ, δ), each encoded by a separate gene, form part of a kinase cascade involved in the response of cells to a variety of stimuli, including osmotic stress, UV light and cytokine mediated events. These four isoforms of p38 are thought to regulate different aspects of intracellular signaling. Its activation is part of a cascade of signaling events that lead to the synthesis and production of pro-inflammatory cytokines like TNFα. P38 functions by phosphorylating downstream substrates that include other kinases and transcription factors. Agents that inhibit p38 kinase have been shown to block the production of cytokines including but not limited to TNFα, IL-6, IL-8 and IL-1β.

[0094] Peripheral blood monocytes (PBMCs) have been shown to express and secrete pro-inflammatory cytokines when stimulated with lipopolysaccharide (LPS) in vitro. P38 inhibitors efficiently block this effect when PBMCs are pretreated with such compounds prior to stimulation with LPS. P38 inhibitors are efficacious in animal models of inflammatory disease. The destructive effects of many disease states are caused by the over production of pro-inflammatory cytokines. The ability of p38 inhibitors to regulate this overproduction makes them useful as disease modifying agents.

[0095] Molecules that block p38 function have been shown to be effective in inhibiting bone resorption, inflammation, and other immune and inflammation-based pathologies. Thus, a safe and effective p38 inhibitor would provide a means to treat debilitating diseases that can be regulated by modulation of p38 signaling. Therefore, compounds of the invention that inhibit p38 activity are useful for the treatment of inflammation, osteoarthritis, rheumatoid arthritis, cancer, autoimmune diseases, and for the treatment of other cytokine mediated diseases.

[0096] Transforming growth factor-beta (TGFβ) denotes a superfamily of proteins that

includes, for example, TGFβ1, TGFβ2, and TGFβ3, which are pleotropic modulators of cell growth and differentiation, embryonic and bone development, extracellular matrix formation, hematopoiesis, immune and inflammatory responses. The members of the TGFβ family initiate intracellular signaling pathways leading ultimately to the expression of genes that regulate the cell cycle, control proliferative responses, or relate to extracellular matrix proteins that mediate outside-in cell signaling, cell adhesion, migration and intercellular communication.

[0097] Consequently, compounds of the invention that are inhibitors of the TGFβ intracellular signaling pathway are useful therapeutics for fibroproliferative diseases, including kidney disorders associated with unregulated TGFβ activity and excessive fibrosis including glomerulonephritis (GN), such as mesangial proliferative GN, immune GN, and crescentic GN. Other renal conditions include diabetic nephropathy, renal interstitial fibrosis, renal fibrosis in transplant patients receiving cyclosporin, and HIV-associated nephropathy. Collagen vascular disorders include progressive systemic sclerosis, polymyositis, scleroderma, dermatomyositis, eosinophilic fascitis, morphea, or those associated with the occurrence of Raynaud's syndrome. Lung fibroses resulting from excessive TGFβ activity include adult respiratory distress syndrome, COPD, idiopathic pulmonary fibrosis, and interstitial pulmonary fibrosis often associated with autoimmune disorders, such as systemic lupus erythematosus and scleroderma, chemical contact, or allergies. Another autoimmune disorder associated with fibroproliferative characteristics is rheumatoid arthritis. Fibroproliferative conditions can be associated with surgical eye procedures. Such procedures include retinal reattachment surgery accompanying proliferative vitreoretinopathy, cataract extraction with intraocular lens implantation, and post glaucoma drainage surgery.

[0098] Fibroblast growth factor receptor 3 was shown to exert a negative regulatory effect on bone growth and an inhibition of chondrocyte proliferation. Thanatophoric dysplasia is caused by different mutations in fibroblast growth factor receptor 3. One mutation, TDII FGFR3, has a constitutive tyrosine kinase activity which activates the transcription factor Stat1, leading to expression of a cell-cycle inhibitor, growth arrest and abnormal bone development (Su et al., Nature, 1997, 386, 288-292). FGFR3 is also often expressed in multiple myeloma-type cancers.

[0099] The kinase, c-Src, transmits oncogenic signals of many receptors. For example, over-expression of EGFR or HER2/neu in tumors leads to the constitutive activation of c-src, which

is characteristic for the malignant cell but absent from the normal cell. On the other hand, mice deficient in the expression of c-src exhibit an osteopetrotic phenotype, indicating a key participation of c-src in osteoclast function and a possible involvement in related disorders.

[0100] The family of human ribosomal S6 protein kinases consists of at least 8 members (RSK1, RSK2, RSK3, RSK4, MSK1, MSK2, p70S6K and p70S6 Kb). Ribosomal protein S6 protein kinases play important pleotropic functions; among them is a key role in the regulation of mRNA translation during protein biosynthesis (Eur. J. Biochem 2000 November; 267(21): 6321-30, Exp Cell Res. Nov. 25, 1999; 253 (1):100-9, Mol Cell Endocrinol. May 25, 1999;151(1-2):65-77). The phosphorylation of the S6 ribosomal protein by p70S6 has also been implicated in the regulation of cell motility (Immunol. Cell Biol. 2000 August;78(4):447-51) and cell growth (Prog. Nucleic Acid Res. Mol. Biol., 2000;65:101-27), and hence, may be important in tumor metastasis, the immune response and tissue repair as well as other disease conditions.

[0101] The SAPK's (also called "jun N-terminal kinases" or "JNK's") are a family of protein kinases that represent the penultimate step in signal transduction pathways that result in activation of the c-jun transcription factor and expression of genes regulated by c-jun. In particular, c-jun is involved in the transcription of genes that encode proteins involved in the repair of DNA that is damaged due to genotoxic insults. Agents that inhibit SAPK activity in a cell prevent DNA repair and sensitize the cell to those cancer therapeutic modalities that act by inducing DNA damage.

[0102] Lck plays a role in T-cell signaling. Mice that lack the Lck gene have a poor ability to develop thymocytes. The function of Lck as a positive activator of T-cell signaling suggests that Lck inhibitors may be useful for treating autoimmune disease such as rheumatoid arthritis.

[0103] Fes is strongly expressed in myeloid hematopoietic cells and is implicated in both differentiation and survival signaling pathways in myeloid leukocytes. CSK is implicated in cancers, particularly colorectal and breast cancers.

[0104] In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (See, "Administration and Pharmaceutical Compositions," *infra*) of a compound of Formula (1), (2A), (2B) or (C), or a pharmaceutically acceptable salt thereof. For any of the

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

Administration and Pharmaceutical Compositions

[0105] A pharmaceutical composition, as used herein, refers to a mixture of a compound of the invention with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions containing a compound of the invention may be administered in therapeutically effective amounts as pharmaceutical compositions by any conventional form and route known in the art including, but not limited to: intravenous, oral, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, otic, nasal, and topical administration.

[0106] One may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot or sustained release formulation. Furthermore, one may administer pharmaceutical composition containing a compound of the invention in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. The liposomes will be targeted to and taken up selectively by the organ. In addition, pharmaceutical compositions containing a compound of the invention may be provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation.

[0107] For oral administration, a compound of the invention may be formulated readily by combining the active compounds with pharmaceutically acceptable carriers or excipients well known in the art. Such carriers enable the compounds described herein to be formulated as tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[0108] Pharmaceutical preparations for oral use may be obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium

carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0109] Dragee cores may be provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0110] Pharmaceutical preparations which may be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

[0111] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in conventional manner. Parental injections may involve bolus injection or continuous infusion. The pharmaceutical composition of a compound of the invention may be in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0112] The compounds of the invention may be administered topically and may be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0113] Formulations suitable for transdermal administration may employ transdermal delivery devices and transdermal delivery patches, and may be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. Still further, transdermal delivery of the compounds of the invention may be accomplished by means of iontophoretic patches and the like. Additionally, transdermal patches may provide controlled delivery of the compounds of the invention. The rate of absorption may be slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers may be used to increase absorption. An absorption enhancer or carrier may include absorbable pharmaceutically acceptable solvents to assist passage through the skin. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[0114] For administration by inhalation, the compounds of the invention may be in a form as an aerosol, a mist or a powder. Pharmaceutical compositions of the compounds of the invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges, such as, by way of example only, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0115] The compounds of the invention may also be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In

suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[0116] Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which may be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art. Pharmaceutical compositions comprising a compound of the invention may be manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0117] The pharmaceutical compositions will include at least one pharmaceutically acceptable carrier, diluent or excipient and a compound of Formula (1), (2A) or (2B) described herein as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. Additionally, the compounds described herein may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions may include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In addition, the pharmaceutical compositions may also contain other therapeutically valuable substances.

[0118] Methods for the preparation of compositions comprising the compounds described herein include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels,

suspensions and creams. The compositions may be in liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions may also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[0119] A summary of pharmaceutical compositions described herein may be found, for example, in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference in their entirety.

Methods of Administration and Treatment Methods

[0120] The compositions containing the compound(s) described herein may be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. It is considered well within the skill of the art for one to determine such therapeutically effective amounts by routine experimentation (including, but not limited to, a dose escalation clinical trial).

[0121] The compounds of the invention may be used in combination with a second therapeutic agent. For example, if one of the side effects experienced by a patient upon receiving one of the compounds herein is inflammation, the compounds of the invention may be administered with in combination with an anti-inflammatory agent. The therapeutic effectiveness of a compound described herein may also be enhanced by administration of an adjuvant. When the compounds of the invention are administered in conjunction with other therapies, dosages of the co-administered compounds will vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In addition, when co-administered with one or more biologically active agents, the compounds of the invention may be administered either simultaneously with the biologically active agent(s), or sequentially. The administration of a compound of the invention in combination with a second therapeutic agent may have an additive or synergistic effect.

[0122] In some examples, the compounds of the invention may be used in combination with an anti-fibrotic agent; e.g., an agent that interferes with or modulates the progression of a fibrotic disease such as scleroderma, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), primary pulmonary hypertension (PPH), primary pulmonary arterial hypertension (PPAH), idiopathic arterial hypertension (IPAH), liver fibrosis, renal fibrosis and cardiac fibrosis. Examples of anti-fibrotic agents which may be used in combination with a compound of the invention include but are not limited to pirfenidone (Nakazoto et al., Eur. J. Pharmacol. 446:177-185 (2002), tacrolimus (Nagano et al., Eur. Respir. J. 27: 460-469 (2006) or 5-chloro-2- {(1E)-3-[2-(4-methoxybenzoyl)-4-methyl-1H-pyrrol-1-yl]prop-1-en-1-yl}-*N*-(methylsulfonyl)benzamide (SMP-534) (Sugaru et al., Am. J. Nephrology 26:50-58 (2006)). The compounds of the invention may also be used in combination with an anti-inflammatory agent, including, but not limited to, corticosteroids and cromolyns, leukotriene antagonists, and IgE blockers such as omalizumab. In other examples, the compounds of the invention may be used in combination with a medication for treating asthma; e.g., bronchodilators such as β_2-agonists, xanthines (e.g.. methylxanthines) and anticholinerigcs; and an anti-inflammatory agent as described above.

[0123] The compounds of the invention may also be used in combination with a chemotherapeutic agent to treat a cell proliferative disorder, including but not limited to, lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor. Examples of chemotherapeutic agents which may be used in the compositions and methods of the invention include but are not limited to anthracyclines, alkylating agents (e.g., mitomycin C), alkyl sulfonates, aziridines, ethylenimines, methylmelamines, nitrogen mustards, nitrosoureas, antibiotics, antimetabolites, folic acid analogs (e.g., dihydrofolate reductase inhibitors such as methotrexate), purine analogs, pyrimidine analogs, enzymes, podophyllotoxins, platinum-containing agents, interferons, and interleukins. Particular examples of known chemotherapeutic agents which may be used in the compositions and methods of the invention include, but are not limited to, busulfan, improsulfan, piposulfan, benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, chlorambucil, chlornaphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine,

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

[0124] 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. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered, e.g. 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.

[0125] Toxicity and therapeutic efficacy of such therapeutic regimens may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. The data obtained from cell culture assays and animal studies may be used in formulating

a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

Processes for Making Compounds of the Invention

[0126] 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 can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

[0127] A compound of the invention may be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention may be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention may be prepared using salts of the starting materials or intermediates.

[0128] The free acid or free base forms of the compounds of the invention may be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example, a compound of the invention in an acid addition salt form may be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). 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.).

[0129] 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.

[0130] 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).

[0131] 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 can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[0132] Compounds of the present invention may be conveniently prepared or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0133] 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, solubility, reactivity, etc.) and may be readily separated by taking advantage of these dissimilarities. The diastereomers may be separated by chromatography, or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[0134] In summary, compounds having Formula (1), (2A) or (2B) may be made by a process which involves:

(a) general procedures as described in the Examples (*infra*); and

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

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

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

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

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

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

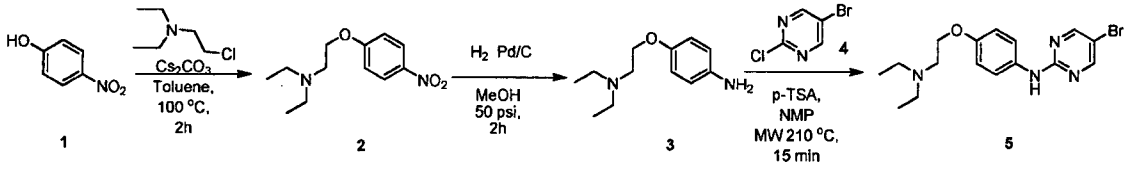
(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

[0135] Insofar as the production of the starting materials is not particularly described, the compounds are known or may 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.

[0136] The following examples are offered to illustrate but not to limit the invention.

Preparation of intermediates

Synthesis of (5-bromo-pyrimidin-2-yl)-[4-(2-diethylamino-ethoxy)-phenyl-amine **5**



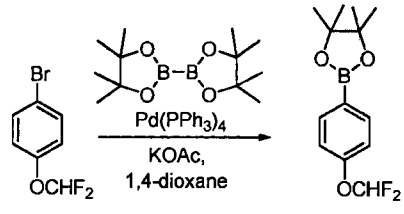
[0137] To a solution of 4-nitro-phenol **1** (36.0 mmol) in toluene (40 mL) is added cesium carbonate (53.8 mmol) and (2-chloro-ethyl)-diethyl-amine hydrochloride (28.7 mmol). The reaction mixture is heated at 100 °C for 2 h then cooled to rt. The solid is filtered under vacuum and washed with warm toluene. The filtrate is concentrated to afford diethyl-[2-(4-nitro-

phenoxy)-ethyl]-amine **2** and used in the next step without further purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 6.86-6.84 (m, 2H), 4.05 (t, J = 4.0 Hz, 2H), 2.81 (t, J = 4.0 Hz), 2.55 (q, J = 8.0 Hz, 4H), 0.98 (t, J = 8.0 Hz, 6H). MS (m/z) $(M+1)^+$: 239.3.

[0138] To a solution of diethyl-[2-(4-nitro-phenoxy)-ethyl]-amine **2** (14.0 mmol) in MeOH (20 mL), in a Parr pressure bottle, is added Pd (10% on carbon, 50% wet, 10% weight). The suspension is shaken at 50 psi of H_2 for 2 h. The reaction mixture is filtered through celite. The solvent is removed and the residue is dissolved in MeOH (20 mL) and treated with HCl (1 eq of a 4N solution in dioxane) to afford 4-(2-diethylamino-ethoxy)-phenylamine **3** as hydrochloride salt. ^{1}H NMR (400MHz, *d6*-DMSO) δ 6.98-6.91 (m, 4H), 4.30 (t, J = 4.0 Hz, 2H), 3.47 (t, J = 4.0 Hz), 3.20 (m, 4H), 1.24 (t, J = 8.0 Hz, 6H). MS (m/z) $(M+1)^+$: 209.3.

[0139] A dry flask charged with 4-(2-diethylamino-ethoxy)-phenylamine **3** (6.1 mmol), p-TSA (6.1 mmol), 5-bromo-2-chloropyrimidine **4** (6.1 mmol) in NMP (5 mL) is heated in a microwave oven at 210 °C for 15 min. The reaction mixture is diluted with water and extracted with EtOAc (5 x 70 mL). The organic layer is washed with water, brine, dried over Na_2SO_4, and concentrated. Purification by silica chromatography (DCM : MeOH : NH_4OH = 95 : 5 : 0.1) affords 5-bromo-pyrimidin-2-yl)-[4-(2-diethylamino-ethoxy)-phenyl-amine **5**. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.37 (s, 2H), 7.43-7.40 (m, 2H), 7.02 (s, 1H), 6.91-6.89 (m, 2H), 4.06 (t, J = 4.0 Hz, 2H), 2.90 (t, J = 4.0 Hz, 2H), 2.67 (q, J = 8.0 Hz, 4H), 1.09 (t, J = 8.0 Hz, 6H). MS (m/z) $(M+1)^+$: 366.1.

Synthesis of 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7**

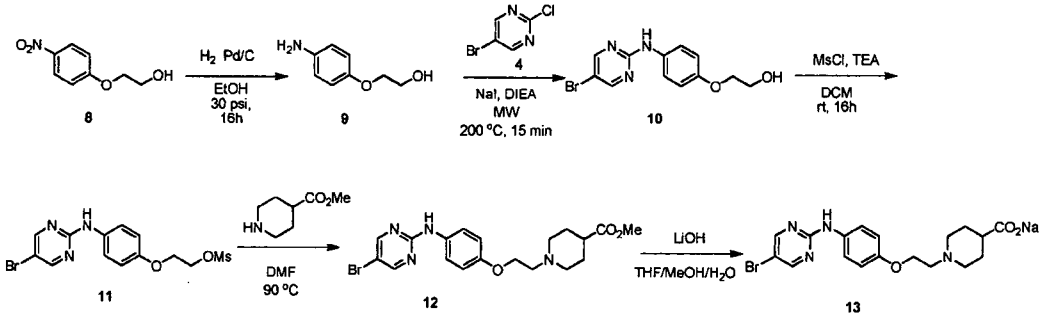


6 **7**

[0140] Bromo-4-(difluoromethoxy)benzene **6** (2.23 g, 10 mmol), potassium acetate (30.0 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (11.0 mmol) and $Pd(PPh_3)_4$ (0.5 mmol) are added to a 40-mL Schlenk flask equipped with a stir bar. The flask is evacuated and backfilled with nitrogen several times. 1,4-Dioxane (10 mL) is added by syringe. The Schlenk flask is sealed and heated at 150 °C for 20 min in a microwave oven. After the reaction is complete, the solvent is removed under vacuum. The residue is

dissolved in DCM (200 mL) and washed with water. The organic phase is dried with anhydrous Na_2SO_4, filtered and concentrated to yield a crude product. Purification by silica gel column chromatography (EtOAc : hexanes, gradient from 0% to 20%) affords 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7**. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.48 (t, J = 73.6 Hz, 1H), 1.27 (s, 12H). MS (m/z) $(M+1)^+$: 271.1.

Synthesis of sodium 1-(2-(4-(5-bromopyrimidin-2-ylamino)phenoxy)ethyl)piperidine-4-carboxylate **13**



[0141] 2-(4-Nitrophenoxy)ethanol **8** (109 mmol) and Pd/C (10% wt.) are suspended in EtOH (50 mL) and allowed to absorb 30 psi of hydrogen in a Parr shaker. The mixture is shaken at rt for 16 h. After filtration and concentration, 2-(4-aminophenoxy)ethanol **9** is obtained as a light pink colored solid and used in the next step without purification. MS (m/z) $(M+1)^+$: 154.1.

[0142] A mixture of 2-(4-aminophenoxy)ethanol **9** (70 mmol), 5-bromo-2-chloropyrimidine **4** (70 mmol), sodium iodide (70 mmol), and diisopropylethylamine (140 mmol) is heated at 200 °C for 15 min in a microwave oven. The reaction mixture is poured into water (300 mL). After filtration, the solid is washed with a mixture of H_2O : MeOH = 1:1 (100 mL) and dried under vacuum for 12 h to give the product **10** as a tannish solid which is used in the next step without purification. MS (m/z) $(M+1)^+$: 310.2, 312.2.

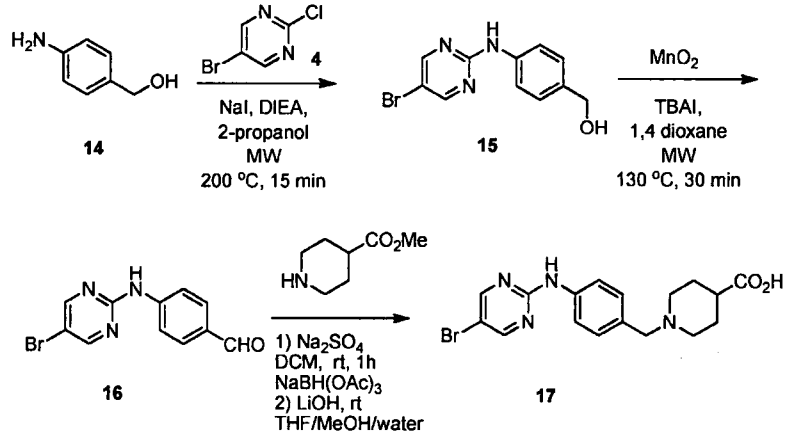
[0143] 2-(4-(5-Bromopyrimidin-2-ylamino)phenoxy)ethanol **10** (26.6 mmol) is dissolved in DCM (50 mL) followed by addition of MsCl (32 mmol). The reaction vessel is chilled in an ice-water bath and triethylamine (53.3 mmol) is added slowly. The mixture is stirred at rt for 16 h. The solvent is removed and the residue is triturated with water (300 mL). The solid is filtered and dried under vacuum for 12 h to give 2-(4-(5-Bromopyrimidin-2-ylamino)phenoxy)ethyl methanesulfonate **11** as off-white solid. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.71 (s, 1H), 8.54 (s,

2H), 7.59 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H), 4.52 (m, 2H), 4.22 (m, 2H), 3.24 (s, 3H). MS (m/z) $(M+1)^+$: 388.0, 340.0.

[0144] 2-(4-(5-Bromopyrimidin-2-ylamino)phenoxy)ethyl methanesulfonate **11** (1.55 mmol) and methyl isonipecotate (3.10 mmol) are dissolved in DMF (5 mL) and stirred at 90 °C for 12 h. After the reaction is completed, 2M Na_2CO_3 (20 mL) is added and the resulting mixture is extracted with EtOAc (50 mL). The organic layer is separated and concentrated to give crude methyl 1-(2-(4-(5-bromopyrimidin-2-ylamino)phenoxy)ethyl)piperidine-4-carboxylate **12**. MS (m/z) $(M+1)^+$: 435.1, 437.1.

[0145] The crude **12** is suspended in a THF /MeOH/H_2O solution (3:2:1, 10 mL) with 6N aq. LiOH (9.3 mmol) and stirred at rt for 2 h. The solvent is removed under vacuum to give an aqueous solution. To the above aqueous solution, 1N NaOH (2.0 mL) is added and the precipitate is filtered and dried to yield sodium 1-(2-(4-(5-bromopyrimidin-2-ylamino)phenoxy)ethyl)piperidine-4-carboxylate **13**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.67 (s, 1H), 8.52 (s, 2H), 7.54 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.01 (t, J = 6.0 Hz, 2H), 2.83 (m, 2H), 2.61 (m, 2H), 1.98 (m, 2H), 1.60-1.81 (m, 3H), 1.42-1.58 (m, 2H). MS (m/z) $(M+1)^+$: 421.1, 423.1.

Synthesis of 1-(4-(5-bromopyrimidin-2-ylamino)benzyl)piperidine-4-carboxylic acid **17**



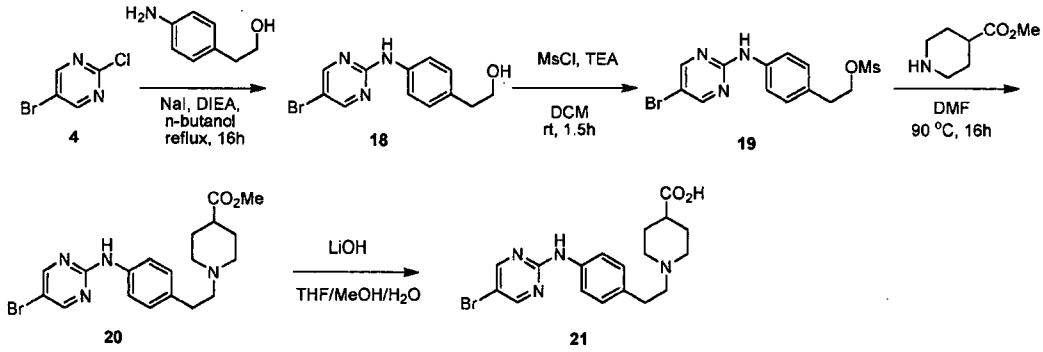
[0146] To a solution of 4-aminobenzyl alcohol **14** (8.12 mmol) and 5-bromo-2-chloro-pyrimidine **4** (9.74 mmol) in 2-propanol (20 mL) is added sodium iodide (8.12 mmol) and diisopropylethylamine (16.2 mmol). The reaction mixture is heated in the microwave oven at 200 °C for 15 min. Purification by silica gel chromatography with hexane : EtOAc = 7 : 3

affords [4-(5-bromo-pyrimidin-2-ylamino)-phenyl]-methanol **15**. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.36 (s, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H) 7.07 (bs, 1H), 4.60 (s, 2H). MS (m/z) $(M+1)^+$: 280.3, 282.3.

[0147] To a solution of [4-(5-bromo-pyrimidin-2-ylamino)-phenyl]-methanol **15** (0.94 mmol) in dioxane (2 mL) is added manganese (IV) oxide (4.7 mmol) and TBAI (0.06 mmol). The reaction mixture is heated in a microwave oven at 130 °C for 30 min. Purification by silica gel chromatography using hexane : EtOAc = 1 : 1 affords 4-[5-(4-methoxy-phenyl)-pyrimidin-2-ylamino]-benzaldehyde **16**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 10.45 (s, 1H), 9.85 (s, 1H), 8.72 (s, 2H), 7.96 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H). MS (m/z) $(M+1)^+$: 278.0, 280.0.

[0148] A mixture of 4-(5-bromopyrimidin-2-ylamino)benzaldehyde **16** (5.0 mmol), isonipecotic acid methyl ester (10 mmol) and Na_2SO_4 (excess) in DCM : MeOH : DMSO (4 : 1 : 0.2 v/v, 26 mL) is stirred at rt for 1 h. Then $NaBH(OAc)_3$ (15.0 mmol) is added and stirred for 12 h. The reaction mixture is quenched with 1 N HCl (1 ml). After filtration, all solvents are removed under vacuum. To the residue is added 6 N LiOH (2.5 mL) and THF : MeOH : water (3 : 2 : 1, 6 mL). The mixture is stirred for 1 h and quenched by 12 N HCl (5 mL). After concentration, EtOH : MeCN (1 : 1 v/v, 100 mL) is added. Inorganic solid is filtered off. The yellow filtrate is concentrated and filtered to give the HCl salt of 1-(4-(5-bromopyrimidin-2-ylamino)benzyl)piperidine-4-carboxylic acid **17** as a yellow solid precipitate. ^{1}H NMR (400MHz, *d6*-DMSO) δ 10.07 (s, 1H), 8.63 (s, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 4.17 (s, 2H), 3.10-3.40 (m, 2H), 2.89 (m, 2H), 1.67-2.06 (m, 5H). MS (m/z) $(M+1)^+$: 391.1, 393.1.

Synthesis of 1-(4-(5-bromopyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylic acid **21**



[0149] A mixture of 2-(4-aminophenyl)ethanol (0.72 mol), 5-bromo-2-chloropyrimidine **4**

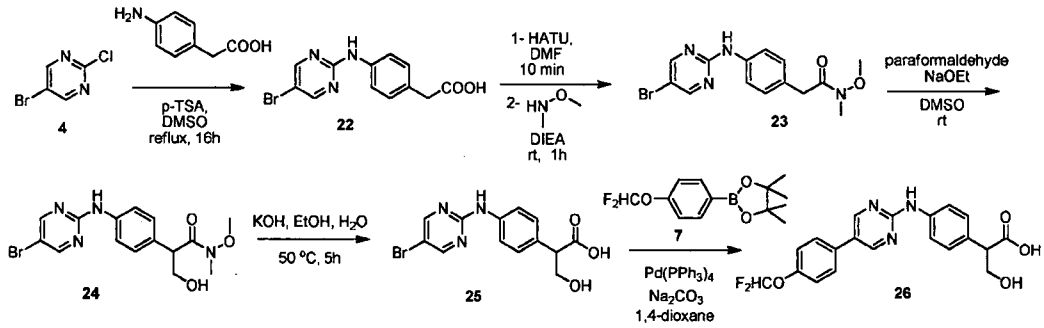
(0.72 mol), sodium iodide (0.72 mol), and diisopropylethylamine (1.45 mol) in *n*-butanol (400 mL) is heated at reflux for 16 h. The reaction is cooled to rt and the mixture is diluted with water. The light yellow solid that precipitates is filtered to give 2-(4-(5-bromopyrimidin-2-ylamino)phenyl)ethanol **18**. ^{1}H NMR (300MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.52 (s, 2H), 7.55 (m, 2H), 7.09 (d, 2H), 4.64 (m, 1H), 3.52 (m, 2H), 2.65 (m, 2H). MS (m/z) $(M+1)^+$: 294.1, 296.1.

[0150] To a solution of 2-(4-(5-bromopyrimidin-2-ylamino)phenyl)ethanol **18** (6.22 mmol) in DCM (30 mL) is added triethylamine (9.33 mmol) and methanesulfonyl chloride (7.47 mmol). The reaction mixture is stirred at rt for 1.5 h. The reaction is diluted with H_2O (10 mL) and washed with Na_2CO_3 solution (3 x 10 mL). The organic layer is washed with brine, dried over $MgSO_4$ and concentrated to afford 4-(5-bromopyrimidin-2-ylamino)phenethyl methanesulfonate **19**. ^{1}H NMR (400MHz, CD_2Cl_2) δ 8.36 (s, 2H), 7.65 (bs, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 4.31 (t, J = 6.8 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H), 2.79 (s, 3H). MS (m/z) $(M+1)^+$: 372.0, 374.0.

[0151] The reaction mixture of 4-(5-bromopyrimidin-2-ylamino)phenethyl methanesulfonate **19** (1.55 mmol) and methyl isonipecotate (3.10 mmol) in DMF (5 mL) is stirred at 90 °C for 12 h. After the reaction is complete, Na_2CO_3 (2.0 M, 20 mL) is added and the resulting mixture is extracted with EtOAc (50 mL). The organic layer is separated and concentrated to give crude methyl 1-(4-(5-bromopyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylate **20**. MS (m/z) $(M+1)^+$:419.1.

[0152] Crude methyl 1-(4-(5-bromopyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylate **20** is suspended in THF/MeOH/H_2O (3 : 2 : 1, 10 mL) and 6N LiOH (9.3 mmol) and stirred at rt for 2 h. After neutralization to pH 6 by addition of HCl (1N), the solvent is removed under vacuum to give a solid which is dissolved in THF (20 mL). To the above suspension, excess Na_2SO_4 is added and filtered. The filtrate is concentrated to yield 1-(4-(5-bromopyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylic acid **21**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.87 (s, 1H), 9.39 (bs, 1H), 8.59 (s, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 3.58-3.64 (m, 2H), 3.48-3.28 (m, 1H), 3.22-3.27 (m, 2H), 2.88-3.03 (m, 4H), 2.05-2.15 (m, 2H), 1.66-1.80 (m, 2H). MS (m/z) $(M+1)^+$: 405.1, 407.1.

Synthesis of 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxypropanoic acid **26**



[0153] 2-(4-Aminophenyl)acetic acid (4.56 mmol), 5-bromo-2-chloropyrimidine **4** (3.26 mmol), and p-TSA (0.842 mmol) are heated at reflux in 1,4-dioxane (10 mL) and DMSO (2 mL) for 16 h. The mixture is poured onto water and extracted with EtOAc. Concentration of the organic phase gives 2-(4-(5-Bromopyrimidin-2-ylamino)phenyl)acetic acid **22** as a yellow solid. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.84 (s, 1H), 8.58 (s, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.50 (s, 2H). MS (m/z) $(M+1)^+$: 308.0, 310.0.

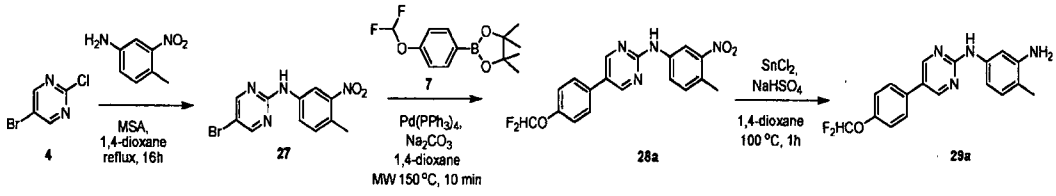
[0154] 2-(4-(5-Bromopyrimidin-2-ylamino)phenyl)acetic acid **22** (5.0 mmol) and HATU (6.0 mmol) are dissolved in dry DMF (10 mL) and stirred for 10 min. Then N,O-dimethylhydroxylamine (7.5 mmol) and diisopropylethylamine (15.0 mmol) are added to the solution. The reaction mixture is stirred for 1 h at rt. After the reaction is complete, the reaction mixture is added dropwise into water (100 mL). The precipitate is filtered and dried to yield 2-(4-(5-bromopyrimidin-2-ylamino)phenyl)-N-methoxy-N-methylacetamide **23**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.82 (s, 1H), 8.58 (s, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 3.67 (s, 3H), 3.34 (s, 2H), 3.10 (s, 3H). MS (m/z) $(M+1)^+$: 351.0, 353.0.

[0155] 2-(4-(5-Bromopyrimidin-2-ylamino)phenyl)-N-methoxy-N-methylacetamide **23** (2.0 mmol), paraformaldehyde (6.0 mmol) and sodium ethoxide (12.0 mmol) are dissolved in DMSO (10 mL). The reaction mixture is stirred at rt for 1 h. Then a solution of KOH (12.0 mmol) in H_2O (5.0 mL) and EtOH (5.0 mL) is added. The reaction mixture is heated at 50 °C for 5 h. After the reaction is completed, the reaction mixture is washed with DCM (50 mL). The aqueous phase is acidified to pH ~ 5 and extracted with DCM (2 x 50 mL). The organic layer is separated, dried and concentrated to yield 2-(4-(5-bromopyrimidin-2-ylamino)phenyl)-3-hydroxypropanoic acid **25**, which is used in the next step without further purification. ^{1}H NMR (400MHz, *d6*-DMSO) δ 12.30 (bs, 1H), 9.84 (s, 1H), 8.57 (s, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.21

(d, J = 8.4 Hz, 2H), 3.90 (t, J = 8.8 Hz, 1H), 3.49-3.61 (m, 2H), 3.35 (bs, 1H). MS (m/z) $(M+1)^+$: 338.0, 340.0.

[0156] To a solution of 2-(4-(5-bromopyrimidin-2-ylamino)phenyl)-3-hydroxypropanoic acid **25** (0.5 mmol) in 1,4-dioxane (2 mL) is added 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (0.5 mmol), Na_2CO_3 (1.5 mmol of a 3.0 M aq. solution) and $Pd(PPh_3)_4$ (0.025 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 150 °C for 10 min. The reaction mixture is diluted with water (10 mL). The aqueous layer is washed with DCM (2 x 50 mL) and acidified to pH 5 using aqueous HCl (1 N). The resulting mixture is extracted with DCM (2 x 50 mL). The organic layer is separated, dried over Na_2SO_4 and concentrated to yield a crude 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxypropanoic acid **26** which is used without further purification. ^1H NMR (400MHz, *d6*-DMSO) δ 9.65 (s, 1H), 8.79 (s, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.60-3.70 (m, 2H), 3.50-3.58 (m, 2H), 3.20-3.26 (m, 2H). MS (m/z) $(M+1)^+$: 402.1.

Synthesis of -(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-yl)-4-methylbenzene-1,3-diamine **29a**



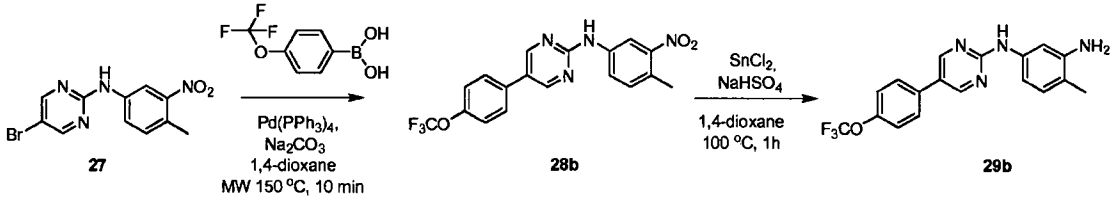
[0157] 5-Bromo-2-chloropyrimidine **4** (50 mmol), 4-methyl-3-nitroaniline (60 mmol) and methylsulphonic acid (15 mmol) are heated at reflux in 1,4-dioxane (100 mL) for 16 h. The mixture is poured into water, filtered and dried under vacuum to give 5-bromo-N-(4-methyl-3-nitrophenyl)pyrimidin-2-amine **27** as a yellow solid. ^1H NMR (400MHz, *d6*-DMSO) δ 10.25 (s, 1H), 8.68 (s, 2H), 8.49 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 2.4, 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 2.46 (s, 3H). MS (m/z) $(M+1)^+$: 309.0, 311.0.

[0158] To a solution of 5-bromo-N-(4-methyl-3-nitrophenyl)pyrimidin-2-amine **27** (0.5 mmol) in 1,4-dioxane (2.0 mL) is added 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (0.5 mmol), Na_2CO_3 (1.5 mmol of a 3.0 M aq. solution) and $Pd(PPh_3)_4$ (0.025 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated in the microwave oven at 150 °C for 10 min. The reaction mixture is diluted with water (10 mL) and

extracted with DCM (2 x 50 mL). The organic layer is separated, dried over Na_2SO_4 and concentrated. Purification by preparative HPLC (ACN gradient 10-70%) affords 4-(difluoromethoxy)phenyl)-N-(4-methyl-3-nitrophenyl)pyrimidin-2-amine **28a**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 10.23 (s, 1H), 8.92 (s, 2H), 8.66 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 2.4, 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 74.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 2.47 (s, 3H). MS (m/z) $(M+1)^+$: 373.1.

[0159] A suspension of 5-(4-(difluoromethoxy)phenyl)-N-(4-methyl-3-nitrophenyl)pyrimidin-2-amine **28a** (1.5 mmol) and $SnCl_2 \cdot 2H_2O$ (4.5 mmol) in 1N $NaHSO_4$ (50 mL) and 1,4-dioxane (50 mL) is heated at 100 °C for 1 h. The solvent is removed under vacuum and the residue dissolved in 5% NaOH and extracted with DCM (3 x 50 mL). The organic layer is washed with 5% NaOH (1 x 50 mL), water (1x 50 mL), brine, dried over Na_2SO_4 and concentrated to afford N1-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-yl)-4-methylbenzene-1,3-diamine **29a** which is used without further purification. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.44 (s, 1H), 8.76 (s, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.30 (t, J = 74.4 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 6.90 (dd, J = 2.0, 8.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 4.95 (bs, 2H), 2.02 (s, 3H). MS (m/z) $(M+1)^+$: 343.1.

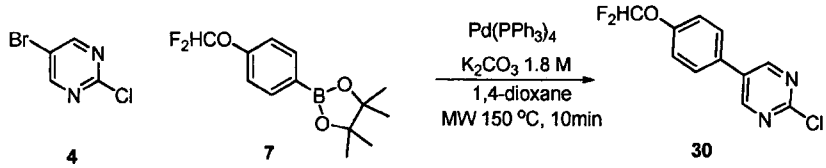
Synthesis of 4-methyl-N1-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)benzene-1,3-diamine **29b**



[0160] To a solution of 5-bromo-N-(4-methyl-3-nitrophenyl)pyrimidin-2-amine **27** (9.7 mmol) in 1,4-dioxane (29 mL) is added 4-(trifluoromethoxy)phenylboronic acid (10.7 mmol), Na_2CO_3 (29.2 mmol of 1.8 M aq. solution) and $Pd(PPh_3)_4$ (1.46 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 100 °C for 12 h. The reaction mixture is diluted with water (20 mL) and extracted with EtOAc (2 x 50 mL). The organic layer is separated, dried over Na_2SO_4 and concentrated. Purification by preparative HPLC (ACN gradient 10-70%) affords N-(4-methyl-3-nitrophenyl)-5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-amine **28b**. MS (m/z) $(M+1)^+$: 390.1.

[0161] N-(4-methyl-3-nitrophenyl)-5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-amine **28b** (7.53 mmol) and $SnCl_2 \cdot 2H_2O$ (33.2 mmol) are suspended in 6N HCl (40 mL). The mixture is heated at 100 °C for 3 h. The reaction vessel is chilled in an ice-water bath and 5% NaOH is added. The organic layer is extracted with EtOAc (3 x 50 mL), washed with brine (1 x 50 mL), dried over Na_2SO_4 and concentrated to afford 4-methyl-N1-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)benzene-1,3-diamine **29b** which is used without further purification. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.54 (s, 1H), 8.84 (s, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 2.4 Hz, 1H), 6.94 (dd, J = 2.0 and 8.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.83 (bs, 2H), 2.07 (s, 3H). MS (m/z) $(M+1)^+$: 361.1.

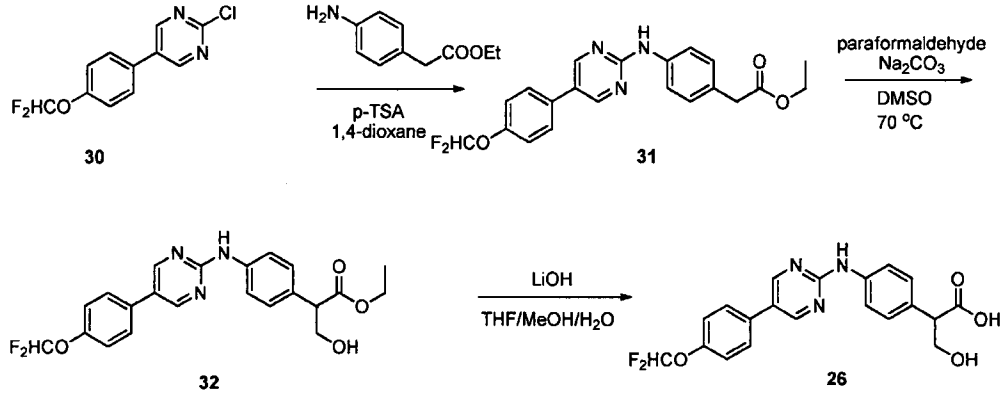
Synthesis of 2-chloro-5-(4-(difluoromethoxy)phenyl)pyrimidine **30**



4 7 30

[0162] To a solution of 5-bromo-2-chloropyrimidine **4** (7.7 mmol) in 1,4-dioxane (1.5 mL) is added 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (8.9 mmol), 1.8M K_2CO_3 aq. (16.2 mmol) and $Pd(PPh_3)_4$ (0.38 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 150 °C for 10 min under microwave. After this time, the reaction mixture is diluted with a saturated solution of NH_4Cl and extracted with DCM (3 x 50 mL). The organic layer is washed with brine, dried over Na_2SO_4 and concentrated. Purification by short silica gel chromatography using a hexane : EtOAc = 3 : 1 mixture affords 2-chloro-5-(4-(difluoromethoxy)phenyl)pyrimidine **30**. ^{1}HNMR (400MHz, $CDCl_3$) δ 8.73 (s, 2H), 7.47-7.52 (m, 2H), 7.20-7.24 (m, 2H), 6.52 (t, J = 72 Hz, 1H). MS (m/z) $(M+1)^+$: 257.0.

Synthesis of 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxypropanoic acid **26**



[0163] A mixture of ethyl 2-(4-aminophenyl)acetate (8 mmol), 2-chloro-5-(4-(difluoromethoxy)phenyl)pyrimidine **30** (4 mmol), and p-TSA (2 mmol) in 1,4-dioxane (4 mL) are heated at reflux for 4 h. The mixture is poured onto 1 N HCl. The solid is filtered, washed with 1 N HCl and dried to afford ethyl 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)acetate **31** as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.57 (s, 2H), 7.92 (s, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 9.1 Hz, 2H), 6.49 (t, J = 73.5 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.54 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H). MS (m/z) $(M+1)^+$: 400.1.

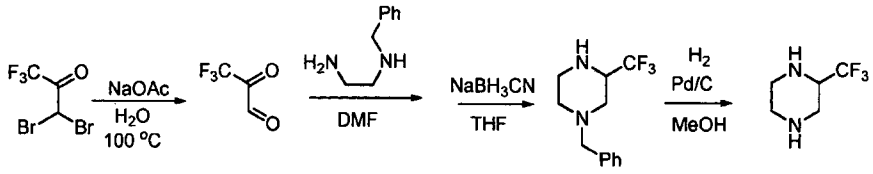
[0164] Ethyl 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)acetate **31** (1 mmol) and paraformaldehyde (5 mmol.) are dissolved in dry DMSO (0.2-0.5M) and heated at 70 °C in the presence of Na_2CO_3 (5 mmol.) for 2-6 h until greater than 50% conversion is achieved by LC/MS monitoring. The mixture is diluted with EtOAc and washed with water. After concentration, the residue is purified by silica gel chromatography to yield ethyl 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxypropanoate **32**. MS (m/z) $(M+1)^+$: 432.1.

[0165] To a solution of ethyl 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxypropanoate **32** (1 mmol) in THF : MeOH : water (3 : 2 : 1 v/v) is added 6 N LiOH (3 mmol). The reaction mixture is stirred at rt for 1 h until complete by LC/MS and diluted with water. The aqueous layer is washed with DCM (2 x 30 mL) and acidified to pH = 5 using aqueous 1N HCl. The resulting mixture is extracted with DCM (3 x 50 mL). The organic layer is separated, dried over Na_2SO_4 and concentrated to yield a crude product, which upon crystallization from water yield 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-

ylamino)phenyl)-3-hydroxypropanoic acid, **26** as off white solid. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.65 (s, 1H), 8.79 (s, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.60-3.70 (m, 2H), 3.50-3.58 (m, 2H), 3.20-3.26 (m, 2H). MS (m/z) $(M+1)^+$: 402.1.

[0166] Chiral HPLC separation using a (R,R)-WelkO-1 column and hexane : ethanol : methanol = 75 : 12.5 : 12.5 0.1% diethylamine as gradient affords the two enantiomers **26a** (first peak eluted) and **26b** (second peak eluted). The enantiomer **26a** is arbitrarily assigned the R configuration whereas enantiomer **26b** is arbitrarily assigned the S configuartion.

Synthesis of 2-(trifluoromethyl)piperazine **35a**



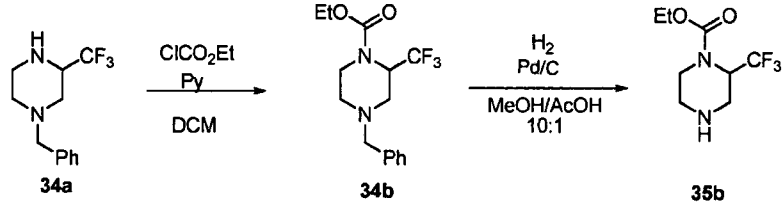
32 **33** **34a** **35a**

[0167] A mixture of 3,3-dibromo-1,1,1-trifluoropropan-2-one **32** (38.4 mmol) and NaOAc (153.7 mmol) in H_2O (50 mL) is heated at 100 °C for 12 h. Extraction of aqueous mixture with EtOAc (2 x 50 mL) and concentration of organic phase affords a crude oil. To the above residue is added DMF (30 mL), and the solution is cooled to 0 °C. Then a solution of N1-benzylethane-1,2-diamine (2.3 mL) in DMF (15 mL) is added. The resulting reaction mixture is stirred at rt for 12 h. Solvent is removed under vacuum to afford a residue which is dissolved in THF (15 mL) and citrate buffer (30 mL), followed by addition of 1M $NaBH_3CN$ (25 mL). The mixture is stirred at rt for 12 h. The organic solvent is removed under vacuum and the resulting residue is basified to pH = 8 by addition of 1N NaOH. Extraction of aqueous solution with DCM (2 x 50 mL) and concentration of the organic phase yield a crude oil which is purified by silica gel chromatography using a hexane : EtOAc = 3 : 1 to afford 1-benzyl-3-(trifluoromethyl)piperazine **34a**. ^{1}H NMR (400MHz, *d*2-DCM) δ 7.37-7.25 (m, 5H), 3.57(d, 2H), 3.35-3.45 (m, 1H), 3.05-3.10 (m, 1H), 2.87-3.00 (m, 2H), 2.74-2.80 (m, 1H), 2.10-2.18 (m, 2H), 1.74 (s, 1H). MS (m/z) $(M+1)^+$: 245.1.

[0168] 1-Benzyl-3-(trifluoromethyl)piperazine **34a** (4.1 mmol) is dissolved in MeOH (50 mL) followed by addition of AcOH (2.0 mL) and 5% mol of Pd/C. The flask is charged with a hydrogen balloon and stirred for 12 h. The mixture is filtered over celite and the filtrate is

concentrated to afford 2-(trifluoromethyl)piperazine **35a**, which is used without further purification. MS (m/z) $(M+1)^+$: 155.1.

Synthesis of Ethyl 2-(trifluoromethyl)piperazine-1-carboxylate **35b**

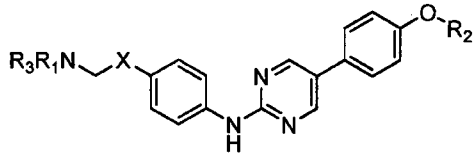


[0169] To a solution of 1-benzyl-3-(trifluoromethyl)piperazine **34a** (1.0 mmol) and pyridine (1.1 mmol) in DCM (5 mL), is added ethyl chloroformate (1.1 mmol). The resulting mixture is stirred at rt for 1 h. After the reaction is complete, the reaction mixture is diluted with DCM (15 mL) and washed with water. The organic layer is separated, dried over Na_2SO_4, filtered, and concentrated to afford ethyl 4-benzyl-2-(trifluoromethyl)piperazine-1-carboxylate **34b**, which is used without purification. MS (m/z) $(M+1)^+$: 317.1.

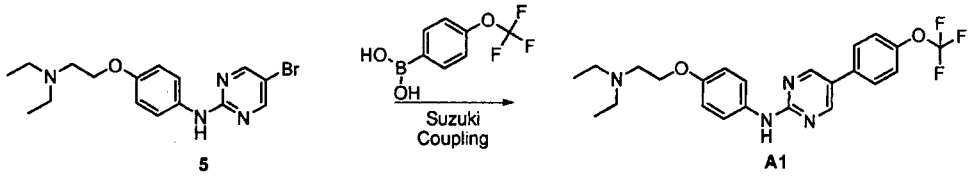
[0170] Ethyl 4-benzyl-2-(trifluoromethyl)piperazine-1-carboxylate **34b** (1.0 mmol) is dissolved in MeOH (10 mL) followed by addition of AcOH (1.0 mL) and 5% mol of Pd/C. The flask is charged with a hydrogen balloon and stirred for 12 h. The mixture is filtered over celite and the filtrate is concentrated to afford 2-(trifluoromethyl)piperazine 1-carboxylate **35b**, which is used without further purification. MS (m/z) $(M+1)^+$: 227.1.

Preparation of final compounds

Type A compounds

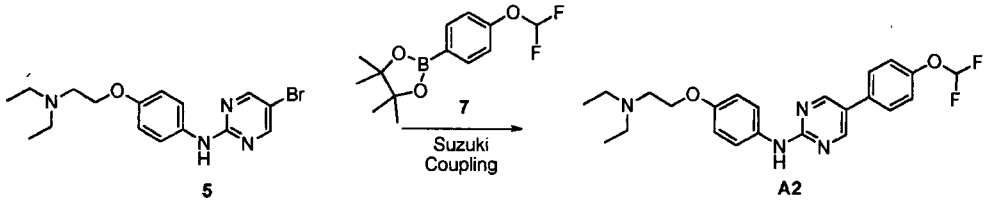


Example **A1**: N-(4-(2-(diethylamino)ethoxy)phenyl)-5-(4-(trifluoromethoxy)phenyl) pyrimidin-2-amine



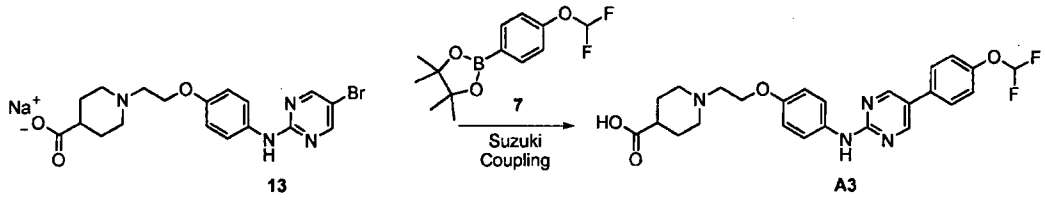
[0171] To a solution of (5-bromo-pyrimidin-2-yl)-[4-(2-diethylamino-ethoxy)-phenyl-amine **5** (0.5 mmol) in 1,4-dioxane (2.0 mL) is added 4-(trifluoromethoxy)phenylboronic acid (0.5 mmol), 3M Na_2CO_3 (1.5 mmol) and $Pd(PPh_3)_4$ (0.025 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 150 °C for 10 min. Purification by preparative HPLC (ACN gradient 10-70%) affords N-(4-(2-(diethylamino)ethoxy)phenyl)-5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-amine **A1**. MS (m/z) $(M+1)^+$: 447.2.

Example **A2**: N-(4-(2-(diethylamino)ethoxy)phenyl)-5-(4-(difluoromethoxy)phenyl) pyrimidin-2-amine



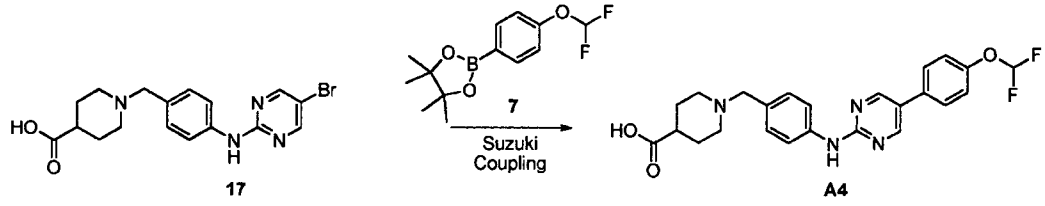
[0172] To a solution of (5-bromo-pyrimidin-2-yl)-[4-(2-diethylamino-ethoxy)-phenyl-amine **5** (0.5 mmol) in 1,4-dioxane (2.0 mL) is added 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (0.5 mmol), 3M Na_2CO_3 (1.5 mmo) and $Pd(PPh_3)_4$ (0.025 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 150 °C for 10 min. Purification by preparative HPLC (ACN gradient 10-70%) affords N-(4-(2-(diethylamino)ethoxy)phenyl)-5-(4-(difluoromethoxy)phenyl)pyrimidin-2-amine **A2**. ^1H NMR (400MHz, *d6*-DMSO) δ 9.68 (s, 1H), 8.78 (s, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 9.2 Hz, 2H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 1H), 4.28 (t, J = 4.8 Hz, 2H), 3.51 (m, 2H), 3.23 (m, 4H), 1.24 (t, J = 7.2, 6H). MS (m/z) $(M+1)^+$: 429.2.

Example A3: 1-(2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy) ethyl)piperidine-4-carboxylic acid



[0173] To a solution of sodium 1-(2-(4-(5-bromopyrimidin-2-ylamino)phenoxy)ethyl)piperidine-4-carboxylate **13** (0.05 mmol) in 1,4-dioxane (1.0 mL) is added 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (0.05 mmol), 3M Na_2CO_3 (0.15 mmol) and $Pd(PPh_3)_4$ (0.0025 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 150 °C for 10 min. Purification by prep-HPLC (ACN gradient 10-70%) affords 1-(2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy)ethyl)piperidine-4-carboxylic acid **A3**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.68 (s, 1H), 8.78 (s, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 9.2 Hz, 2H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 1H), 4.28 (t, J = 4.8 Hz, 2H), 3.51 (m, 2H), 3.23 (m, 4H), 1.24 (t, J = 7.2, 6H). MS (m/z) $(M+1)^+$: 485.2.

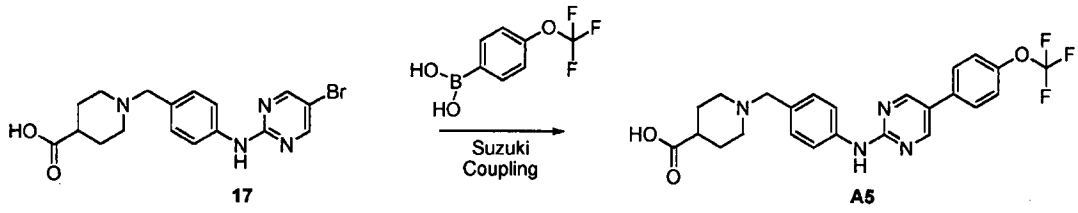
Example A4: 1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl) piperidine-4-carboxylic acid



[0174] To a solution of 1-(4-(5-bromopyrimidin-2-ylamino)benzyl)piperidine-4-carboxylic acid **17** (0.05 mmol) in 1,4-dioxane (1.0 mL) is added 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (0.05 mmol), 3M Na_2CO_3 (0.15 mmol) and $Pd(PPh_3)_4$ (0.0025 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 150 °C for 10 min. Purification by preparative HPLC (ACN gradient 10-70%) affords 1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl)piperidine-4-carboxylic acid **A4**. ^{1}H NMR (400MHz, *d4*-MeOH) δ 8.64 (s, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H),

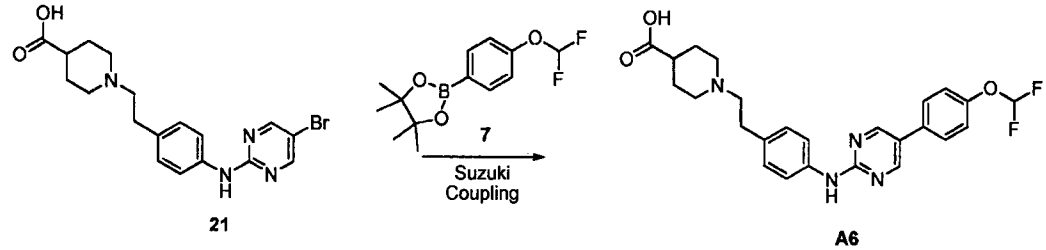
7.32 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.78 (t, J = 74.0 Hz, 1H), 4.11 (s, 2H), 3.31 (m, 2H), 2.92 (m, 2H), 2.36 (m, 1H), 2.02 (m, 2H), 1.81 (m, 2H). MS (m/z) $(M+1)^+$: 455.2.

Example **A5**: 1-(4-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl) piperidine-4-carboxylic acid



[0175] To a solution of 1-(4-(5-bromopyrimidin-2-ylamino)benzyl)piperidine-4-carboxylic acid **17** (0.05 mmol) in 1,4-dioxane (1.0 mL) is added 4-(trifluoromethoxy)phenylboronic acid (0.05 mmol), 3M Na_2CO_3 (0.15 mmol) and $Pd(PPh_3)_4$ (0.0025 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 150 °C for 10 min. Purification by preparative HPLC (ACN gradient 10-70%) affords 1-(4-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl)piperidine-4-carboxylic acid **A5**. ^1H NMR (400MHz, *d6*-DMSO) δ 10.06 (s, 1H), 8.89 (s, 2H), 7.88 (M, 4H), 7.48 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 4.23 (s, 2H), 2.95 (m, 1H), 2.51 (m, 4H), 2.09 (m, 2H), 1.71 (m, 2H). MS (m/z) $(M+1)^+$: 473.2.

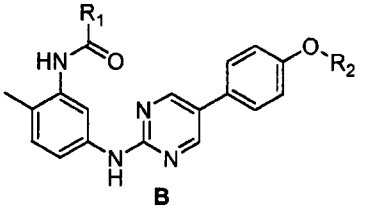
Example **A6**: 1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl) piperidine-4-carboxylic acid



[0176] To a solution of 1-(4-(5-bromopyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylic acid **21** (0.05 mmol) in 1,4-dioxane (1.0 mL) is added 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (0.05 mmol), 3M Na_2CO_3 (0.15 mmol) and $Pd(PPh_3)_4$ (0.0025 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated in a microwave oven at 150 °C for 10 min. Purification by

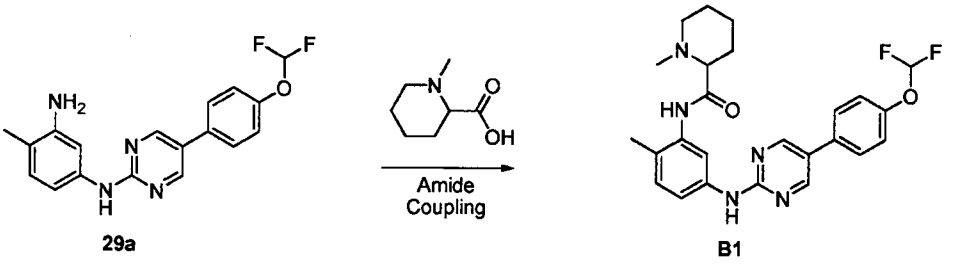
preparative HPLC (ACN gradient 10-70%) affords 1-(4-(5-(4-(difluoromethoxy)phenyl) pyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylic acid **A6**. MS (m/z) $(M+1)^+$: 469.2.

Type B compounds



B

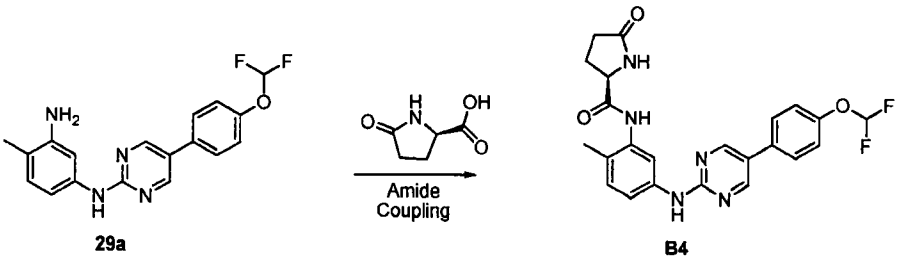
Example **B1**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1-methylpiperidine-2-carboxamide



29a B1

[0177] N1-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-yl)-4-methylbenzene-1,3-diamine **29a** (0.1 mmol), 1-methylpiperidine-2-carboxylic acid (0.1 mmol) and HATU (0.15 mmol) are dissolved in dry DMF (0.5 mL) at rt. Diisopropylethylamine (0.50 mmol) is added to the solution. The reaction mixture is stirred for 1 h at rt. HPLC purification affords the target compound **B1** as a TFA salt. MS (m/z) $(M+1)^+$: 468.2.

Example **B4**: (R)-N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-5-oxopyrrolidine-2-carboxamide

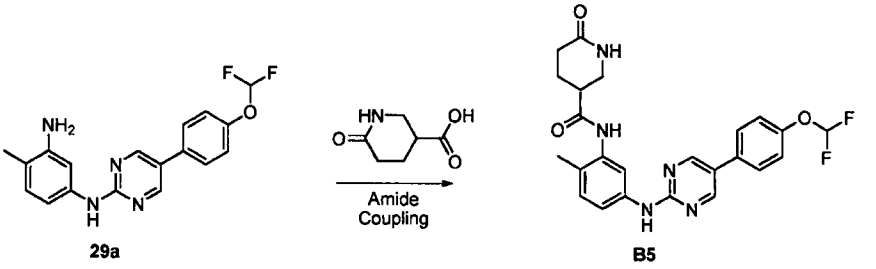


29a B4

[0178] Similar to the preparation of **B1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.76 (s, 1H), 9.47 (s, 1H), 8.81 (s, 2H), 7.95 (s, 1H), 7.77 (m, 3H), 7.55 (dd, J = 2.0, 8.8 Hz, 1H), 7.29 (t, J = 74.4

Hz, 1H), 7.27 (d, J = 9.2 Hz, 2H), 7.13 (d, J = 8.4 Hz, 1H), 4.26 (m, 1H), 2.40 (m, 2H), 2.14 (s, 3H), 2.04 (m, 2H). MS (m/z) $(M+1)^+$: 454.2.

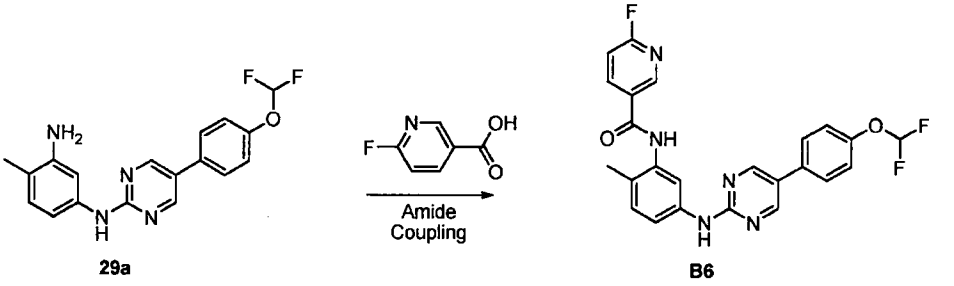
Example **B5**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-6-oxopiperidine-3-carboxamide



29a B5

[0179] Similar to the preparation of **B1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.75 (s, 1H), 9.50 (s, 1H), 8.81 (s, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 2.0 Hz, 1H), 7.56 (m, 2H), 7.30 (t, J = 74.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 1H), 3.34 (m, 2H), 2.86 (m, 1H), 2.25 (m, 2H), 2.12 (s, 3H), 2.03 (m, 1H), 1.92 (m, 1H). MS (m/z) $(M+1)^+$: 468.2.

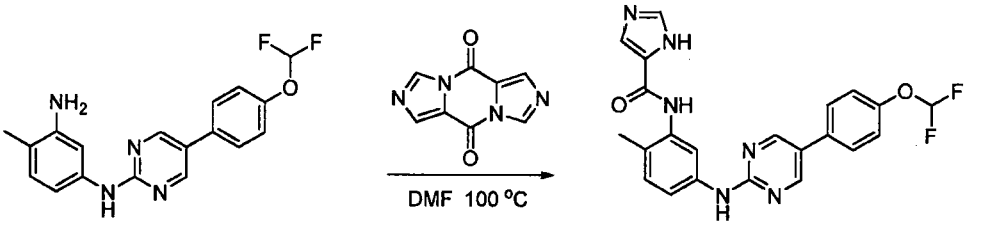
Example **B6**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-6-fluoropyridine-3-carboxamide



29a B6

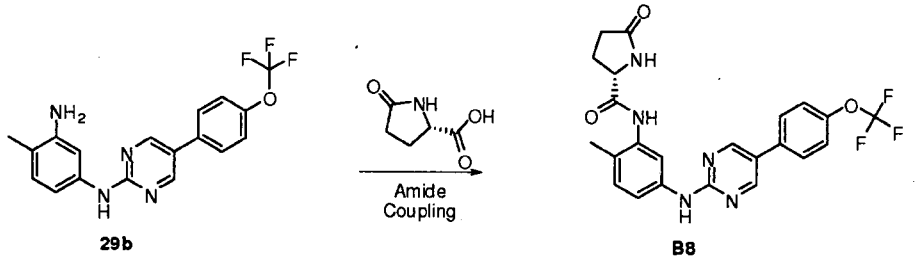
[0180] Similar to the preparation of **B1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 10.21 (s, 1H), 9.85 (s, 1H), 8.88 (s, 1H), 8.55 (m, 1H), 7.86 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.64 (dd, J = 2.0, 8.4 Hz, 1H), 7.40 (dd, J = 2.4, 8.4 Hz, 1H), 7.31 (t, J = 74.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.4 Hz, 1H), 2.21 (s, 3H). MS (m/z) $(M+1)^+$: 466.1.

Example **B7**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1H-imidazole-5-carboxamide



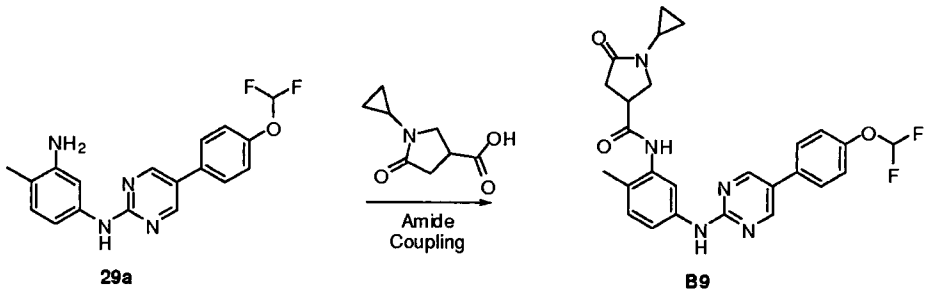
[0181] N1-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-yl)-4-methylbenzene-1,3-diamine **29a** (0.1 mmol) and 5H,10H-diimidazo[1,5-a:1',5'-d]pyrazine-5,10-dione (0.1 mmol) in dry DMF (0.5 mL) are heated at 110 °C for 24 h. HPLC purification affords the target compound **B7** as a TFA salt. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.80 (s, 2H), 8.81 (s, 2H), 8.44 (s, 1H), 8.04 (s, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.57 (m, 1H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 1H), 2.20 (s, 3H). MS (m/z) $(M+1)^+$: 437.2.

Example **B8**: (S)-N-(2-methyl-5-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-5-oxopyrrolidine-2-carboxamide



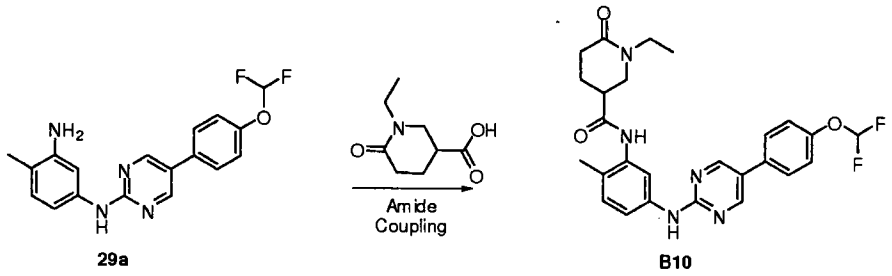
[0182] 4-Methyl-N1-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)benzene-1,3-diamine **29b** (0.1 mmol), (S)-5-oxopyrrolidine-2-carboxylic acid (0.1 mmol) and HATU (0.15 mmol) are dissolved in dry DMF (0.5 mL) at rt. Diisopropylethylamine (0.50 mmol) is added to the solution and the reaction mixture is stirred for 1 h at rt. HPLC purification affords the target compound **B8** as a TFA salt. MS (m/z) $(M+1)^+$: 473.1.

Example **B9**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1-cyclopropyl-5-oxopyrrolidine-3-carboxamide



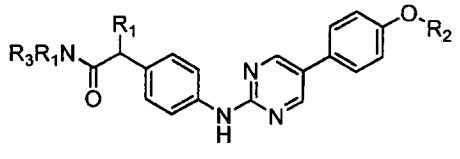
[0183] Similar to the preparation of **B1**. ^{1}H NMR (400MHz, *d4*-MeOD) δ 8.84 (s, 2H), 7.71 (m, 3H), 7.36 (s, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.91 (t, J = 74.0 Hz, 1H), 3.52-3.56 (m, 2H), 3.46 (m, 1H), 2.74 (m, 2H), 2.64 (m, 1H), 2.29 (s, 3H), 0.77 (m, 4H). MS (m/z) $(M+1)^+$: 494.2.

Example **B10**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1-ethyl-6-oxopiperidine-3-carboxamide



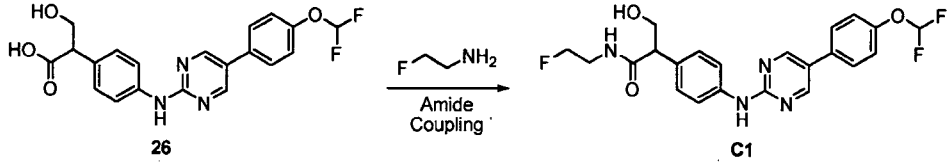
[0184] Similar to the preparation of **B1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.75 (s, 1H), 9.52 (s, 1H), 8.79 (s, 2H), 7.76 (m, 3H), 7.55 (m, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 74.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 3.2-3.5 (m, 2H), 2.9-3.0 (m, 1H), 2.5 (m, 2H), 2.3 (m, 2H), 2.13 (s, 3H), 1.80-2.08 (m, 2H), 1.05 (t, J = 6.8 Hz, 3H). MS (m/z) $(M+1)^+$: 496.2.

Type C compounds



C

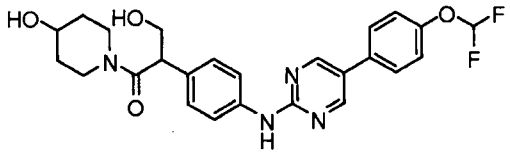
Example **C1**: 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-N-(2-fluoroethyl)-3-hydroxypropanamide



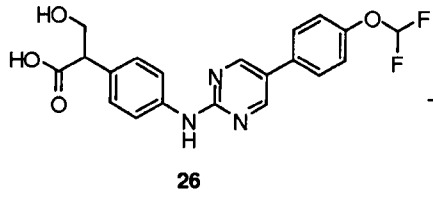
26 C1

[0185] 2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxypropanoic acid **26** (0.1 mmol), 2-fluoroethanamine (0.1 mmol) and HATU (0.15 mmol) are dissolved in dry DMF (0.5 mL) at rt. Diisopropylethylamine (0.50 mmol) is added to the solution. The reaction mixture is stirred for 1h at rt. HPLC purification (ACN gradient 10-90%) affords 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-N-(2-fluoroethyl)-3-hydroxypropanamide **C1** as a TFA salt. MS (m/z) $(M+1)^+$: 447.2.

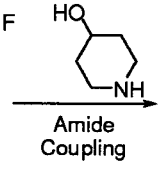
Example **C2**: 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one

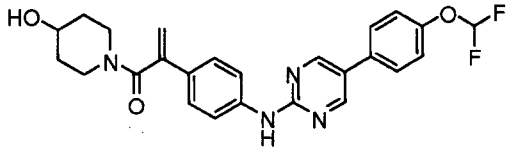


C2

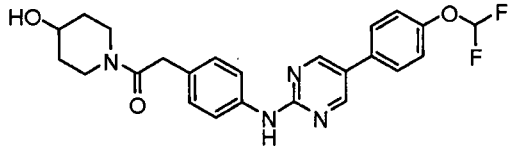


26





C32



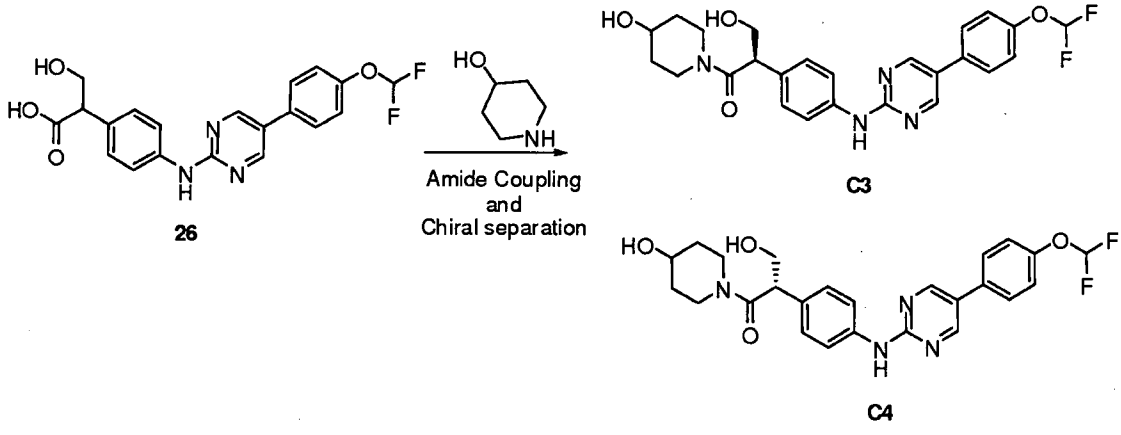
C33

[0186] Similar to the preparation of **C1**. ^{1}H NMR (400MHz, *d4*-MeOH) δ 8.88 (d, J = 2.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 8.8 Hz, 2H), 7.43 (m, 2H), 7.31 (d, J = 8.4 Hz,

2H), 6.92 (t, J = 74.0 Hz, 1H), 4.20 (m, 2H), 4.13 (m, 1H), 3.80 (m, 2H), 3.70 (m, 2H), 1.56 (m, 2H), 1.50 (m, 2H), 1.28 (m, 1H). MS (m/z) $(M+1)^+$: 485.2.

Example **C3**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one

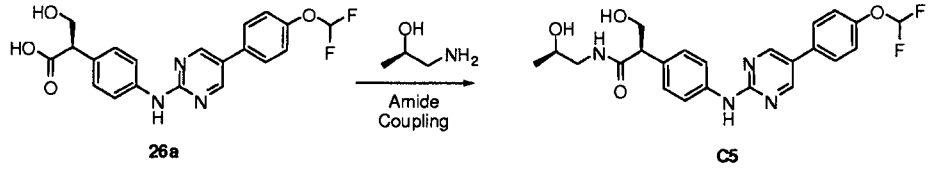
Example **C4**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one



[0187] Similar to the preparation of **C1**. Chiral separation on (R,R)-WelkO-1 column and hexane : isopropanol = 70 : 30 as gradient affords the two enantiomers **C3** (first peak eluted) and **C4** (second peak eluted). **C3** is arbitrarily assigned the R configuration. ^{1}H NMR (400MHz, *d4*-MeOH) δ 8.88 (d, J = 2.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 8.8 Hz, 2H), 7.43 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.92 (t, J = 74.0 Hz, 1H), 4.20 (m, 2H), 4.13 (m, 1H), 3.80 (m, 2H), 3.70 (m, 2H), 1.56 (m, 2H), 1.50 (m, 2H), 1.28 (m, 1H). MS (m/z) $(M+1)^+$: 485.2.

[0188] **C4** is arbitrarily assigned the S configuration. ^{1}H NMR (400MHz, *d4*-MeOH) δ 8.88 (d, J = 2.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 8.8 Hz, 2H), 7.43 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.92 (t, J = 74.0 Hz, 1H), 4.20 (m, 2H), 4.13 (m, 1H), 3.80 (m, 2H), 3.70 (m, 2H), 1.56 (m, 2H), 1.50 (m, 2H), 1.28 (m, 1H). MS (m/z) $(M+1)^+$: 485.2.

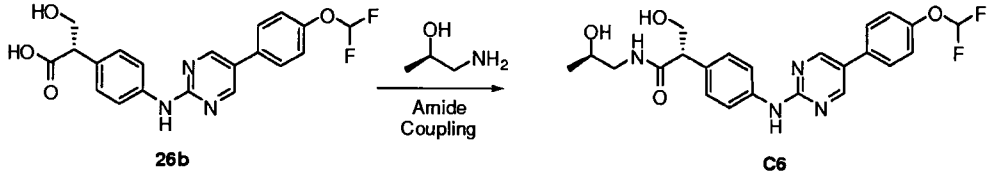
Example **C5**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((R)-2-hydroxypropyl)propanamide



26a C5

[0189] 2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxypropanoic acid **26a** (0.1 mmol), (R)-1-aminopropan-2-ol (0.1 mmol) and HATU (0.12 mmol) are dissolved in dry DMF (0.5 mL) at rt. Diisopropylethylamine (0.40 mmol) is added and the reaction mixture is stirred for 1h at rt. HPLC purification (ACN gradient 10-70%) affords (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((R)-2-hydroxypropyl)propanamide **C5** as a TFA salt. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.73 (s, 1H), 8.80 (s, 2H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.77 (m, 2H), 7.30 (t, *J* = 74.0 Hz, 1H), 7.28 (m, 2H), 7.22 (m, 2H), 7.45 (t, *J* = 4.0 Hz, 1H), 3.91 (m, 1H), 3.59 (m, 2H), 3.40 (quint., *J* = 8.0 Hz, 1H), 0.95 (d, *J* = 8.0 Hz, 3H). MS (m/z) $(M+1)^+$: 459.2.

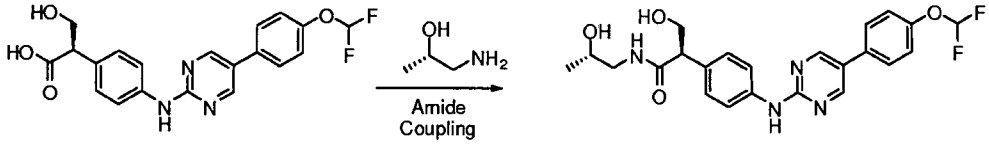
Example **C6**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((R)-2-hydroxypropyl)propanamide



26b C6

[0190] 2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxypropanoic acid **26b** (0.1 mmol), (R)-1-aminopropan-2-ol (0.1 mmol) and HATU (0.12 mmol) are dissolved in dry DMF (0.5 mL) at rt. Diisopropylethylamine (0.40 mmol) is added to the solution. The reaction mixture is stirred for 1h at rt. HPLC purification (ACN gradient 10-70%) affords (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((R)-2-hydroxypropyl)propanamide **C6** as a TFA salt. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.80 (s, 2H), 7.93 (m, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 72.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 3.93 (m, 1H), 3.61 (m, 1H), 2.99 (m, 2H), 2.51 (m, 2H), 0.95 (d, J = 6.0 Hz, 3H). MS (m/z) $(M+1)^+$: 459.1.

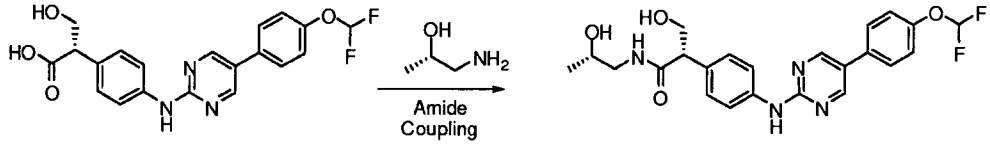
Example C7: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((S)-2-hydroxypropyl)propanamide



26a C7

[0191] Similar to the preparation of **C5**. ^{1}H NMR (400MHz, *d4*-MeOH) δ 8.69 (s, 2H), 7.67 (m, 4H), 7.31 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.88 (t, J = 76.0 Hz, 1H), 4.62 (s, 1H), 4.14 (m, 1H), 3.83 (m, 1H), 3.70 (m, 2H), 3.26 (dd J = 8.0, 12.0 hz, 1H), 3.10 (dd, J = 8.0, 12.0 Hz, 1H), 1.09 (d, J = 4.0 Hz, 3H). MS (m/z) $(M+1)^+$: 459.1.

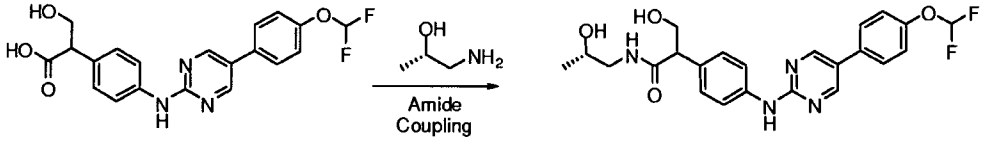
Example C8: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((S)-2-hydroxypropyl)propanamide



26b C8

[0192] Similar to the preparation of **C6**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.80 (s, 2H), 7.93 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.23 (t, J = 76 Hz, 1H), 7.21 (d, J = 8 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 3.84 (m, 1H), 3.42 (m, 3H), 3.28 (m, 1H), 1.72 (m, 3H), 1.02 (m, 6H). MS (m/z) $(M+1)^+$: 459.1.

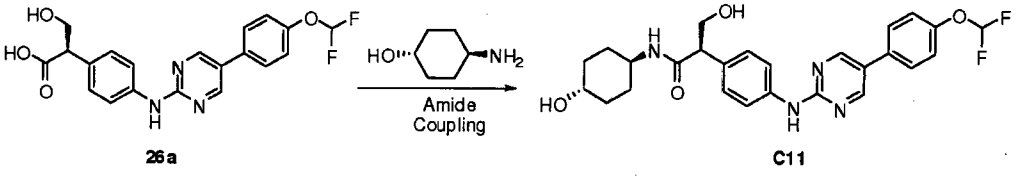
Example C9: 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((S)-2-hydroxypropyl)propanamide



26 C9

[0193] Similar to the preparation of **C1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.70 (s, 1H), 8.79 (s, 2H), 8.13 (s, 1H), 7.93 (d, J = 2.1 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8 Hz, 2H), 7.26 (t, J = 75 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 3.92 (dt, J = 8.7, 2.5 Hz, 1H), 3.0 (m, 2H), 2.5 (m, 5H), 2.07 (s, 1H), 0.96 (t, *J* = 5.7 Hz, 3H). MS (m/z) $(M+1)^+$: 459.1.

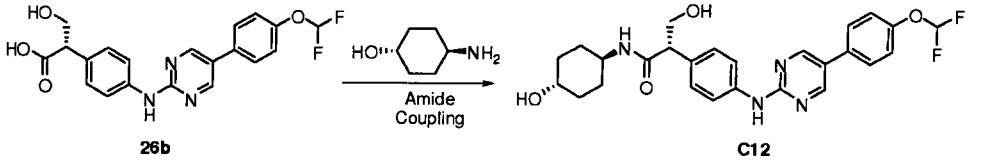
Example **C11**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1r,4R)-4-hydroxycyclohexyl)propanamide



26a C11

[0194] Similar to the preparation of **C5**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.73 (s, 1H), 8.80 (s, 2H), 7.93 (m, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 76.0 Hz, 1H), 7.27 (d, J = 8 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 3.93 (m, 1H), 3.59 (m, 1H), 3.0 (m, 2H), 2.51 (m, 2H), 0.97 (d, J = 6Hz, 3H). MS (m/z) $(M+1)^+$: 499.1.

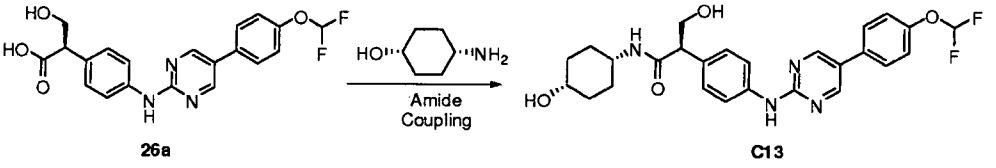
Example **C12**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1r,4R)-4-hydroxycyclohexyl)propanamide



26b C12

[0195] Similar to the preparation of **C6**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.80 (s, 2H), 8.14 (s, 1H), 7.79 (m, 3H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.6 Hz, 2H), 7.27 (t, J = 79.6 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 3.91 (m, 1H), 2.51 (m, 4H), 1.76 (m, 2H), 1.62 (m, 1H), 1.19 (m, 5H). MS (m/z) $(M+1)^+$: 499.2.

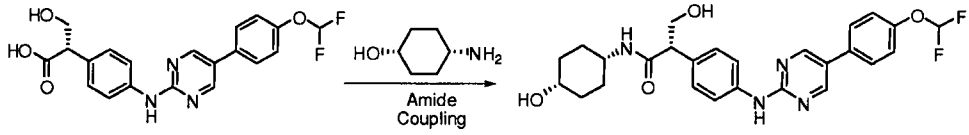
Example **C13**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1s,4S)-4-hydroxycyclohexyl)propanamide



26a C13

[0196] Similar to the preparation of **C5**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.74 (s, 1H), 8.81 (s, 2H), 7.84 (m, 1H), 7.78 (m, 2H), 7.68 (m, 2H), 7.30 (t, J = 76.0 Hz, 1H), 7.27 (d, J = 8 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.73 (t, J = 4.0Hz, 1H), 4.37 (d, J = 4.0Hz, 1H), 3.93 (m, 1H), 3.65 (bm, 1H), 3.58 (m, 2H), 3.48 (m, 1H), 1.62 (m, 2H), 1.38 (m, 8H). MS (m/z) $(M+1)^+$: 499.1.

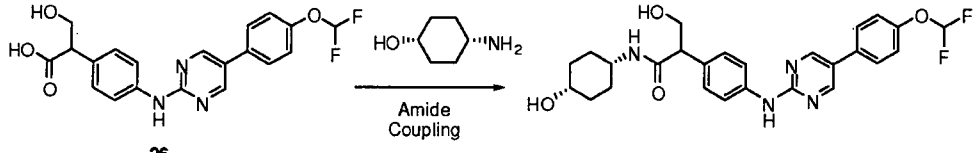
Example **C14**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1s,4S)-4-hydroxycyclohexyl)propanamide



26b C14

[0197] Similar to the preparation of **C6**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.83 (d, J = 7.6Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 7.6 Hz, 2H), 7.26 (t, J = 79.6 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 3.91 (m, 1H), 3.58 (m, 1H), 2.51 (m, 4H), 1.59 (m, 2H), 1.46 (m, 5H). MS (m/z) $(M+1)^+$: 499.2.

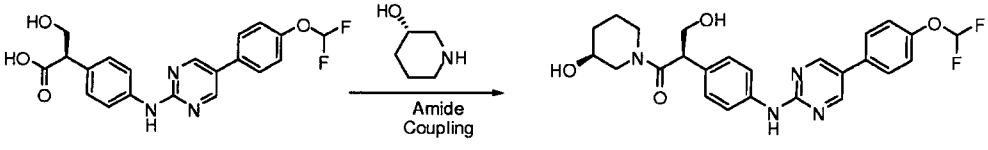
Example **C15**: 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1s,4s)-4-hydroxycyclohexyl)propanamide



26 C15

[0198] Similar to the preparation of **C1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 74 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.91 (t, J = 9 Hz, 1H), 3.6 (m, 2H), 2.51 (m, 3H), 1.46 (m, 9H). MS (m/z) $(M+1)^+$: 499.4.

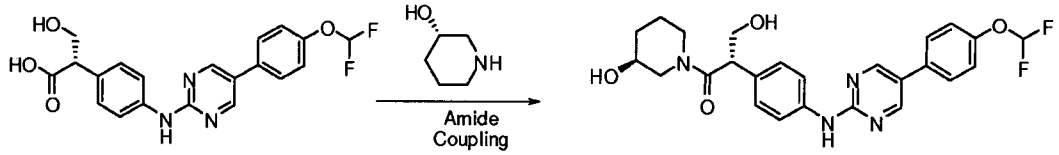
Example **C18**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((S)-3-hydroxypiperidin-1-yl)propan-1-one



26a C18

[0199] Similar to the prepararion of **C5**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.75 (s, 1H), 8.82 (s, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.70 (m, 2H), 7.28 (t, J = 70.0 Hz, 1H), 7.27 (m, 4H), 4.32 (m, 1H), 4.20 (m, 1H), 3.95 (m, 2H), 3.74 (m, 1H), 2.91 (m, 1H), 1.90 (m, 2H), 1.68 (m, 1H), 1.41 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

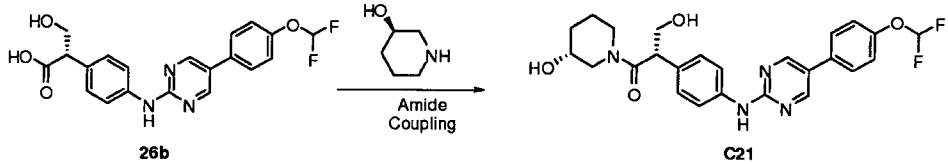
Example **C19**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((S)-3-hydroxypiperidin-1-yl)propan-1-one



26b C19

[0200] Similar to the preparartion of **C6**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.76 (d, J = 10.8 Hz, 1H), 8.82 (s, 2H), 7.77 (d, J = 7.6 Hz, 2H), 7.71 (m, 2H), 7.28 (t, J = 67.6 Hz, 1H), 7.27 (d, J = 6.8 Hz, 2H), 3.95 (m, 2H), 2.92 (m, 1H), 2.55 (m, 6H), 2.53 (m, 2H), 1.68 (m, 1H), 1.37 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

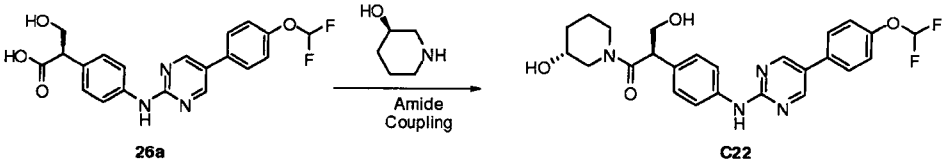
Example **C21**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((R)-3-hydroxypiperidin-1-yl)propan-1-one



26b C21

[0201] Similar to the preparartion of **C6**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.77 (s, 1H), 8.82 (s, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.71 (m, 2H), 7.28 (t, J = 68 Hz, 1H), 7.27 (d, J = 6.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 3.95 (m, 2H), 2.92 (m, 1H), 2.55 (m, 6H), 2.53 (m, 2H), 1.68 (m, 1H), 1.37 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

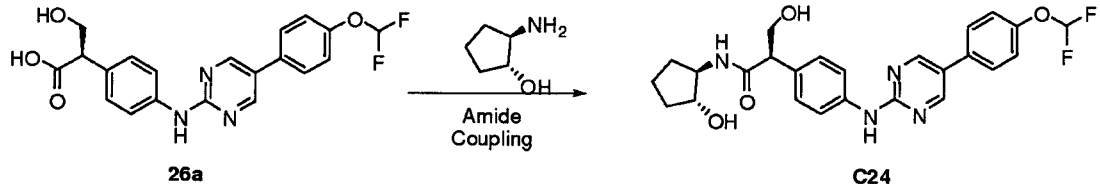
Example **C22**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((R)-3-hydroxypiperidin-1-yl)propan-1-one



26a C22

[0202] Similar to the preparartion of **C5**. ^{1}H NMR (400MHz, *d4*-MeOH) δ 8.68 (s, 2H), 7.58 (m, 4H), 7.22 (m, 4H), 6.79 (t, J = 72.0 Hz, 1H), 4.20 (m, 1H), 4.01 (m, 2H), 3.93 (m, 1H), 3.59 (bm, 2H), 3.38 (m, 1H), 3.33 (m, 1H), 3.06 (m, 1H), 2.72 (m, 1H), 2.64 (m, 1H). MS (m/z) $(M+1)^+$: 485.1.

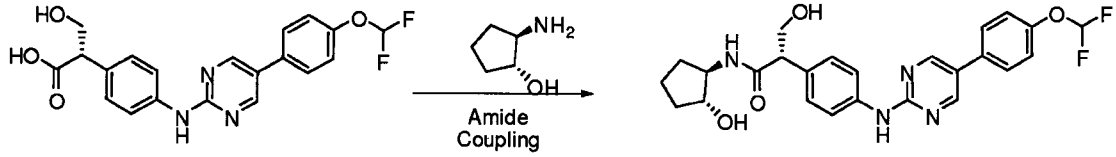
Example **C24**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1R,2R)-2-hydroxycyclopentyl)propanamide



26a C24

[0203] Similar to the preparartion of **C5**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.71 (s, 1H), 8.79 (s, 2H), 7.09 (d, J = 6.8 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 71.6 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 3.92 (m, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.53 (m, 2H), 1.43 (m, 1H), 1.24 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

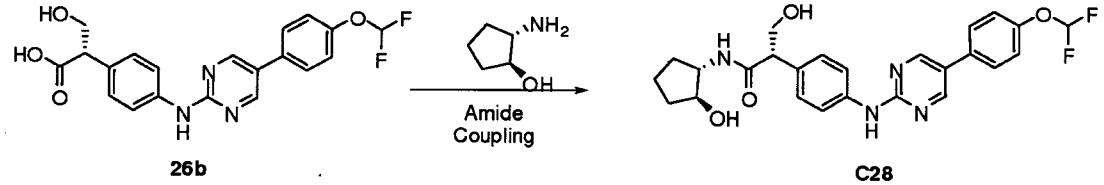
Example **C27**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1R,2R)-2-hydroxycyclopentyl)propanamide



26b C27

[0204] Similar to the preparation of **C6**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.89 (d, J = 6.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 74.4 Hz, 1H) 7.27 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.91 (m, 1H), 3.73 (m, 2H), 1.99 (m, 3H), 1.65 (m, 3H), 1.38 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

Example **C28**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2S)-2-hydroxycyclopentyl)propanamide

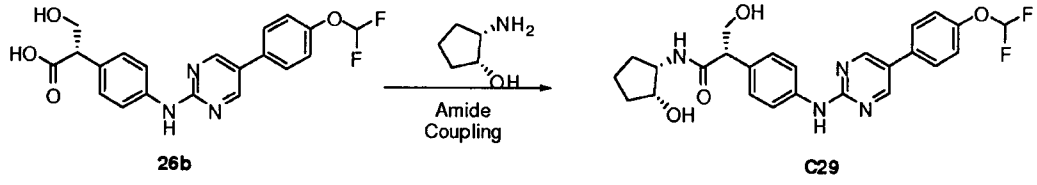


26b C28

[0205] Similar to the preparation of **C6**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.89 (d, J = 6.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (t, J =

74.4 Hz, 1H) 7.27 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.89 (m, 2H), 3.74 (m, 1H), 1.99 (m, 2H), 1.87 (m, 1H), 1.79 (m, 1H), 1.57 (m, 2H), 1.43 (m, 1H), 1.19 (m, 1H). MS (m/z) $(M+1)^+$: 485.2.

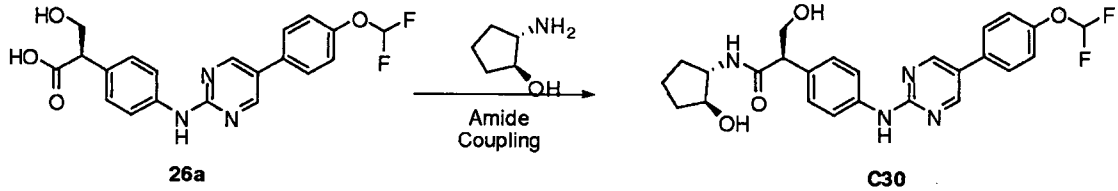
Example **C29**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2R)-2-hydroxycyclopentyl)propanamide



26b C29

[0206] Similar to the preparation of **C6**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.89 (d, J = 6.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 74.4 Hz, 1H) 7.27 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.97 (m, 2H), 3.80 (m, 1H), 1.99 (s, 2H), 1.71 (m, 3H), 1.54 (m, 1H), 1.41 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

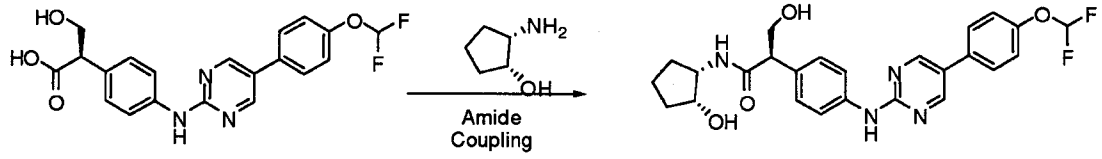
Example **C30**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2S)-2-hydroxycyclopentyl)propanamide



26a C30

[0207] Similar to the preparation of **C5**. ^{1}H NMR (400MHz, *d4*-MeOH) δ 8.68 (s, 2H), 7.56 (m, 4H), 7.22 (m, 4H), 6.77 (t, J = 72.0 Hz, 1H), 4.01 (m, 1H), 3.84 (m, 1H), 3.81 (m, 1H), 3.57 (m, 2H),), 2.01 (m, 1H), 1.74 (m, 1H), 1.69 (m, 2H), 1.44 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

Example **C31**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2R)-2-hydroxycyclopentyl)propanamide



26a C31

[0208] Similar to the preparation of **C5**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.71 (s, 1H), 8.80 (s, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.2 Hz, 1H), 7.27 (t, J = 65.6 Hz, 1H) 7.26 (m, 4H), 3.90 (m, 4H), 3.65 (m, 1H), 1.79 (m, 1H), 1.70 (m, 2H), 1.52 (m, 3H). MS (m/z) $(M+1)^+$: 485.2.

Example **C32**: 2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(4-hydroxypiperidin-1-yl)prop-2-en-1-one

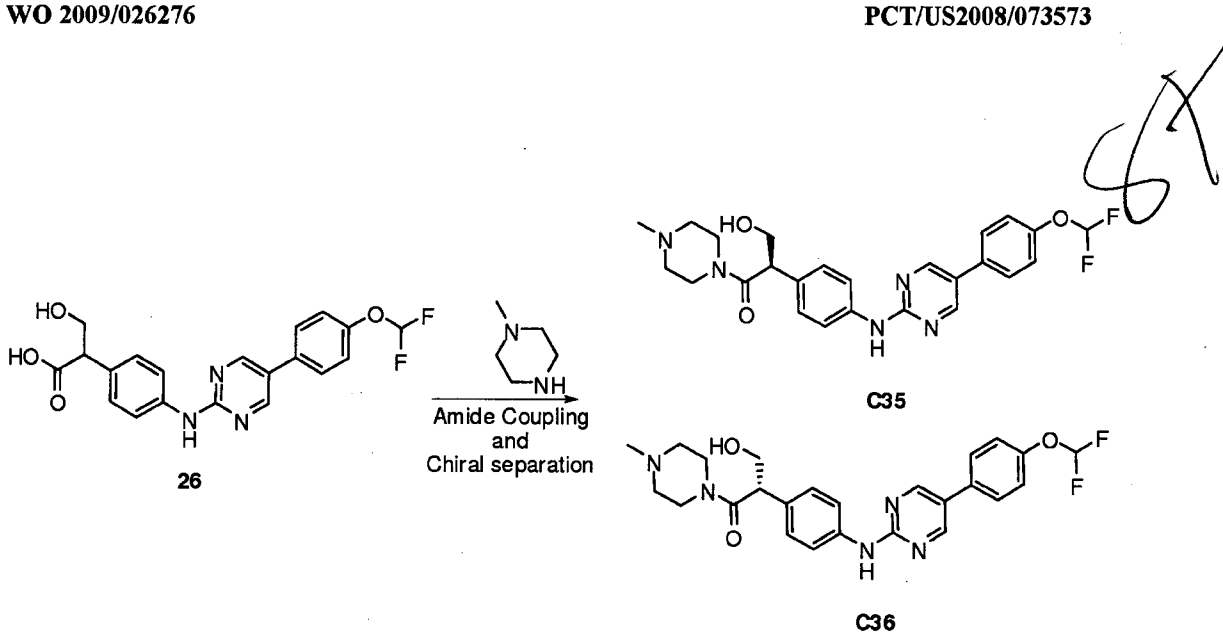
[0209] 2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(4-hydroxypiperidin-1-yl)prop-2-en-1-one **C32** is obtained as a minor side product during the preparation of Example **C2**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.97 (s, 1H), 8.85 (s, 2H), 7.2 (m, 4H), 7.35 (m, 4H), 7.29 (t, J = 74.0 Hz, 1H), 5.70 (s, 1H), 5.11 (s, 1H), 4.06 (m, 1H), 3.70 (m, 1H), 3.15 (m, 2H), 1.78 (m, 1H), 1.58 (m, 1H), 1.35 (m, 1H), 1.16 (m, 1H). MS (m/z) $(M+1)^+$: 467.2.

Example **C33**: 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(4-hydroxypiperidin-1-yl)ethanone

[0210] 2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(4-hydroxypiperidin-1-yl)ethanone **C33** is obtained as a minor side product during the preparation of Example **C2**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.76 (s, 1H), 8.81 (s, 2H), 7.77 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.29 (t, J = 71 Hz, 1H), 7.28 (d, J = 7.4 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 3.94 (dd, J = 6.2, 4.1 Hz, 1H), 3.73 (dd, J = 8.4, 5.3 Hz, 1H), 3.64 (m, 2H), 3.15 (dd, J = 10.6, 8.6 Hz, 1H), 2.97 (m, 1H), 1.62 (m, 2H), 1.2 (m, 4H). MS (m/z) $(M+1)^+$: 455.2.

Example **C35**: (R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-methylpiperazin-1-yl)propan-1-one

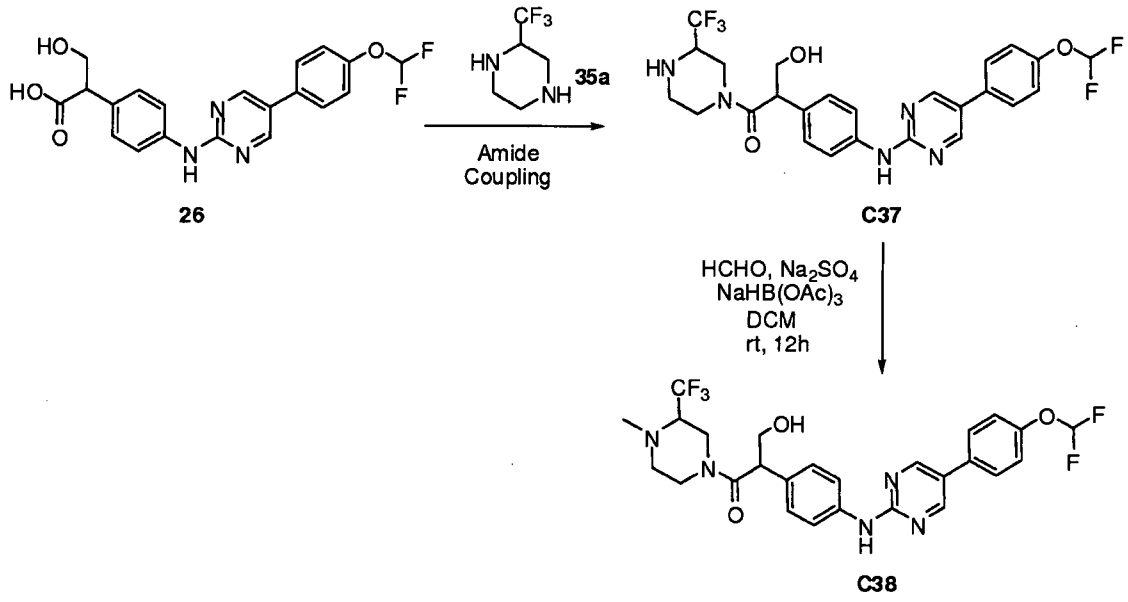
Example **C36**: (S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-methylpiperazin-1-yl)propan-1-one



[0211] Similar to the preparation of **C1**. Chiral HPLC separation on (R,R)-WelkO-1 column and hexane : isopropanol = 70 : 30 as gradient affords the two enantiomers **C35** (first peak eluted) and **C36** (second peak eluted). **C35** is arbitrarily assigned the R configuration. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.80 (s, 1H), 8.81 (s, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.1-7.5 (m, 5H), 4.09 (s, 1H), 3.96 (t, J = 8.8 Hz, 1H), 2.7-2.9 (m, 2H), 2.55 (m, 4H), 2.51 (m, 4H), 2.07 (s, 3H). MS (m/z) $(M+1)^+$: 484.2.

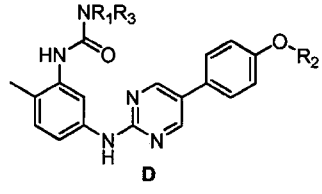
[0212] **C36** is arbitrarily assigned the S configuration. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.80 (s, 1H), 8.81 (s, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.1-7.5 (m, 5H), 4.09 (s, 1H), 3.96 (t, J = 8.8 Hz, 1H), 2.7-2.9 (m, 2H), 2.55 (m, 4H), 2.51 (m, 4H), 2.07 (s, 3H). MS (m/z) $(M+1)^+$: 484.2.

Example **C38**: 2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(3-(trifluoromethyl)-4-methylpiperazin-1-yl)-3-hydroxypropan-1-one

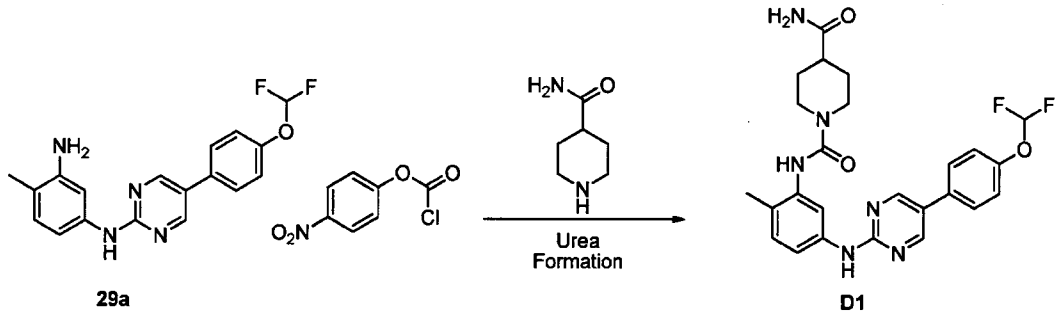


[0213] A solution of 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(3-(trifluoromethyl)piperazin-1-yl)-3-hydroxypropan-1-one **C37** (prepared as described for **C1**, 0.05 mmol), HCHO (0.15 mmol, 30% aqueous) and anhydrous Na_2SO_4 (1.5 mmol) in DCM (2 mL) is stirred at rt for 30 min. Then $NaHB(OAc)_3$ (0.3 mmol) is added and the resulting mixture is stirred for 12 h. Purification by prep-HPLC (ACN gradient 10-70%) affords 2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(3-(trifluoromethyl)-4-methylpiperazin-1-yl)-3-hydroxypropan-1-one **C38**. MS (m/z) $(M+1)^+$: 552.2.

Type D compounds



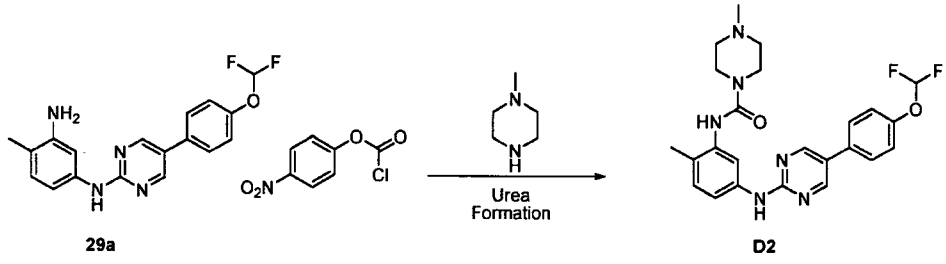
Example **D1**: N1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)piperidine-1,4-dicarboxamide



29a D1

[0214] N1-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-yl)-4-methylbenzene-1,3-diamine **29a** (0.1 mmol), 4-nitrophenyl chloroformate (0.12 mmol) and pyridine (0.24 mmol) in dry DCM (0.5 mL) are stirred at rt for 10 min. Then piperidine-4-carboxamide (0.12 mmol) is added and the reaction mixture is stirred for 2 h. HPLC purification affords the target compound **D1** as the TFA salt. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.68 (s, 1H), 8.81 (s, 2H), 8.05 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.62 (s, 1H), 7.48 (m, 1H), 7.26 (m, 4H), 7.08 (d, J = 8.4 Hz, 1H), 6.80 (s, 1H), 4.09 (m, 2H), 2.81 (t, J = 12.4 Hz, 2H), 2.32 (m, 1H), 2.10 (s, 3H), 1.70 (m, 2H), 1.48 (m, 2H). MS (m/z) $(M+1)^+$: 497.2.

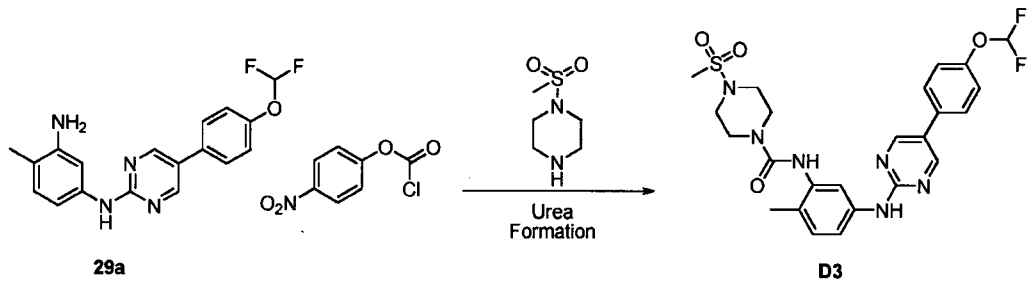
Example **D2**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methylpiperazine-1-carboxamide



29a D2

[0215] Similar to the preparation of **D1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.74 (s, 1H), 8.80 (s, 2H), 8.37 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.64 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.29 (s, 2H), 7.27 (t, J = 74.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 2.86 (s, 3H), 2.51 (m, 4H), 2.54 (m, 4H), 2.11 (s, 3H). MS (m/z) $(M+1)^+$: 469.2.

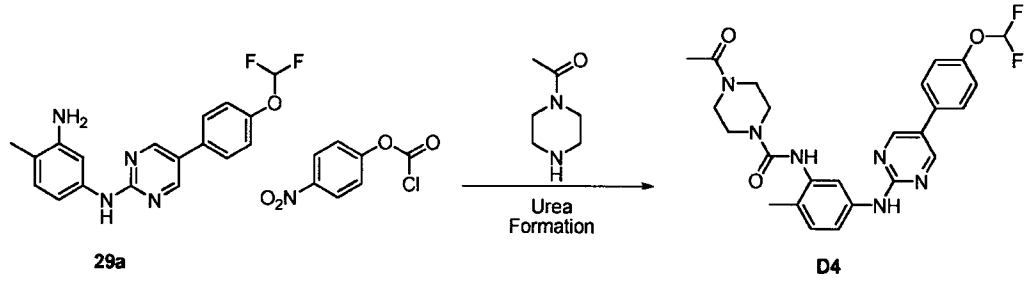
Example **D3**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methanesulfonyl-piperazine-1-carboxamide



29a D3

[0216] Similar to the preparation of **D1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.70 (s, 1H), 8.80 (s, 2H), 8.25 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.62 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 3.56 (m, 4H), 3.15 (m, 4H), 2.92 (s, 3H), 2.10 (s, 3H). MS (m/z) $(M+1)^+$: 533.2.

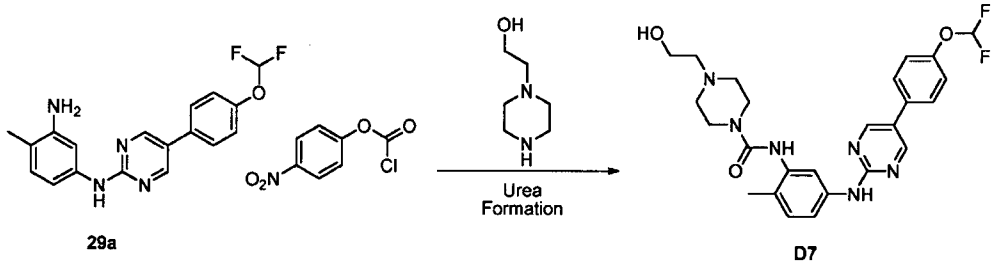
Example **D4**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-acetylpiperazine-1-carboxamide



29a D4

[0217] Similar to the preparation of **D1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.69 (s, 1H), 8.80 (s, 2H), 8.18 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 74.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 3.56 (m, 4H), 3.35 (m, 4H), 2.10 (s, 3H), 2.04 (s, 3H). MS (m/z) $(M+1)^+$: 497.2.

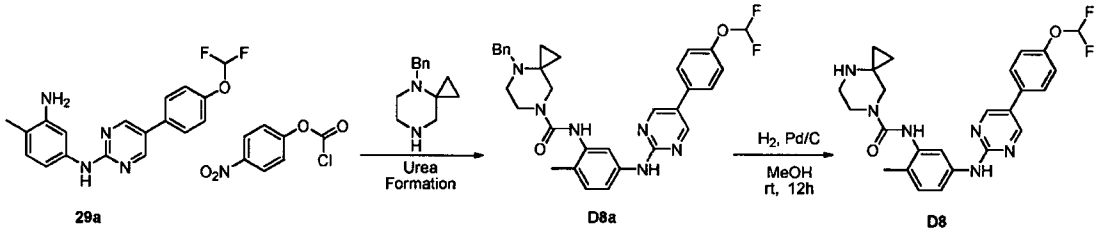
Example **D7**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-(2-hydroxyethyl)piperazine-1-carboxamide



29a D7

[0218] Similar to the preparation of **D1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 8.4 (s, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.64 (m, 1H), 7.28 (m, 2H), 7.2 (t, J = 50 Hz, 1H), 7.1 (m, 2H), 3.8 (t, J = 4.9 Hz, 2H), 3.24 (t, J = 5 Hz, 2H), 2.51 (m, 8H), 2.11 (s, 3H). MS (m/z) $(M+1)^+$: 499.2.

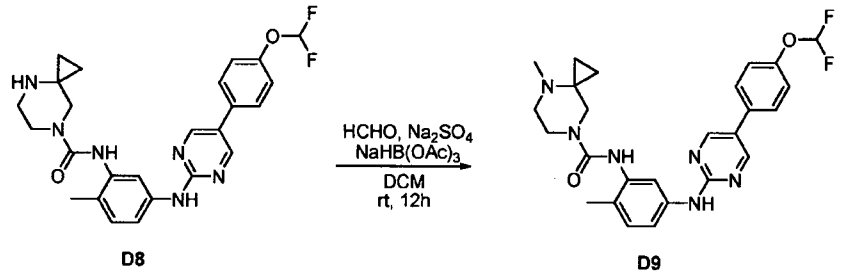
Example **D8**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4,7-diazaspiro[2.5]octane-7-carboxamide



29a D8a D8

[0219] N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)- 4-(phenylmethyl)-4,7-diazaspiro[2.5]octane-7-carboxamide **D8a** (prepared as described for **D1**; 0.2 mmol) is dissolved in 10 mL MeOH followed by addition of 5% mol of Pd/C (10% in weight). The flask is charged with a hydrogen balloon for 12 h stirring. The mixture is filtered over a celite pad and the filtrate is concentrated to afford N-(5-(5-(4-(difluoromethoxy)phenyl) pyrimidin-2-ylamino)-2-methylphenyl)-4,7-diazaspiro[2.5]octane-7-carboxamide **D8**, which is used without further purification. MS (m/z) $(M+1)^+$: 523.1.

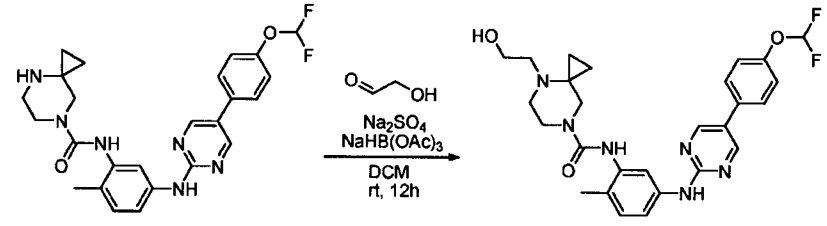
Example **D9**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-4,7-diazaspiro[2.5]octane-7-carboxamide



D8 D9

[0220] A solution of N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4,7-diazaspiro[2.5]octane-7-carboxamide **D8** (0.05 mmol), HCHO (0.15 mmol, 30% aqueous) and anhydrous Na_2SO_4 (1.5 mmol) in DCM (2 mL) is stirred at rt for 30 min. Then $NaHB(OAc)_3$ (0.3 mmol) is added and the resulting mixture is stirred for 12 h. Purification by prep-HPLC (ACN gradient 10-70%) affords N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-4,7-diazaspiro[2.5]octane-7-carboxamide **D9**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.67 (s, 1H), 8.79 (s, 2H), 7.98 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 76.0 Hz, 1H),7.08 (d, J = 8.4 Hz, 1H), 2.78 (m, 2H), 2.51 (m, 4H), 2.31 (s, 3H), 2.10 (s, 3H), 0.62 (m, 2H), 0.50 (m, 2H). MS (m/z) $(M+1)^+$: 537.1.

Example **D10**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-(2-hydroxyethy)-4,7-diazaspiro[2.5]octane-7-carboxamide

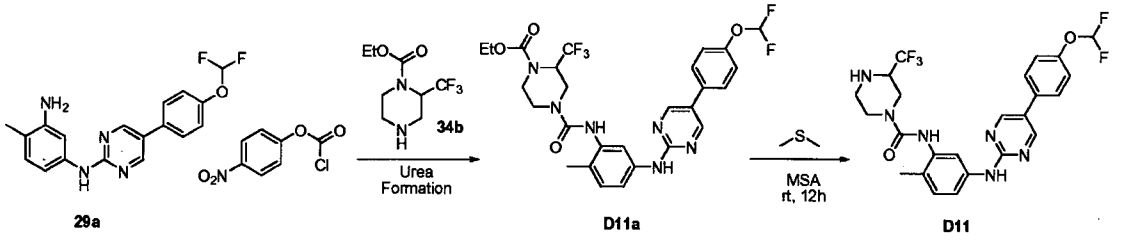


D8 D10

[0221] A solution of N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4,7-diazaspiro[2.5]octane-7-carboxamide **D8** (0.05 mmol), 2-hydroxyacetaldehyde (0.6 mmol) and anhydrous Na_2SO_4 (1.5 mmol) in DCM (2 mL) is stirred at rt for 30 min. Then $NaHB(OAc)_3$ (0.3 mmol) is added and the resulting mixture is stirred for 12 h. Purification by prep-HPLC (ACN gradient 10-70%) affords N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-(2-hydroxyethy)-4,7-diazaspiro[2.5]octane-7-carboxamide **D10**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.67 (s, 1H), 8.79

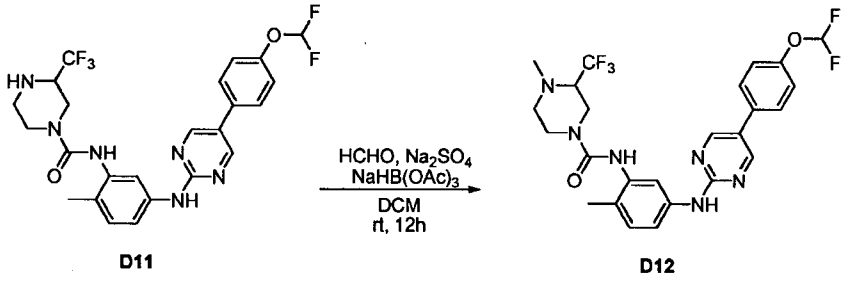
(s, 2H), 7.95 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 76.0 Hz, 1H),7.08 (d, J = 8.4 Hz, 1H), 2.89 (m, 2H), 2.77 (m, 2H), 2.54 (m, 2H), 2.51 (m, 4H), 2.10 (s, 3H), 0.50-0.62 (m, 4H). MS (m/z) $(M+1)^+$: 525.2.

Example **D11**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-(trifluoromethyl)piperazine-1-carboxamide



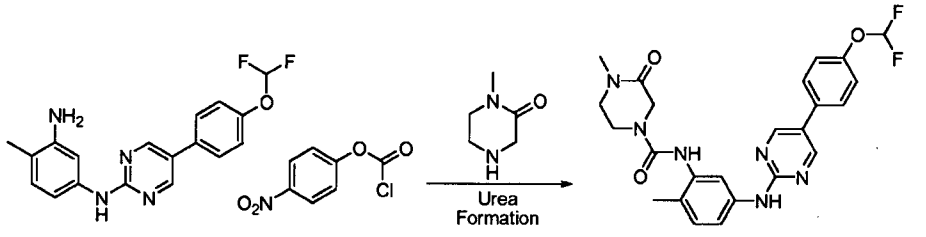
[0222] N1-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-yl)-4-methylbenzene-1,3-diamine **29a** (0.4 mmol), 4-nitrophenyl chloroformate (0.48 mmol) and pyridine (0.8 mmol) in dry DCM (2 mL) are stirred at rt for 10 min. Then ethyl 2-(trifluoromethyl)piperazine-1-carboxylate **34b** (0.48 mmol) is added and the reaction mixture is stirred for 2 h. After the reaction is complete, the mixture is diluted with 20 mL of DCM and washed with water. The organic layer is separated, dried over Na_2SO_4, filtered and concentrated under vacuum to afford a residue **D11a**. To this residue is added dimethylsulfide (1.2 mmol) and methanesulfonic acid (1.0 mL) and the resulting mixture is stirred at rt for 12 h. HPLC purification (ACN gradient 10-70%) affords **D11** as a TFA salt. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.73 (s, 1H), 8.80 (s, 2H), 8.43 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 74.0 Hz, 1H),7.11 (d, J = 8.4 Hz, 1H), 4.27 (m, 1H), 4.02 (m, 1H), 3.17 (m, 1H), 3.0 (s, 1H), 2.51 (m, 4H), 2.11 (s, 3H). MS (m/z) $(M+1)^+$: 523.2.

Example **D12**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-3-(trifluoromethyl)piperazine-1-carboxamide



[0223] A solution of N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-(trifluoromethyl)piperazine-1-carboxamide **D11** (0.05 mmol), HCHO (0.15 mmol, 30% aqueous) and anhydrous Na_2SO_4 (1.5 mmol) in DCM (2 mL) is stirred at rt for 30 min. Then $NaHB(OAc)_3$ (0.3 mmol) is added and the resulting mixture is stirred for 12 h. Purification by prep-HPLC (ACN gradient 10-70%) affords N-(5-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-(trifluoromethyl)-4-methylpiperazine-1-carboxamide **D12** as a TFA salt. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.69 (s, 1H), 8.80 (s, 2H), 8.15 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.61 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.4 Hz, 1H), 3.68 (m, 1H), 3.54 (m, 1H), 2.88 (m, 1H), 2.51 (m, 4H), 2.47 (s, 1H), 2.09 (s, 3H). MS (m/z) $(M+1)^+$: 537.2.

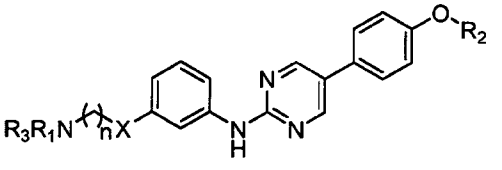
Example **D13**: N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-3-oxopiperazine-1-carboxamide



29a D13

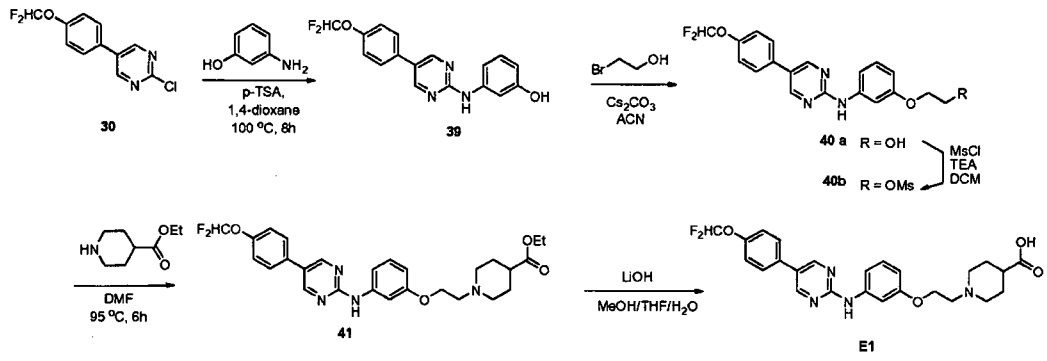
[0224] Similar to the preparation of **D1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.70 (s, 1H), 8.80 (s, 2H), 8.21 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 4.06 (s, 2H), 2.89 (s, 3H), 2.51 (m, 4H), 2.10 (s, 3H). MS (m/z) $(M+1)^+$: 483.2.

Type E compounds



E

Example **E1**: 1-(2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy)ethyl)piperidine-4-carboxylic acid



[0225] To a mixture of 2-chloro-5-(4-(difluoromethoxy)phenyl)pyrimidine **30** (3.2 mmol) and 3-aminophenol (6.42 mmol) in 1,4-dioxane (5 mL) is added p-TSA(5.4 mmol). The reaction mixture is heated at 100 °C for 12 h. After this time, the reaction is diluted with a 2M solution of Na_2CO_3 and extracted with DCM (3 x 50 mL). The organic layer is washed with brine, dried over Na_2SO_4, and concentrated. Purification by short SiO_2 chromatography using a DCM : EtOAc = 7 : 3 as eluant affords (3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenol **39**. MS (m/z) $(M+1)^+$: 330.1.

[0226] A solution of 3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenol **39** (1.2 mmol), 2-bromoethanol (1.4 mmol) and cesium carbonate (1.6 mmol) in acetonitrile (10 mL) is heated to 85 °C for 12h then cooled to rt. The reaction is evaporated to dryness then re-dissolved in DCM. The organic mixture is washed with water and brine then dried over magnesium sulfate, filtered and reduced to dryness. Purification by silica gel chromatography with hexane : EtOAc = 1 : 1 as eluant affords 2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy)ethanol **40a** as white solid. MS (m/z) $(M+1)^+$: 373.8.

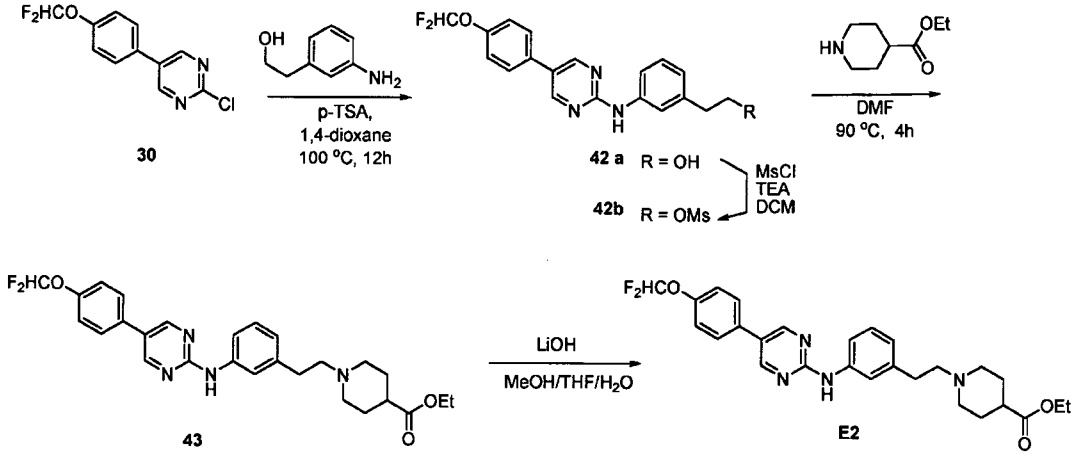
[0227] To a solution of 2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy)ethanol **40** (0.4 mmol) in DCM (15 mL) is added triethyl amine (0.4 mmol) and methanesulfonyl chloride (0.4 mmol). The reaction mixture is stirred at rt for 12 h then washed with brine and dried over magnesium sulfate, filtered and reduced to dryness. The resulting crude 2-(3-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy)ethyl methanesulfonate **40b** as tan solid is used without further purification.

[0228] 2-(3-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy)ethyl methanesulfonate **40b** (0.4 mmol), ethyl piperidine-4-carboxylate (0.9 mmol) are dissolved in DMF (3 mL) and heated to 95 °C for 6h then cooled to rt. The reaction mixture is partitioned with EtOAC and water. The organic layer is washed with water, brine, dried over magnesium

sulfate, filtered, and reduced to dryness. The crude product is triturated with MeOH and filtered to yield ethyl 1-(2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy)ethyl)piperidine-4-carboxylate **41** as white solid. MS (m/z) $(M+1)^+$: 513.2.

[0229] To ethyl 1-(2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy)ethyl)piperidine-4-carboxylate **41** (78 umol) is added THF (3 mL), MeOH (2 mL) and 3M lithium hydroxide (0.5 mmol). The reaction mixture is stirred at rt for 6 h until complete as detected by LCMS. Subsequently the organic solvents are evaporated and the reaction mixture is diluted with water (5 mL) and neutralized with 3M HCl (0.5 mmol). The resulting precipitate is filtered, washed with water and air dried to yield 1-(2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy)ethyl)piperidine-4-carboxylic acid **E1** as white solid. ^{1}H NMR (400MHz, *d6*-DMSO) δ 12.12 (s, 1H), 9.79 (s, 1H), 8.85 (s, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.52 (bs, 1H), 7.34 (bd, J = 8.0 Hz, 1H), 7.31 (t, J = 74.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.56 (bd, J = 8.0 Hz, 1H) 4.05 (m, 2H), 2.88 (m, 2H), 2.67 (m, 2H), 2.20 (m, 1H), 2.09 (m, 2H), 1.78 (m, 2H), 1.57 (m, 2H). MS (m/z) $(M+1)^+$: 484.2.

Example **E2**: 1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl) piperidine-4-carboxylic acid



[0230] A solution of 2-(3-aminophenyl)ethanol (1.8 mmol), 2-chloro-5-(4-difluoromethoxy-phenyl)-pyrimidine **30** (1.8 mmol) and p-TSA (1.8 mmol) in dioxane (10 mL) is heated at 100 °C for 12 h then cooled to rt. The reaction mixture is slowly added to water (100 mL) with stirring. The resulting precipitate is collected by filtration, washed with water and air dried. The crude precipitate of 2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)ethanol

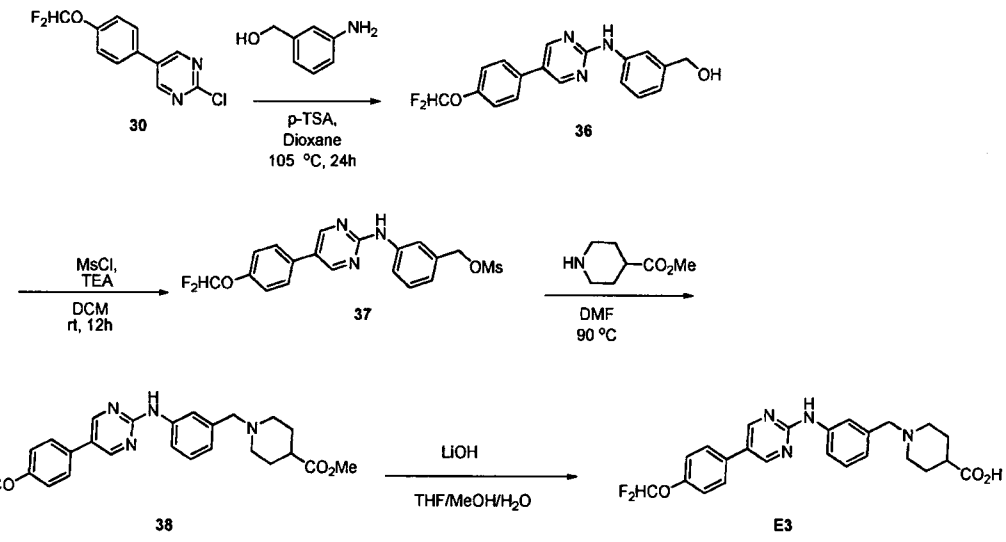
42a is used without further purification. MS (m/z) $(M+1)^+$: 357.9.

[0231] To a solution of 2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)ethanol **42a** (0.7 mmol) in DCM (20 mL) is added triethyl amine (0.8 mmol) and methanesulfonyl chloride (0.8 mmol). The reaction mixture is stirred at rt for 12 h then washed with brine and dried over magnesium sulfate, filtered, and reduced to dryness. The resulting 3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl methanesulfonate **42b** as crude tan solid, is used without further purification.

[0232] 3-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl methanesulfonate **42b** (0.7 mmol) and ethyl piperidine-4-carboxylate (1.7 mmol) are dissolved in DMF (6 mL) and heated to 95 °C for 6 h then cooled to rt. The reaction mixture is partitioned with EtOAc and water. The organic layer is washed with water, brine, dried over magnesium sulfate, filtered and reduced to dryness. The crude material is purified by column chromatography on silica with hexane : EtOAc = 1 : 1 to 100% EtOAc as eluant to yield ethyl 1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylate **43** as clear crystalline solid. MS (m/z) $(M+1)^+$: 497.2.

[0233] To ethyl 1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylate **43** (0.3 mmol) is added THF (3 mL), MeOH (2 mL) and 3.0M lithium hydroxide (1.8 mmol). The reaction mixture is stirred at rt for 6 h until complete as detected by LCMS. Subsequently the organic solvents are evaporated and the reaction mixture is diluted with water (10 mL) then neutralized with 3M HCl (1.8 mmol). The resulting precipitate is filtered, washed with water and air dried to yield **E2** as white solid. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.75 (s, 1H), 8.83 (s, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.65 (m, 2H), 7.31 (t, J = 74.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.21 (t, J = 8.0 Hz, 1H), 6.83 (d, J = 7.2 Hz, 1H), 2.71 (m, 2H), 2.21 (m, 1H), 2.03 (m, 2H), 1.81 (m, 2H), 1.58 (m, 2H). MS (m/z) $(M+1)^+$: 468.2.

Example **E3**: 1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl) piperidine-4-carboxylic acid



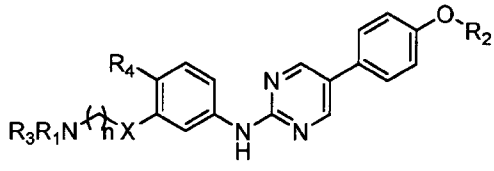
[0234] To a mixture of 2-chloro-5-(4-(difluoromethoxy)phenyl)pyrimidine **30** (0.40 mmol) and (3-aminophenyl)methanol (0.40 mmol) in 1,4-dioxane (0.5 mL) is added p-TSA (0.4 mmol). The reaction mixture is heated at 105 °C for 2 days. After this time, the reaction mixture is diluted with a solution of 2M Na_2CO_3 (30 mL) and extracted with DCM (3 x 30 mL). The organic layer is washed with brine, dried over Na_2SO_4 and concentrated. Purification by short silica gel chromatography using a hexane : EtOAc = 1 : 2 affords (3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)methanol **36**. ^{1}H NMR (400MHz, *d4*-MeOH) δ 8.56 (s, 2H), 7.65 (m, 1H), 7.48-7.52 (m, 1H), 7.42-7.46 (m, 2H), 7.29 (t, J = 8 Hz, 1H), 7.15-7.18 (m, 3H), 6.99-7.03 (m, 1H), 6.49 (t, J = 73.6 Hz, 1H), 4.67 (s, 2H). MS (m/z) $(M+1)^+$ 344.1.

[0235] To a solution of (3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)methanol **36** (6.22 mmol) in DCM (30 mL) is added triethylamine (9.33 mmol) and methanesulfonyl chloride (7.47 mmol). The reaction mixture is stirred at rt for 1.5 h. The reaction is diluted with H_2O (10 mL) and washed with Na_2CO_3 solution (3 x 20 mL). The organic layer is washed with brine, dried over $MgSO_4$ and concentrated to afford 3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl methanesulfonate **37**. MS (m/z) $(M+1)^+$ 422.1.

[0236] To a solution of 3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl methanesulfonate **37** (0.050 mmol) in anhydrous DMF (1 mL) is added methyl piperidine-4-carboxylate (0.10 mmol) and the solution is heated at 100 °C for 8 h. After the reaction is complete, the mixture is diluted with THF : MeOH : H_2O (3 : 2 : 1, 5 mL). To the reaction

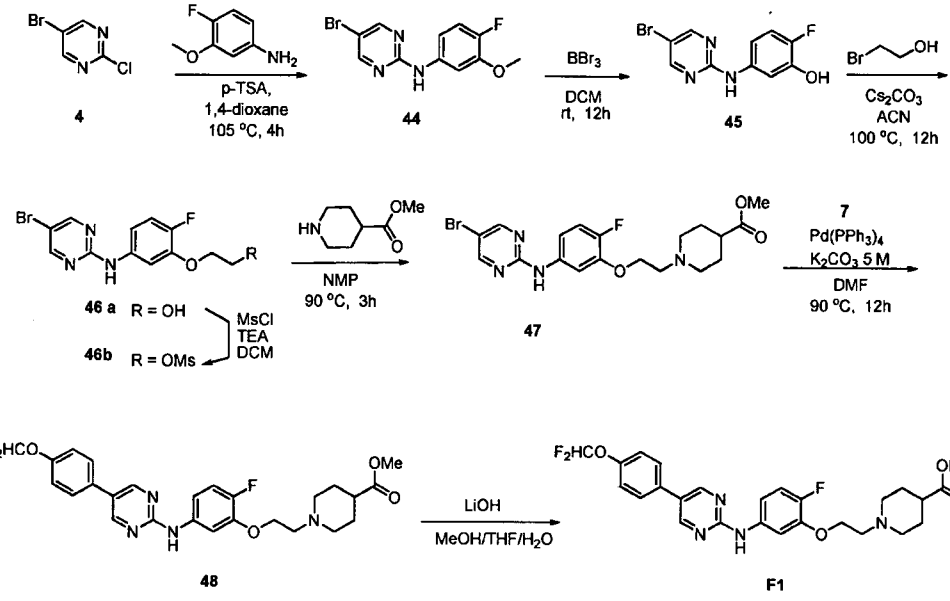
mixture is added 6N LiOH (0.30 mmol). The reaction is stirred at rt for 1 h. Purification by preparative LC/MS affords 1-(3-(5 (4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl)piperidine-4-carboxylic acid **E3**. ^{1}H NMR (400MHz, *d4*-MeOH) δ 8.64 (s, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.78 (t, J = 74.0 Hz, 1H), 4.11 (s, 2H), 3.31 (m, 2H), 2.92 (m, 2H), 2.36 (m, 1H), 2.02 (m, 2H), 1.81 (m, 2H). MS (m/z) $(M+1)^+$: 455.2.

Type F compounds



F

Example **F1**: 1-(2-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-fluorophenoxy)ethyl)piperidine-4-carboxylic acid



[0237] To a mixture of -5-bromo 2-chloropyrimidine **4** (1.1 mmol) and 4-fluoro-3-methoxyaniline (1.1 mmol) in 5 mL of 1,4-dioxane is added p-TSA (1.0 mmol). The reaction mixture is heated at 105 °C for 4 h. After this time, the reaction mixture is diluted with a 2M

Na_2CO_3 solution and extracted with DCM (3 x 50 mL). The organic layer is washed with brine, dried over Na_2SO_4 and concentrated. Purification prep HPLC (ACN gradient 20-70%) 5-bromo-N-(4-fluoro-3-methoxyphenyl)pyrimidin-2-amine **44** as brown solid. MS (m/z) $(M+1)^+$: 299.1.

[0238] To a solution of of 5-bromo-N-(4-fluoro-3-methoxyphenyl)pyrimidin-2-amine **44** (0.25 mmol) in 3 mL of anhydrous DCM at 0 °C is added BBr_3 (1.27 mmol) drop wise. The reaction mixture is stirred at rt for 12 h. After this time the reaction mixture is diluted with a 2M solution of Na_2CO_3 and extracted with DCM (2 x 20 mL). The organic layer is washed with brine, dried over Na_2SO_4 and concentrated to afford 5-(5-bromopyrimidin-2-ylamino)-2-fluorophenol **45** as brownish solid which is used without further purification. MS (m/z) $(M+1)^+$: 286.2.

[0239] A solution of 5-(5-bromopyrimidin-2-ylamino)-2-fluorophenol **45** (0.25 mmol), 2-bromoethanol (0.28 mmol) and cesium carbonate (0.36 mmol) in acetonitrile (3 mL) is heated to 100 °C for 12 h. The reaction is evaporated to dryness then re-dissolved in DCM. The organic mixture is washed with water and brine then dried over magnesium sulfate, filtered and reduced to dryness to yield 2-(5-(5-bromopyrimidin-2-ylamino)-2-fluorophenoxy)ethanol **46a** as a brown solid which is used without further purification. MS (m/z) $(M+1)^+$: 329.2.

[0240] To a solution of 2-(5-(5-bromopyrimidin-2-ylamino)-2-fluorophenoxy)ethanol **46a** (0.24 mmol) in DCM (15 mL) is added triethylamine (0.24 mmol) and methanesulfonyl chloride (0.24 mmol). The reaction mixture is stirred at rt for 12 h then washed with brine and dried over magnesium sulfate, filtered and reduced to dryness. The resulting tan solid of 2-(5-(5-bromopyrimidin-2-ylamino)-2-fluorophenoxy)ethyl methanesulfonate **46b** is used without further purification. MS (m/z) $(M+1)^+$: 407.1.

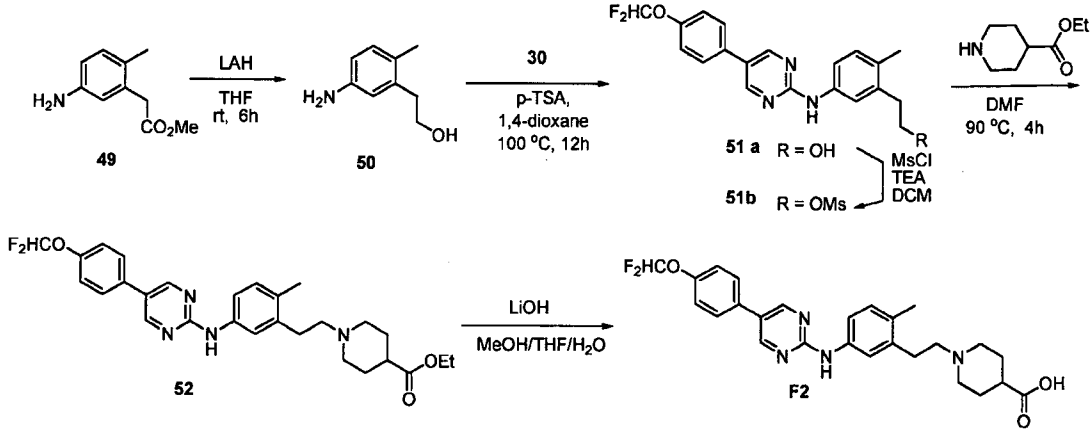
[0241] 2-(5-(5-bromopyrimidin-2-ylamino)-2-fluorophenoxy)ethyl methanesulfonate **46b** (0.24 mmol) and methyl piperidine-4-carboxylate (0.48 mmol) are dissolved in NMP (2 mL) and heated to 90 °C for 3h. The reaction mixture is cooled to rt and diluted with water and extracted with EtOAc (2 x 30 mL). The organic layer is washed with water, brine, dried over sodium sulfate, and concentrated to dryness. The crude product is purified by short SiO_2 chromatography using DCM : hexane = 9 : 1 as eluant to yield methyl 1-(2-(5-(5-bromopyrimidin-2-ylamino)-2-fluorophenoxy)ethyl)piperidine-4-carboxylate **47** as light brown solid. MS (m/z) $(M+1)^+$: 454.1.

[0242] To a solution of methyl 1-(2-(5-(5-bromopyrimidin-2-ylamino)-2-fluorophenoxy)ethyl)piperidine-4-carboxylate **47** (0.24 mmol) in 1,4-dioxane (2.0 mL) is added

2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (0.28 mmol), 1.8M K_2CO_3 (0.5 mmol) and $Pd(PPh_3)_4$ (0.017 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 90 °C for 12 h. The reaction mixture is cooled to rt, diluted with water (10 mL) and extracted with DCM (2 x 20 mL). The organic layer is separated, dried over Na_2SO_4 and concentrated. Purification by preparative HPLC (ACN gradient 20-70%) affords methyl 1-(2-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-fluorophenoxy)ethyl)piperidine-4-carboxylate **48** as white solid. MS (m/z) $(M+1)^+$: 517.1.

[0243] To methyl 1-(2-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-fluorophenoxy)ethyl)piperidine-4-carboxylate **48** (0.072 mmol) is added THF (1 mL), MeOH (0.8 mL) and 6M lithium hydroxide (0.42 mmol). The reaction mixture is stirred at rt for 6 h until complete by LCMS. The organic solvents are evaporated and the reaction mixture is diluted with water and neutralized with 6M HCl (0.42 mmol). The resulting precipitate is filtered, washed with water and air dried to yield **F1** as white solid. ^{1}H NMR (400MHz, *d6*-DMSO) δ 9.88 (s, 1H), 8.85 (s, 2H), 7.79 (m, 2H), 7.71 (dd, J = 8.0, 12.0 Hz, 1H), 7.46 (m, 1H), 7.31 (m, 2H), 7.29(t, J = 69.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 4.41 (m, 2H), 3.58 (m, 6H), 3.14 (m, 2H), 2.12 (m, 2H),1.77 (m, 1H). MS (m/z) $(M+1)^+$: 503.2.

Example **F2**: 1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenethyl)piperidine-4-carboxylic acid



[0244] To a solution of (5-amino-2-methyl-phenyl)-acetic acid methyl ester **49** (1.4 mmol) in THF (7 mL) at 0°C is added 1M lithium aluminum hydride THF solution (1.4 mmol). The reaction is stirred at rt for 6 h and subsequently quenched with ice water and partitioned with ethyl acetate. The organic layer is washed with brine, dried over magnesium sulfate, filtered and

reduced to dryness to yield 2-(5-amino-2-methylphenyl)ethanol **50** as tan crystalline solid, which is used without further purification.

[0245] A solution of 2-chloro-5-(4-difluoromethoxy-phenyl)-pyrimidine **30** (1.3mmol), 2-(5-Amino-2-methyl-phenyl)-ethanol **50** (1.3 mmol) and p-TSA (0.24 g, 1.3mmol) in dioxane (10 mL) is heated at 100 °C for 12 h then cooled to rt. The reaction mixture is slowly added to water (100 mL) with stirring. The resulting precipitate is collected by filtration, washed with water and air dried. The crude precipitate is purified by column chromatography on silica with hexanes : EtOAc = 1:1 as eluant to yield 2-{5-[5-(4-difluoromethoxy-phenyl)-pyrimidin-2-ylamino]-2-methyl-phenyl}-ethanol **51a** as solid. MS (m/z) $(M+1)^+$: 372.3.

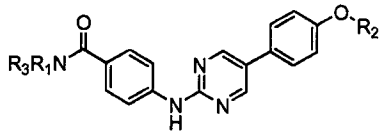
[0246] To a solution of 2-{5-[5-(4-difluoromethoxy-phenyl)-pyrimidin-2-ylamino]-2-methyl-phenyl}-ethanol **51a** (0.8 mmol) in DCM (25 mL) is added triethyl amine (1.0 mmol) and methanesulfonyl chloride (0.9 mmol). The reaction mixture is stirred at rt for 12 h then washed with brine and dried over magnesium sulfate, filtered and reduced to dryness. The resulting 5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenethyl methanesulfonate **51b** as clear amber oil is used without further purification. MS (m/z) $(M+1)^+$: 450.1.

[0247] 5-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenethyl methanesulfonate **51b** (0.9 mmol), ethyl piperidine-4-carboxylate (2.2 mmol) are dissolved in DMF (10 mL) and heated to 90 °C for 4 h then cooled to rt. The reaction mixture is partitioned with EtOAc and water. The organic layer is washed with water, brine, dried over magnesium sulfate, filtered and reduced to dryness. The crude material is purified by column chromatography on silica with hexane : EtOAc = 1 : 1 to 100% EtOAc as eluant to yield ethyl 1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenethyl)piperidine-4-carboxylate **52** as clear viscous oil. MS (m/z) $(M+1)^+$: 511.2.

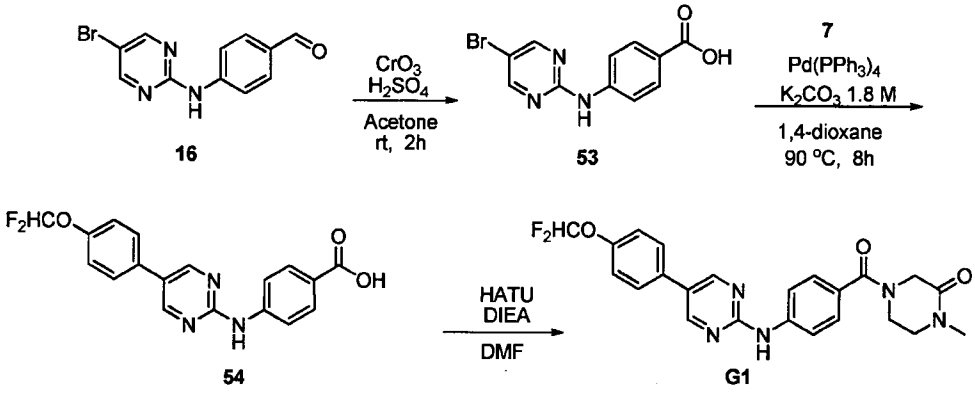
[0248] To ethyl 1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenethyl)piperidine-4-carboxylate **52** (0.6 mmol) is added THF (3 mL), MeOH (2 mL) and 3M lithium hydroxide (7.3 mmol). The reaction mixture is stirred at rt for 6 h until complete as detected by LCMS. Subsequently, the organic solvents are evaporated and the reaction mixture is diluted with water (10 mL) then neutralized with 3M HCl (7.3 mmol). The resulting precipitate is filtered, washed with water and air dried. The crude precipitate is purified by preparative LCMS to yield 1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenethyl)piperidine-4-carboxylic acid **F2** as white solid. ^{1}H NMR

(400MHz, *d6*-DMSO) δ 9.69 (s, 1H), 8.79 (s, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.60 (bd, J = 8.0 Hz, 1H), 7.56 (bs, 1H), 7.46 (s, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 1H), 3.19 (m, 1H), 2.96 (m, 2H), 2.27 (s, 3H), 2.10 (m, 2H), 1.75 (m, 2H). MS (m/z) $(M+1)^+$: 483.2.

Type G compounds



Example **G1**: 4-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-1-methylpiperazin-2-one



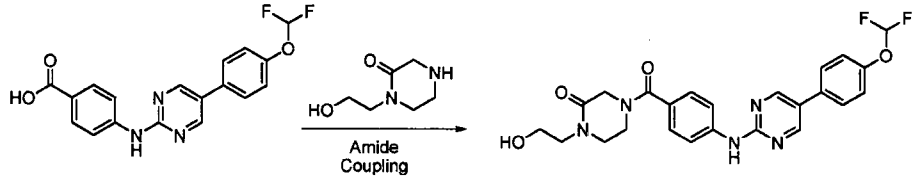
[0249] To a solution of 4-(5-bromopyrimidin-2-ylamino)benzaldehyde **16** (1.26 mmol) in acetone (5 mL) is added Jones' reagent (3.0 mmol of a 4M solution) portionwise until complete conversion as detected by LCMS. Isopropanol (10 mL) is added and the reaction mixture is stirred at rt for 1 h, then the solvent is removed under vacuum. The green residue is re-dissolved in water and partitioned with ethyl acetate. The organic layer is washed with water, brine, dried over sodium sulfate, filtered and reduced to dryness to afford 4-(5-bromopyrimidin-2-ylamino)benzoic acid **53** as yellow solid which is used without further purification. MS (m/z) $(M+1)^+$: 295.1.

[0250] To 4-(5-bromopyrimidin-2-ylamino)benzoic acid **53** (0.25 mmol) in 1,4-dioxane (2.0 mL) is added 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (0.28 mmol), 1.8M K_2CO_3 (0.5 mmol) and $Pd(PPh_3)_4$ (0.017 mmol). The reaction is evacuated and backfilled with nitrogen twice then heated at 90 °C for 8 h. The reaction mixture is diluted with water (10 mL) neutralized with 2M HCl and extracted with DCM (3 x 20 mL). Purification by

preparative HPLC (ACN gradient 20-70%) affords 4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoic acid **54** as white solid. MS (m/z) $(M+1)^+$: 358.2.

[0251] 4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoic acid **54** (0.022 mmol), HATU (0.027 mmol) and 1-methylpiperazin-2-one (0.022 mmol) are dissolved in dry DMF (0.5 mL) at rt. Diisopropylethylamine (0.06 mmol) is added to the solution. The reaction mixture is stirred for 1 h at rt. HPLC purification affords 4-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-1-methylpiperazin-2-one **G1** as a TFA salt. ^{1}H NMR (400MHz, *d6*-DMSO) δ 10.1 (s, 1H), 8.87 (s, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.4Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 51.2 Hz, 1H), 4.1 (s, 2H), 2.87 (s, 3H), 2.55 (m, 4H). MS (m/z) $(M+1)^+$: 454.2.

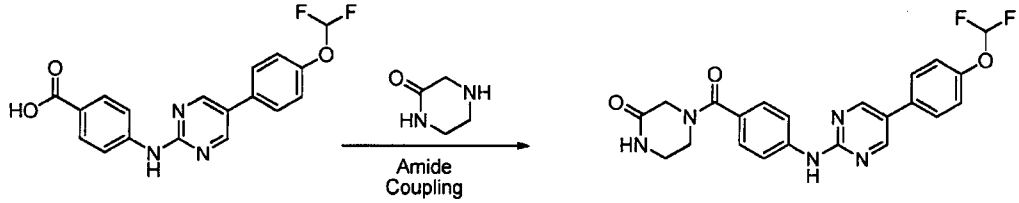
Example **G2**: 4-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-1-(2-hydroxyethyl)piperazin-2-one



54 G2

[0252] Similar to the preparation of **G1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 10.1 (s, 1H), 8.87 (s, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.2 (t, J = 50.2 Hz, 1H), 4.1 (s, 2H), 2.55 (m, 6H), 2.51 (m, 4H). MS (m/z) $(M+1)^+$: 484.1.

Example **G3**: 4-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl) piperazin-2-one

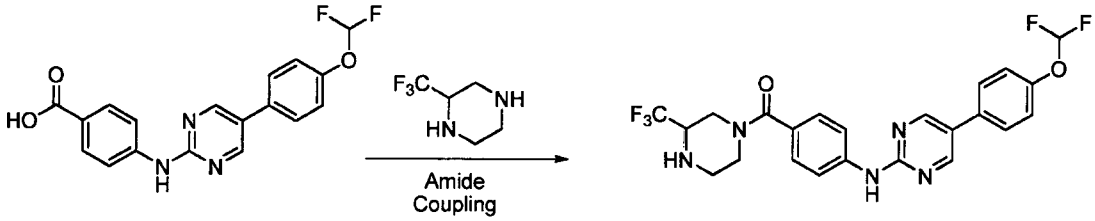


54 G3

[0253] Similar to the preparation of **G1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 10.12 (s, 1H), 8.89 (s, 2H), 8.14 (bs, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz,

2H), 7.31 (t, J = 72.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 4.01 (s, 2H), 3.65 (m, 2H), 3.28 (m, 4H). MS (m/z) $(M+1)^+$: 440.2.

Example **G4**: (4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)(3-(trifluoromethyl)piperazin-1-yl)methanone

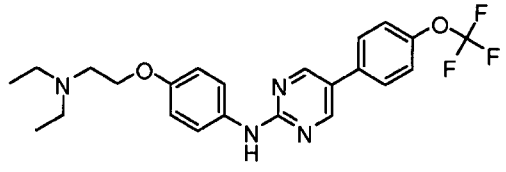
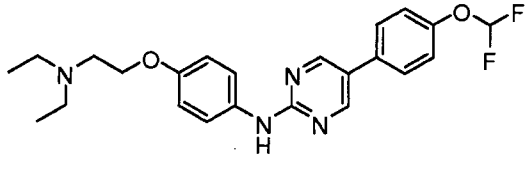


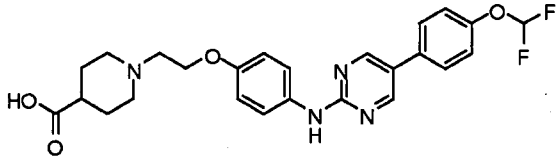
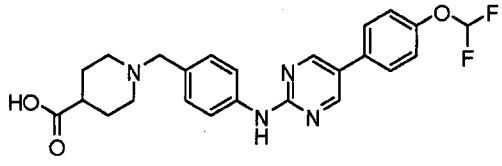
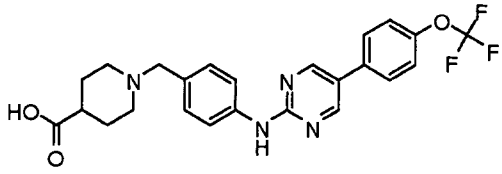
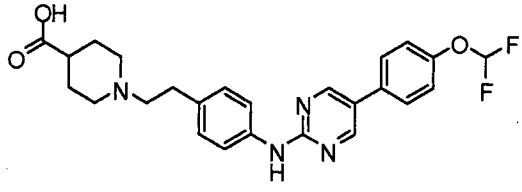
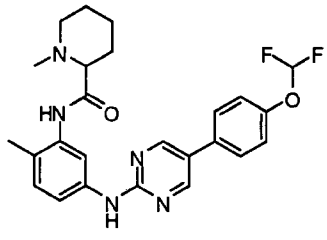
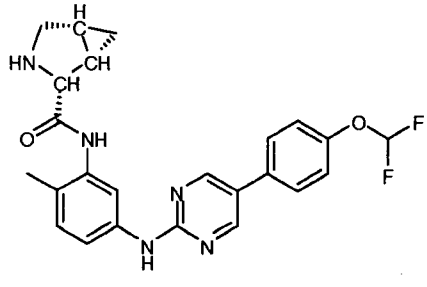
54 G4

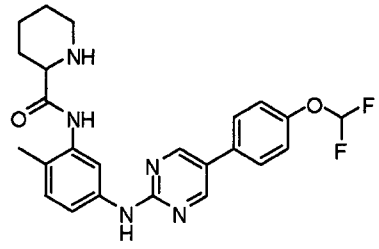
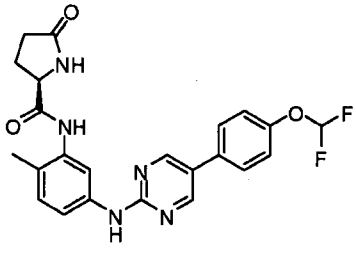
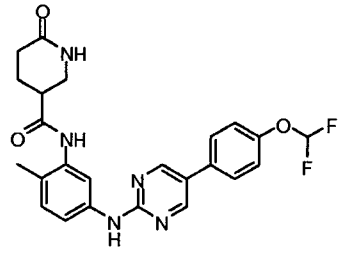
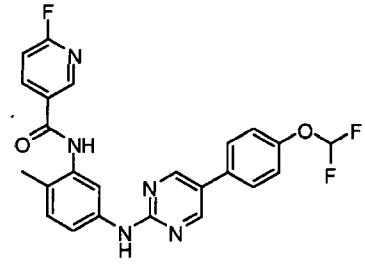
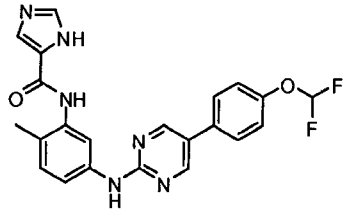
[0254] Similar to the preparation of **G1**. ^{1}H NMR (400MHz, *d6*-DMSO) δ 10.13 (s, 1H), 8.89 (s, 2H), 7.93 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 76.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 4.01 (bs, 4H), 3.30 (bs, 2H), 3.28 (bs, 2H). MS (m/z) $(M+1)^+$: 494.2.

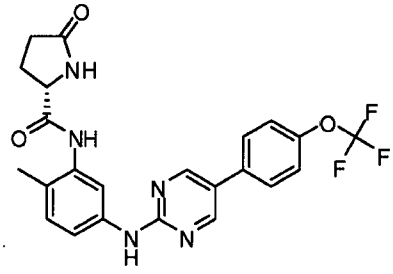
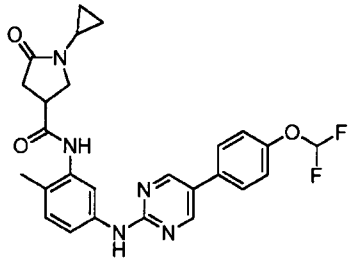
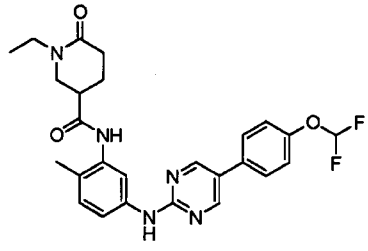
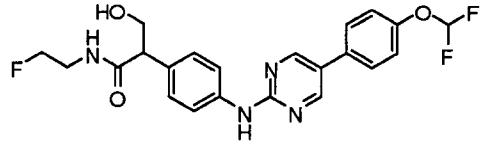
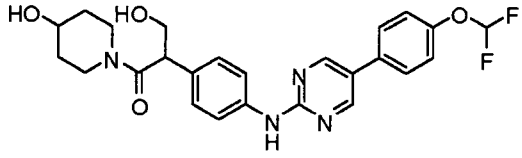
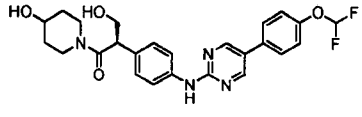
[0255] Table 1 describes representative compounds of the invention, prepared following the procedures described above. Compounds in Table 1 have an activity of < 1 μM in c-kit Mo7e assay and/or PDGFR TG-HA-VSMC assay.

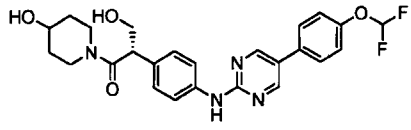
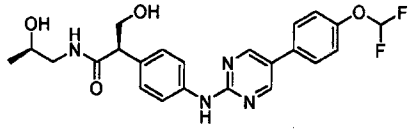
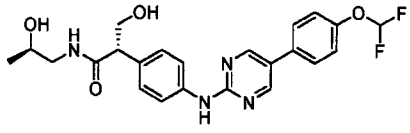
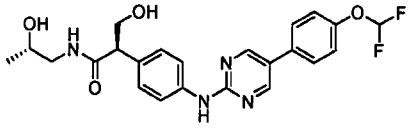
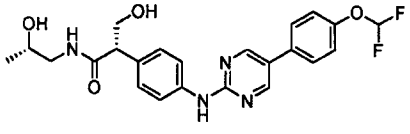
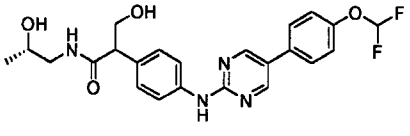
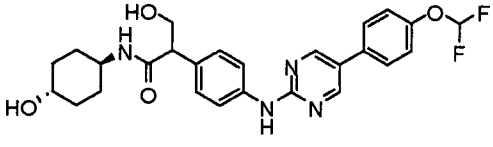
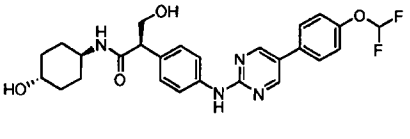
Table 1

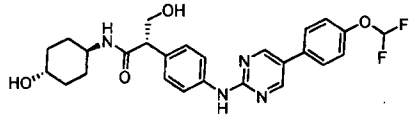
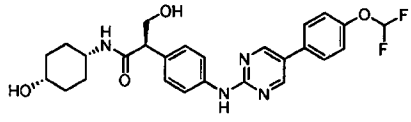
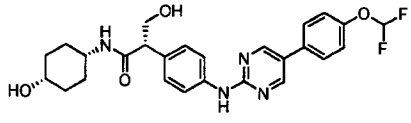
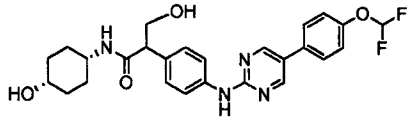
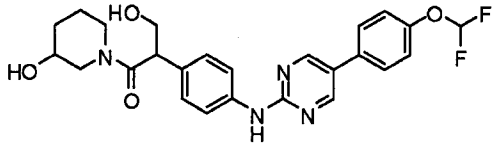
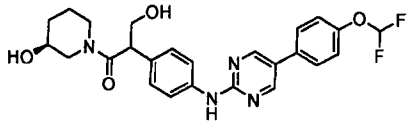
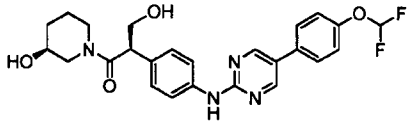
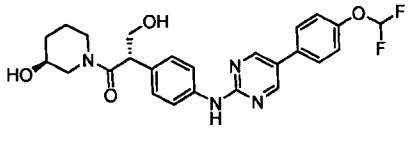
Example No.	Structure	MS $[M+1]^+$
A1		447.2
A2		429.2

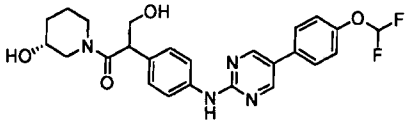
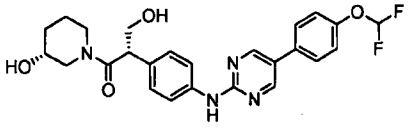
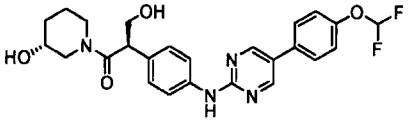
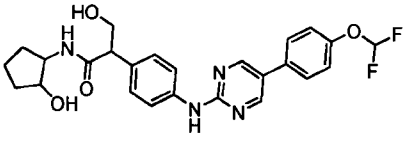
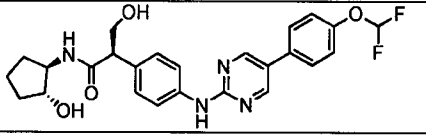
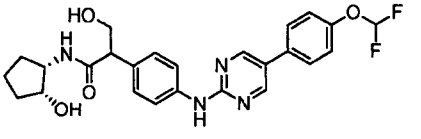
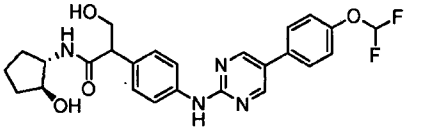
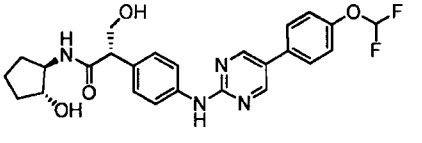
Example No.	Structure	MS $[M+1]^+$
A3		485.2
A4		455.2
A5		473.2
A6		469.2
B1		468.2
B2		452.2

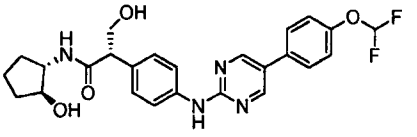
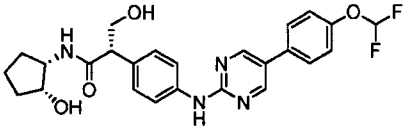
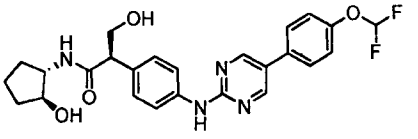
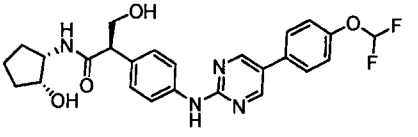
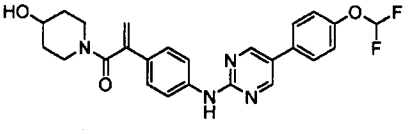
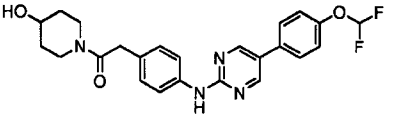
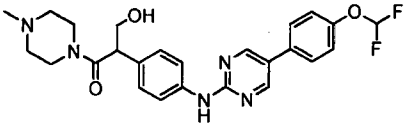
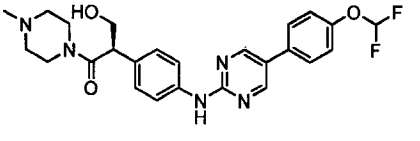
Example No.	Structure	MS $[M+1]^+$
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B4		454.2
B5		468.2
B6		466.1
B7		437.2

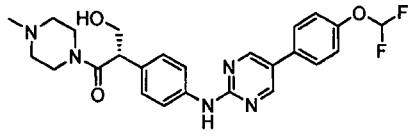
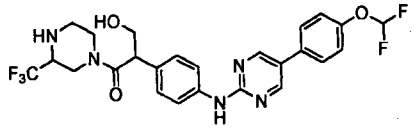
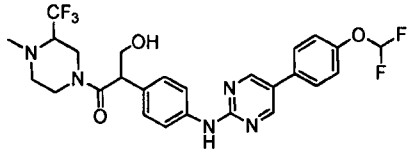
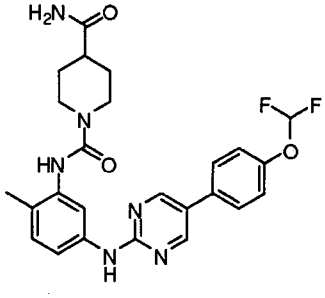
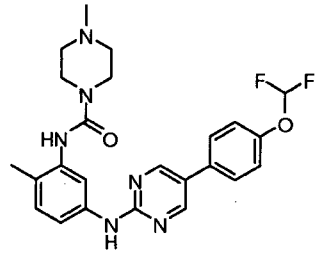
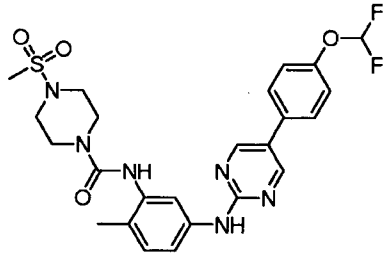
Example No.	Structure	MS $[M+1]^+$
B8		472.2
B9		494.1
B10		496.2
C1		447.2
C2		485.2
C3		485.1

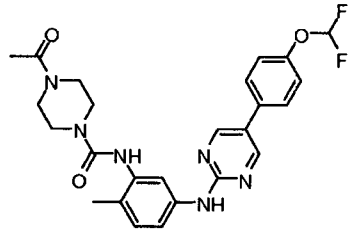
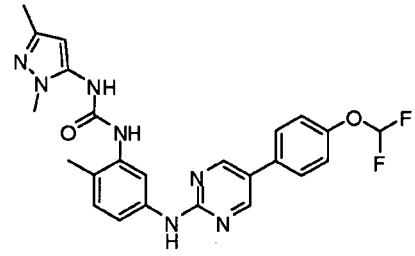
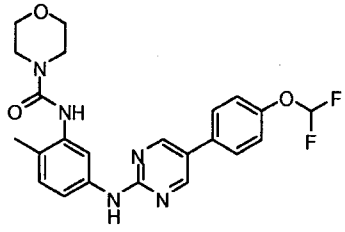
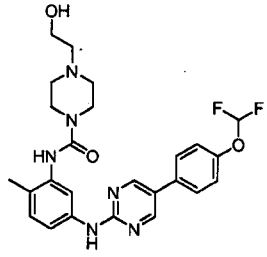
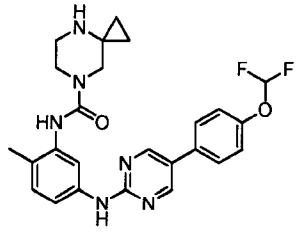
Example No.	Structure	MS $[M+1]^+$
C4		485.1
C5		459.1
C6		459.1
C7		459.1
C8		459.1
C9		459.2
C10		499.2
C11		499.1

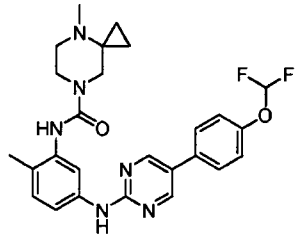
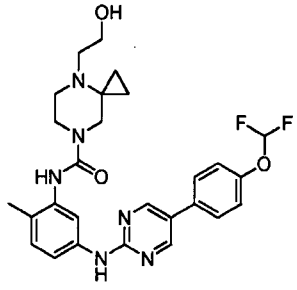
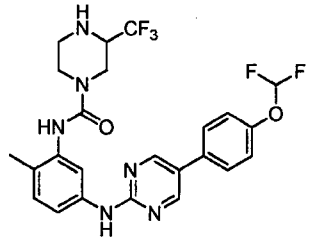
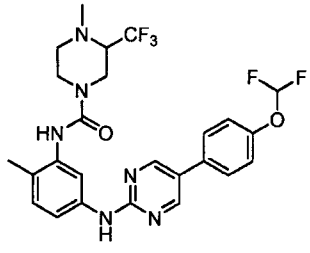
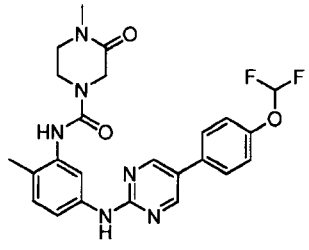
Example No.	Structure	MS $[M+1]^+$
C12		499.2
C13		499.1
C14		499.2
C15		499.2
C16		485.2
C17		485.2
C18		485.1
C19		485.1

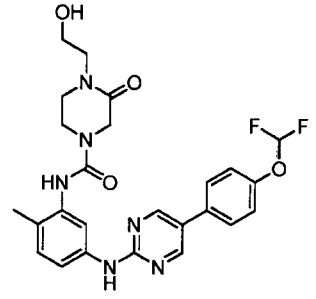
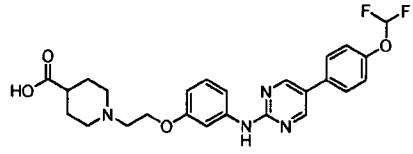
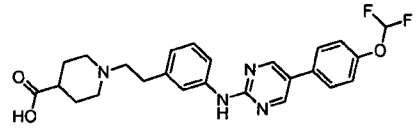
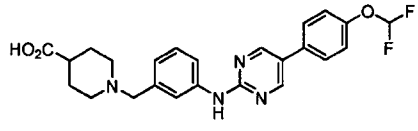
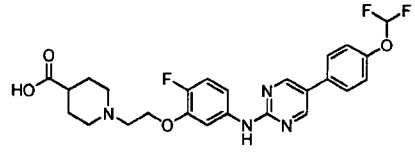
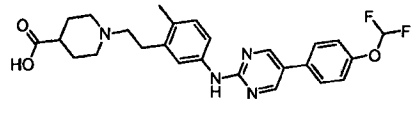
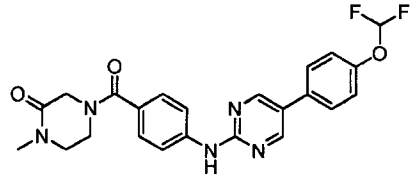
Example No.	Structure	MS $[M+1]^+$
C20		485.2
C21		485.1
C22		485.2
C23		485.2
C24		485.1
C25		485.2
C26		485.2
C27		485.1

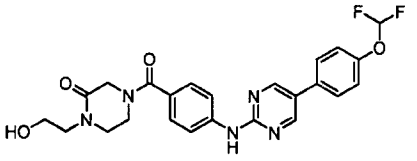
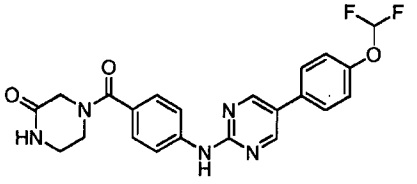
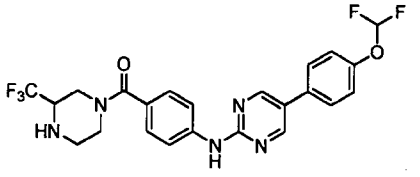
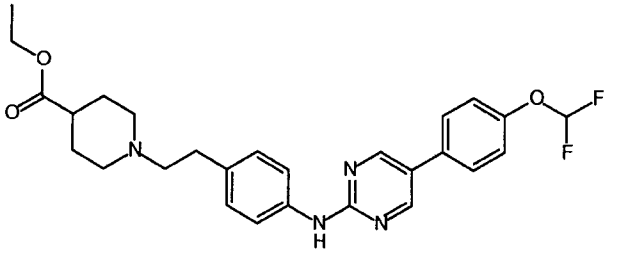
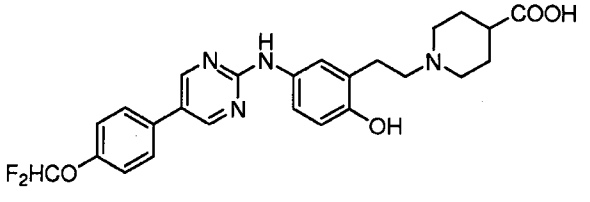
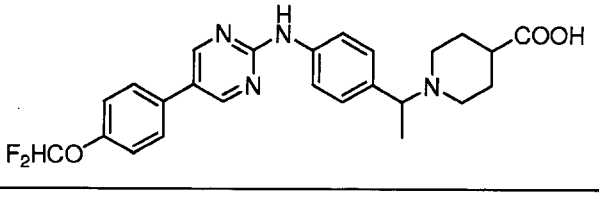
Example No.	Structure	MS $[M+1]^+$
C28		485.1
C29		485.2
C30		485.1
C31		485.2
C32		467.2
C33		455.1
C34		484.4
C35		484.1

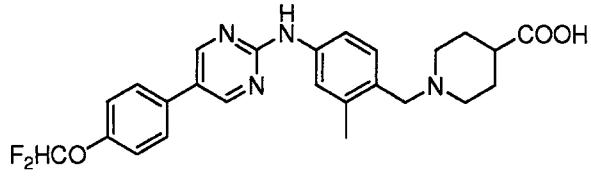
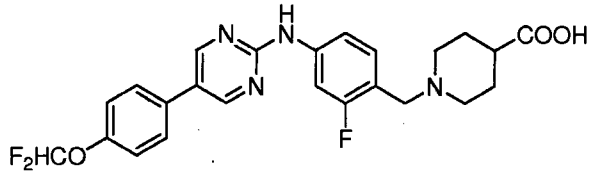
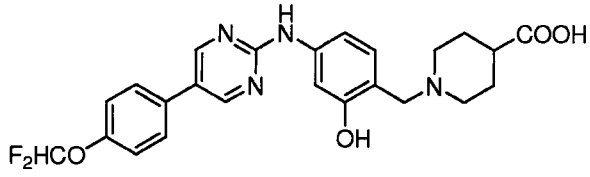
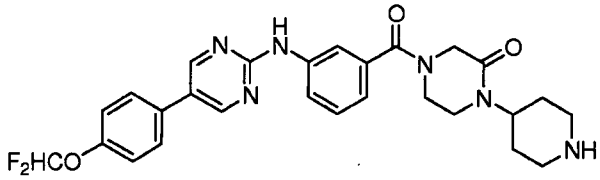
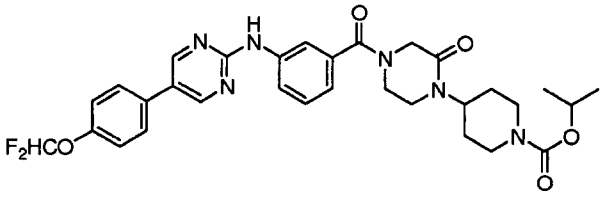
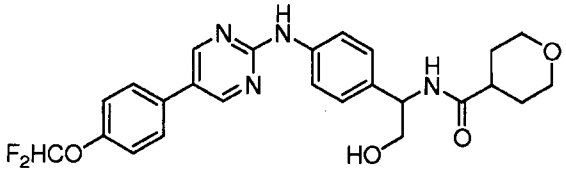
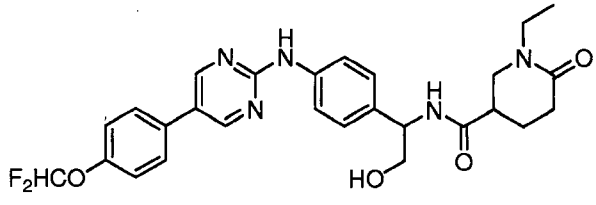
Example No.	Structure	MS $[M+1]^+$
C36		484.2
C37		538.1
C38		552.1
D1		497.2
D2		469.2
D3		533.2

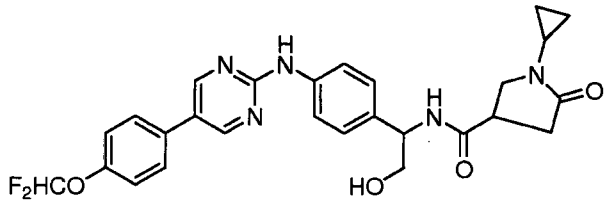
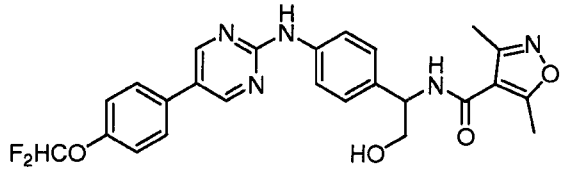
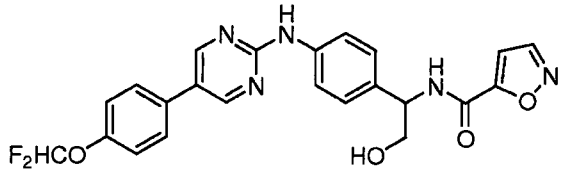
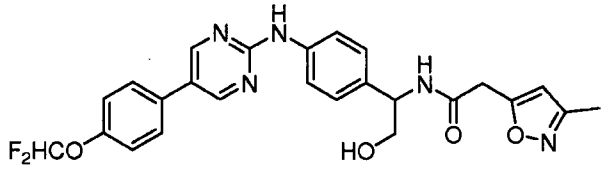
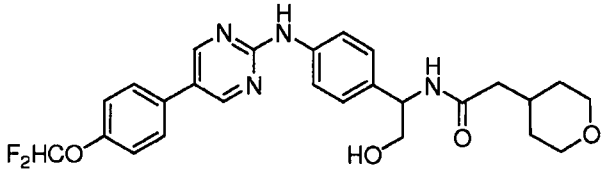
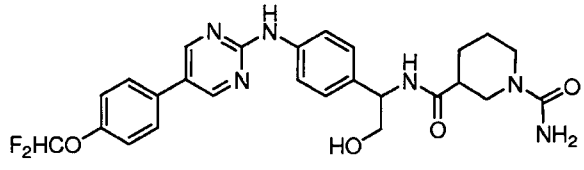
Example No.	Structure	MS $[M+1]^+$
D4		497.2
D5		480.2
D6		456.2
D7		499.2
D8		481.2

Example No.	Structure	MS $[M+1]^+$
D9		495.2
D10		524.56
D11		522.47
D12		536.50
D13		483.2

Example No.	Structure	MS $[M+1]^+$
D14		513.1
E1		485.2
E2		469.2
E3		455.1
F1		503.2
F2		483.2
G1		454.2

Example No.	Structure	MS $[M+1]^+$
G2		485.2
G3		439.4
G4		495.1
		
		
		

Example No.	Structure	MS $[M+1]^+$
		
		
		
		
		
		
		

Example No.	Structure	MS $[M+1]^+$
		
		
		
		
		
		

Assays

[0256] Compounds of the present invention are assayed to measure their capacity to selectively inhibit the proliferation of wild type Ba/F3 cells and Ba/F3 cells transformed with Tel c-kit kinase and Tel PDGFR fused tyrosine kinases. In addition, compounds of the

invention may selectively inhibit SCF dependent proliferation in Mo7e cells. Further, compounds are assayed to measure their capacity to inhibit Abl, ARG, BCR-Abl, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 and TrkB kinases.

Proliferation Assay : BaF3 Library –Bright glo Readout Protocol

[0257] Compounds are tested for their ability to inhibit the proliferation of wt Ba/F3 cells and Ba/F3 cells transformed with Tel fused tyrosine kinases. Untransformed Ba/F3 cells are maintained in media containing recombinant IL3. Cells are plated into 384 well TC plates at 5,000 cells in 50ul media per well and test compound at 0.06 nM to 10 μM is added. The cells are then incubated for 48 hours at 37 °C, 5% CO_2. After incubating the cells, 25 μL of BRIGHT GLO® (Promega) is added to each well following manufacturer's instructions and the plates are read using Analyst GT – Luminescence mode – 50000 integration time in RLU. IC_{50} values are determined from a dose response curve.

Mo7e Assay

[0258] The compounds described herein are tested for inhibition of SCF dependent proliferation using Mo7e cells which endogenously express c-kit in a 96 well format. Two-fold serially diluted test compounds (Cmax=10μM) are evaluated for their antiproliferative activity of Mo7e cells stimulated with human recombinant SCF. After 48 hours of incubation at 37 °C, cell viability is measured by using a MTT colorimetric assay from Promega.

c-kit HTRF protocol

[0259] An aliquot (5 μL) of a 2x concentration of c-kit enzyme mix 25 ng c-kit (5 ng/μL) and 2 μM of Biotin-EEEPQYEEIPIYLELLP-NH_2 peptide in kinase buffer (20 mM Tris pH 7.5, 10 mM $MgCl_2$, 0.01% BSA, 0.1 % Brij35, 1 mM DTT, 5% glycerol, 0.05 mM Na_3VO_4) is added to each well of a 384 proxiplate (Packard). Each well of the last row of the proxiplate has 5 μL of c-kit enzyme mix without c-kit to ascertain the background level. Compounds of the invention are added to each well and the plates are incubated for 30 minutes at room temperature. 2x ATP (40μM) in kinase buffer (5μL) is added to each well and the plate is incubated at room temperature form 3 hours. Detection mix (50% KF, 40% kinase buffer, 10% EDTA, 1:100 diluted Mab PT66-K (cat# 61T66KLB) and 1:100 diluted Streptavidin-XL (cat#

121

611SAXLB)0 (10μL) is added to each well and the plates are further incubated for 1 to 2 hours at room temperature. The HTRF signal is then read on a detector.

Human TG-HA-VSMC proliferation assay

[0260] Human TG-HA-VSMC cells (ATCC) are grown in DMEM supplemented with 10% FBS to 80-90% confluence prior to resuspending in DMEM supplemented with 1% FBS and 30 ng/mL recombinant human PDGF-BB at 6e4 cells/mL. Cells are then aliquoted into 384 well plates at 50uL/well, incubated for 20 h at 37 °C, then treated with 0.5 μL of 100x compounds for 48 h at 37 °C. After the treatment, 25 μL of CellTiter-Glo is added to each well for 15 min, then the plates are read on the CLIPR (Molecular Devices).

PDGFRα/β Lance Assay protocol

[0261] An aliquot (2.5 μL) of a 2x concentration of PDGFRβ peptide and ATP mix (4 μM biotin-βA-βA-βA-AEEEEYVFIEAKKK peptide, 20 μM ATP in assay buffer (20 mM Hepes, 54 mM $MgCl_2$, 0.01% BSA, 0.05% Tween-20, 1 mM DTT, 10% glycerol, 50 μM Na_3VO_4)) is added to each well of a 384 proxiplate (Packard). The plates are centrifuged and compounds of the invention (50 nL) are added to each well via a pintool dispenser. To each well is added (2.5 μL) of a 2x concentration of enzyme mix (PDGFRα at 4.5 ng/μL (cat# PV4117) or PDGFRβ at 1.5 ng/μL (cat# PV3591) in assay buffer) or assay buffer alone without PDGFRα/β enzyme. The plates are incubated for 1.5 hours at room temperature. Detection mix (5μL; 50% 1M KF, 40% kinase buffer, 10% EDTA, 1:100 diluted Mab PT66-K (cat# 61T66KLB) and 1:100 diluted Streptavidin-XL (cat# 611SAXLB) is added to each well and the proxiplate is incubated for 1 hour at room temperature before reading the HTRF signal on a detector.

Ba/F3 FL FLT3 proliferation assay

[0262] The murine cell line used is the Ba/F3 murine pro-B cell line that over expresses full length FLT3 construct. These cells are maintained in RPMI 1640/10% fetal bovine serum (RPMI/FBS) supplemented with penicillin 50 μg/mL, streptomycin 50 μg/mL and L-glutamine 200 mM with the addition of murine recombinant IL3. Ba/F3 full length FLT3 cells undergo IL3 starvation for 16 hours and then plated into 384 well TC plates at 5,000 cells in 25uL media per well and test compound at 0.06 nM to 10 μM is added. After the compound addition FLT3 ligand or IL3 for cytotoxicity control are added in 25ul media per well at the appropiate

concentations. The cells are then incubated for 48 hours at 37 °C, 5% CO_2. After incubating the cells, 25 µL of BRIGHT GLO® (Promega) is added to each well following manufacturer's instructions and the plates are read using Analyst GT – Luminescence mode – 50000 integration time in RLU.

Inhibition of cellular BCR-Abl dependent proliferation (High Throughput method)

[0263] The murine cell line used is the 32D hemopoietic progenitor cell line transformed with BCR-Abl cDNA (32D-p210). These cells are maintained in RPMI/10% fetal calf serum (RPMI/FCS) supplemented with penicillin 50 µg/mL, streptomycin 50 µg/mL and L-glutamine 200 mM. Untransformed 32D cells are similarly maintained with the addition of 15% of WEHI conditioned medium as a source of IL3.

[0264] 50 µL of a 32D or 32D-p210 cells suspension are plated in Greiner 384 well microplates (black) at a density of 5000 cells per well. 50nL of test compound (1 mM in DMSO stock solution) is added to each well (STI571 is included as a positive control). The cells are incubated for 72 hours at 37 °C, 5% CO_2. 10 µL of a 60% Alamar Blue solution (Tek diagnostics) is added to each well and the cells are incubated for an additional 24 hours. The fluorescence intensity (Excitation at 530 nm, Emission at 580 nm) is quantified using the Acquest™ system (Molecular Devices).

Inhibition of cellular BCR-Abl dependent proliferation

[0265] 32D-p210 cells are plated into 96 well TC plates at a density of 15,000 cells per well. 50 µL of two fold serial dilutions of the test compound (C_{max} is 40 µM) are added to each well (STI571 is included as a positive control). After incubating the cells for 48 hours at 37 °C, 5% CO_2, 15 µL of MTT (Promega) is added to each well and the cells are incubated for an additional 5 hours. The optical density at 570 nm is quantified spectrophotometrically and IC_{50} values are determined from a dose response curve.

Effect on cell cycle distribution

[0266] 32D and 32D-p210 cells are plated into 6 well TC plates at $2.5x10^6$ cells per well in 5 mL of medium and a test compound at 1 or 10 µM is added (STI571 is included as a control). The cells are then incubated for 24 or 48 hours at 37 °C, 5% CO_2. 2 mL of cell suspension is washed with PBS, fixed in 70% EtOH for 1 hour and treated with PBS/EDTA/RNase A for 30

minutes. Propidium iodide (Cf= 10 μg/ml) is added and the fluorescence intensity is quantified by flow cytometry on the FACScalibur™ system (BD Biosciences). Test compounds of the present invention demonstrate an apoptotic effect on the 32D-p210 cells but do not induce apoptosis in the 32D parental cells.

Effect on Cellular BCR-Abl Autophosphorylation

[0267] BCR-Abl autophosphorylation is quantified with capture ELISA using a c-abl specific capture antibody and an antiphosphotyrosine antibody. 32D-p210 cells are plated in 96 well TC plates at $2x10^5$ cells per well in 50 μL of medium. 50 μL of two fold serial dilutions of test compounds (C_{max} is 10 μM) are added to each well (STI571 is included as a positive control). The cells are incubated for 90 minutes at 37 °C, 5% CO_2. The cells are then treated for 1 hour on ice with 150 μL of lysis buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 5 mM EDTA, 1 mM EGTA and 1% NP-40) containing protease and phosphatase inhibitors. 50 μL of cell lysate is added to 96 well optiplates previously coated with anti-abl specific antibody and blocked. The plates are incubated for 4 hours at 4 °C. After washing with TBS-Tween 20 buffer, 50 μL of alkaline-phosphatase conjugated anti-phosphotyrosine antibody is added and the plate is further incubated overnight at 4 °C. After washing with TBS-Tween 20 buffer, 90 μL of a luminescent substrate are added and the luminescence is quantified using the Acquest™ system (Molecular Devices). Test compounds of the invention that inhibit the proliferation of the BCR-Abl expressing cells, inhibit the cellular BCR-Abl autophosphorylation in a dose-dependent manner.

Effect on proliferation of cells expressing mutant forms of Bcr-abl

[0268] Compounds of the invention are tested for their antiproliferative effect on Ba/F3 cells expressing either wild type or the mutant forms of BCR-Abl (G250E, E255V, T315I, F317L, M351T) that confers resistance or diminished sensitivity to STI571. The antiproliferative effect of these compounds on the mutant-BCR-Abl expressing cells and on the non transformed cells are tested at 10, 3.3, 1.1 and 0.37 μM as described above (in media lacking IL3). The IC_{50} values of the compounds lacking toxicity on the untransformed cells are determined from the dose response curves obtained as describe above.

FGFR3 (Enzymatic Assay)

[0269] Kinase activity assay with purified FGFR3 (Upstate) is carried out in a final volume of 10 μL containing 0.25 μg/mL of enzyme in kinase buffer (30 mM Tris-HCl pH 7.5, 15 mM $MgCl_2$, 4.5 mM $MnCl_2$, 15 μM Na_3VO_4 and 50 μg/mL BSA), and substrates (5 μg/mL biotin-poly-EY(Glu, Tyr) (CIS-US, Inc.) and 3μM ATP). Two solutions are made: the first solution of 5 μL containing the FGFR3 enzyme in kinase buffer is first dispensed into 384- format ProxiPlate® (Perkin-Elmer) followed by adding 50 nL of compounds dissolved in DMSO. A 5 μL of second solution containing the substrate (poly-EY) and ATP in kinase buffer is then added to each wells. The reactions are incubated at room temperature for one hour, stopped by adding 10 μL of HTRF detection mixture, which contains 30 mM Tris-HCl pH7.5, 0.5 M KF, 50 mM ETDA, 0.2 mg/mL BSA, 15 μg/mL streptavidin-XL665 (CIS-US, Inc.) and 150 ng/mL cryptate conjugated anti-phosphotyrosine antibody (CIS-US, Inc.). After one hour of room temperature incubation to allow for streptavidin-biotin interaction, time resolved florescent signals are read on Analyst GT (Molecular Devices Corp.). IC_{50} values are calculated by linear regression analysis of the percentage inhibition of each compound at 12 concentrations (1:3 dilution from 50 μM to 0.28 nM). In this assay, compounds of the invention have an IC_{50} in the range of 10 nM to 2 μM.

FGFR3 (Cellular Assay)

[0270] Compounds of the invention are tested for their ability to inhibit transformed Ba/F3-TEL-FGFR3 cells proliferation, which is depended on FGFR3 cellular kinase activity. Ba/F3-TEL-FGFR3 are cultured up to 800,000 cells/mL in suspension, with RPMI 1640 supplemented with 10% fetal bovine serum as the culture medium. Cells are dispensed into 384-well format plate at 5000 cell/well in 50 μL culture medium. Compounds of the invention are dissolved and diluted in dimethylsufoxide (DMSO). Twelve points 1:3 serial dilutions are made into DMSO to create concentrations gradient ranging typically from 10 mM to 0.05 μM. Cells are added with 50 nL of diluted compounds and incubated for 48 hours in cell culture incubator. AlamarBlue® (TREK Diagnostic Systems), which can be used to monitor the reducing environment created by proliferating cells, are added to cells at final concentration of 10%. After an additional four hours of incubation in a 37 °C cell culture incubator, fluorescence signals from reduced AlamarBlue® (Excitation at 530 nm, Emission at 580 nm) are quantified

on Analyst GT (Molecular Devices Corp.). IC_{50} values are calculated by linear regression analysis of the percentage inhibition of each compound at 12 concentrations.

b-Raf – enzymatic assay

[0271] Compounds of the invention are tested for their ability to inhibit the activity of b-Raf. The assay is carried out in 384-well MaxiSorp plates (NUNC) with black walls and clear bottom. The substrate, IκBα is diluted in DPBS (1:750) and 15μL is added to each well. The plates are incubated at 4 °C overnight and washed 3 times with TBST (25 mM Tris, pH 8.0, 150 mM NaCl and 0.05% Tween-20) using the EMBLA plate washer. Plates are blocked by Superblock (15μL/well) for 3 hours at room temperature, washed 3 times with TBST and pat-dried. Assay buffer containing 20μM ATP (10μL) is added to each well followed by 100nL or 500nL of compound. B-Raf is diluted in the assay buffer (1μL into 25μL) and 10μL of diluted b-Raf is added to each well (0.4μg/well). The plates are incubated at room temperature for 2.5 hours. The kinase reaction is stopped by washing the plates 6 times with TBST. Phosph-IκBα (Ser32/36) antibody is diluted in Superblock (1:10,000) and 15μL is added to each well. The plates are incubated at 4 °C overnight and washed 6 times with TBST. AP-conjugated goat-anti-mouse IgG is diluted in Superblock (1:1,500) and 15μL is added to each well. Plates are incubated at room temperature for 1 hour and washed 6 times with TBST. 15μL of fluorescent Attophos AP substrate (Promega) is added to each well and plates are incubated at room temperature for 15 minutes. Plates are read on Acquest or Analyst GT using a Fluorescence Intensity Program (Excitation 455 nm, Emission 580 nm).

b-Raf – cellular assay

[0272] Compounds of the invention are tested in A375 cells for their ability to inhibit phosphorylation of MEK. A375 cell line (ATCC) is derived from a human melanoma patient and it has a V599E mutation on the B-Raf gene. The levels of phosphorylated MEK are elevated due to the mutation of B-Raf. Sub-confluent to confluent A375 cells are incubated with compounds for 2 hours at 37 °C in serum free medium. Cells are then washed once with cold PBS and lysed with the lysis buffer containing 1% Triton X100. After centrifugation, the supernatants are subjected to SDS-PAGE, and then transferred to nitrocellulose membranes. The membranes are then subjected to western blotting with anti-phospho-MEK antibody

(ser217/221) (Cell Signaling). The amount of phosphorylated MEK is monitored by the density of phospho-MEK bands on the nitrocellulose membranes.

Upstate KinaseProfiler™ – Radio-enzymatic filter binding assay

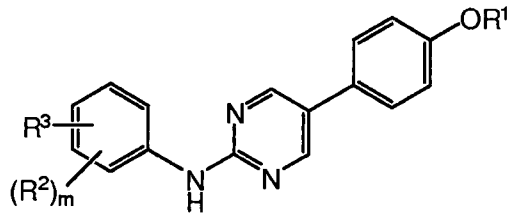
[0273] Compounds of the invention are assessed for their ability to inhibit individual members of the kinase panel. The compounds are tested in duplicates at a final concentration of 10 μM following this generic protocol. Kinase buffer (2.5μL, 10x - containing $MnCl_2$ when required), active kinase (0.001-0.01 Units; 2.5μL), specific or Poly(Glu4-Tyr) peptide (5-500μM or .01mg/ml) in kinase buffer and kinase buffer (50μM; 5μL) are mixed in an eppendorf on ice. A Mg/ATP mix (10μL; 67.5 (or 33.75) mM $MgCl_2$, 450 (or 225) μM ATP and 1 μCi/μl [γ-^{32}P]-ATP (3000Ci/mmol)) is added and the reaction is incubated at about 30°C for about 10 minutes. The reaction mixture is spotted (20μL) onto a 2cm x 2cm P81 (phosphocellulose, for positively charged peptide substrates) or Whatman No. 1 (for Poly (Glu4-Tyr) peptide substrate) paper square. The assay squares are washed 4 times, for 5 minutes each, with 0.75% phosphoric acid and washed once with acetone for 5 minutes. The assay squares are transferred to a scintillation vial, 5 ml scintillation cocktail are added and ^{32}P incorporation (cpm) to the peptide substrate is quantified with a Beckman scintillation counter. Percentage inhibition is calculated for each reaction.

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[0274] 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):

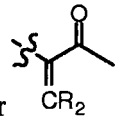


(1)

or a pharmaceutically acceptable salt thereof;

R^1 is a haloalkyl having 1-6 fluorine atoms;

R^2 is 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; halo, cyano, nitro, $(CR_2)_kOR^7$, $(CR_2)_kO(CR_2)_{1-4}R^7$, $(CR_2)_kSR^7$, $(CR_2)_kNR^9R^{10}$, $(CR_2)_kC(O)O_{0-1}R^7$, $OC(O)R^7$, $(CR_2)_kC(S)R^7$, $(CR_2)_kC(O)NR^9R^{10}$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^9R^{10}$, $(CR_2)_kS(O)_{1-2}R^8$, $(CR_2)_kNRS(O)_{1-2}R^8$ or $(CR_2)_kR^6$; or any two adjacent R^2 groups together may form an optionally substituted 5-8 membered carbocyclic, heterocyclic, aryl or heteroaryl ring;

R^3 is -L-NR^4R^5, -X-NR-C(O)R^8 or -X-NR-C(O)NR^4R^5 wherein L is –X-C(O), -X-OC(O), -$(CR_2)_j$, -$SO_{0-2}(CR_2)_j$, -$O(CR_2)_{1-4}$, or  ; and X is $(CR_2)_j$ or [C(R)(CR_2OR)];

R^4, R^5, R^9 and R^{10} are independently 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, alkoxy, cyano, carboxyl or R^6; $(CR_2)_kCN$, $(CR_2)_{1-6}NR^7R^7$, $(CR_2)_{1-6}OR^7$, $(CR_2)_kC(O)O_{0-1}R^7$, $(CR_2)_kC(O)NR^7R^7$ or $(CR_2)_k$-R^6;

R^6 is an optionally substituted C_{3-7} cycloalkyl, C_{6-10} aryl, or a 5-10 membered heteroaryl or 5-7 membered heterocyclic ring;

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

alternatively, R^4 and R^5 together with N in each NR^4R^5, R^7 and R^7 together with N in NR^7R^7 or R^9 and R^{10} together with N in NR^9R^{10} may form a 4-7 membered heterocyclic ring optionally substituted with 1-3 R^{11} groups;

R^{11} is R^8, $(CR_2)_k$–OR^7, CO_2R^7, $(CR_2)_k$–C(O)-$(CR_2)_k$-R^8, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ or $(CR_2)_kNRS(O)_{1-2}R^8$;

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

each k is 0-6; and

j and m are independently 0-4;

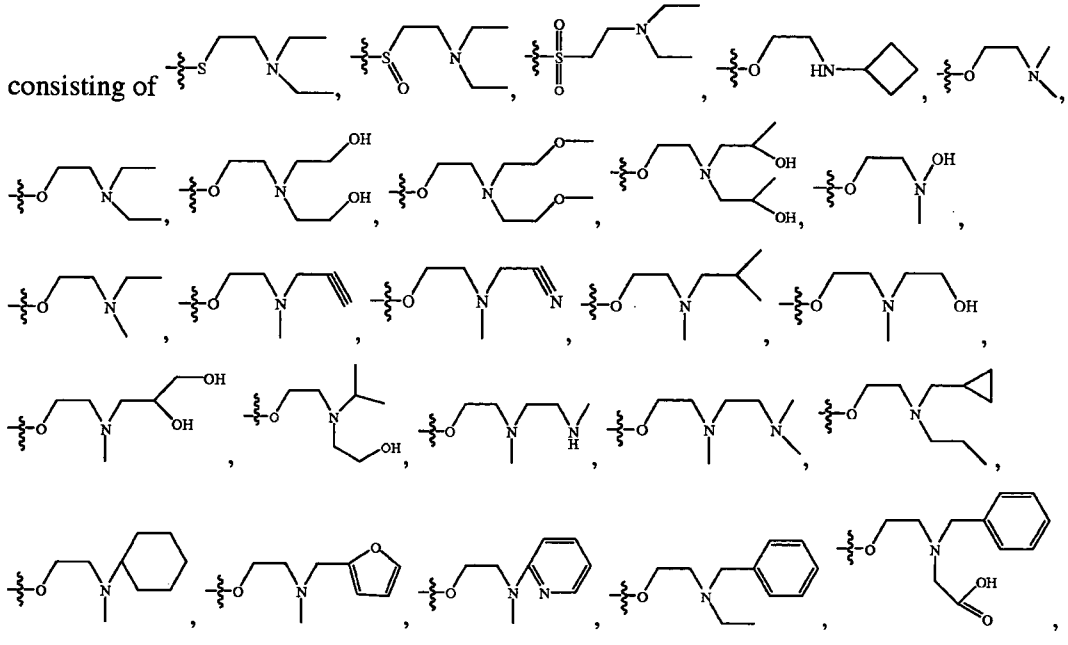
provided R^1 is not trifluoromethoxy when R^3 is $C(O)NH_2$, $C(O)NR^{12}R^{13}$ or $SO_2NH(CH_2)_{2-3}NR^{14}R^{15}$; wherein R^{12} and R^{13} together form piperazinyl and R^{14} and R^{15} together form morpholinyl.

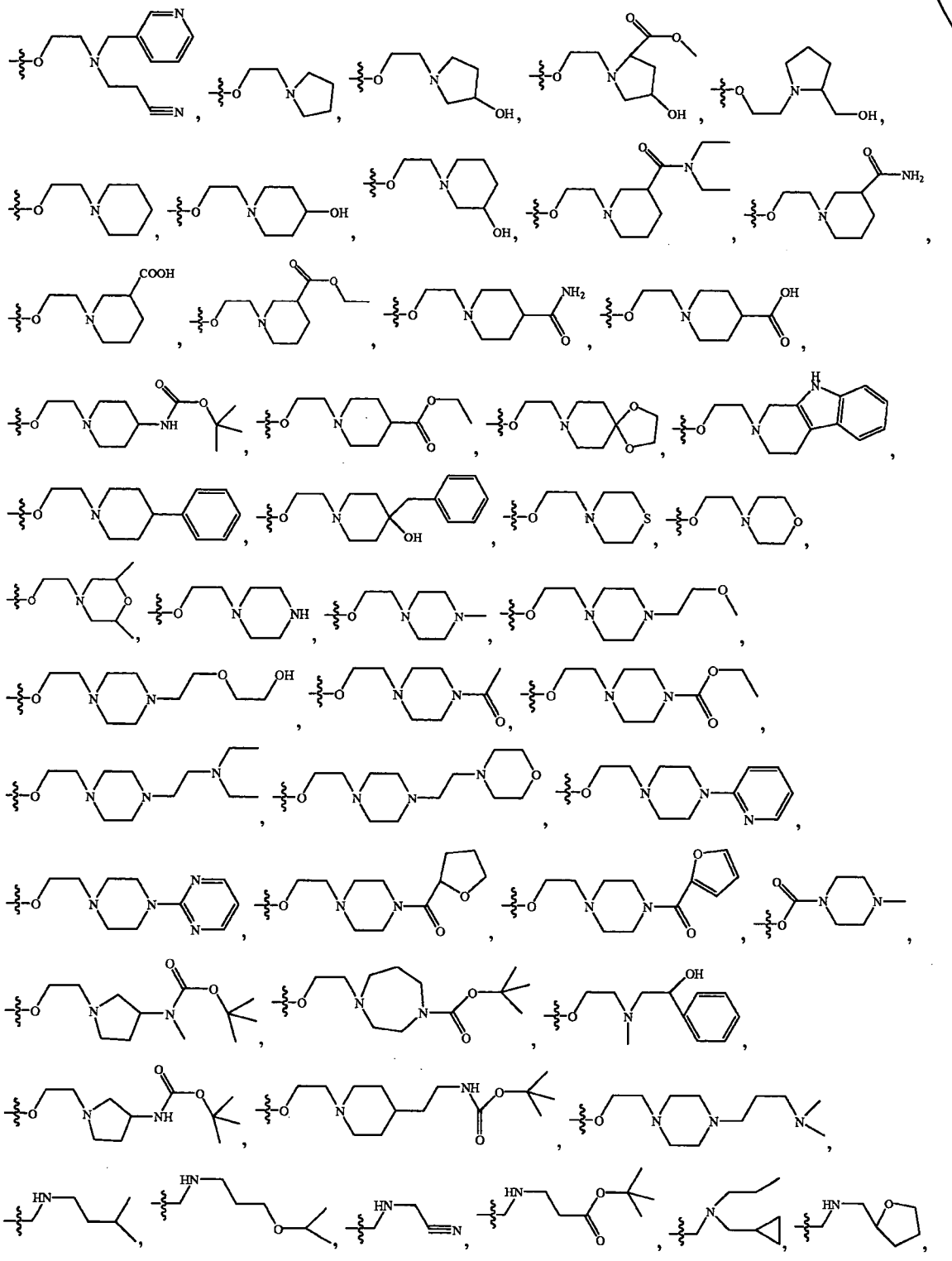
2. The compound of claim 1, wherein R^1 is $OCHF_2$, OCF_3, OCH_2CF_3, OCF_2CH_3 or OCH_2CF_3.

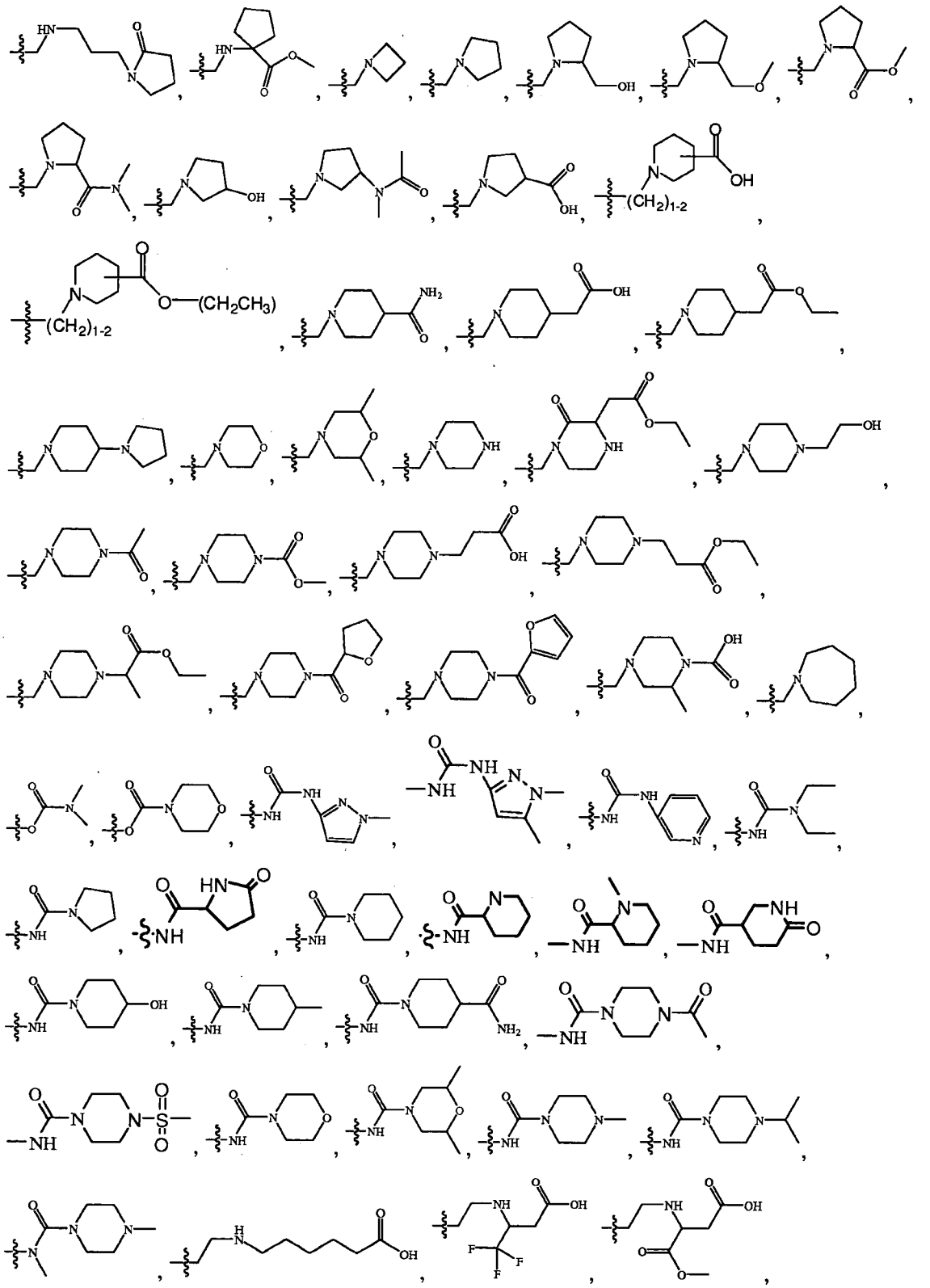
3. The compound of claim 2, wherein R^1 is $OCHF_2$.

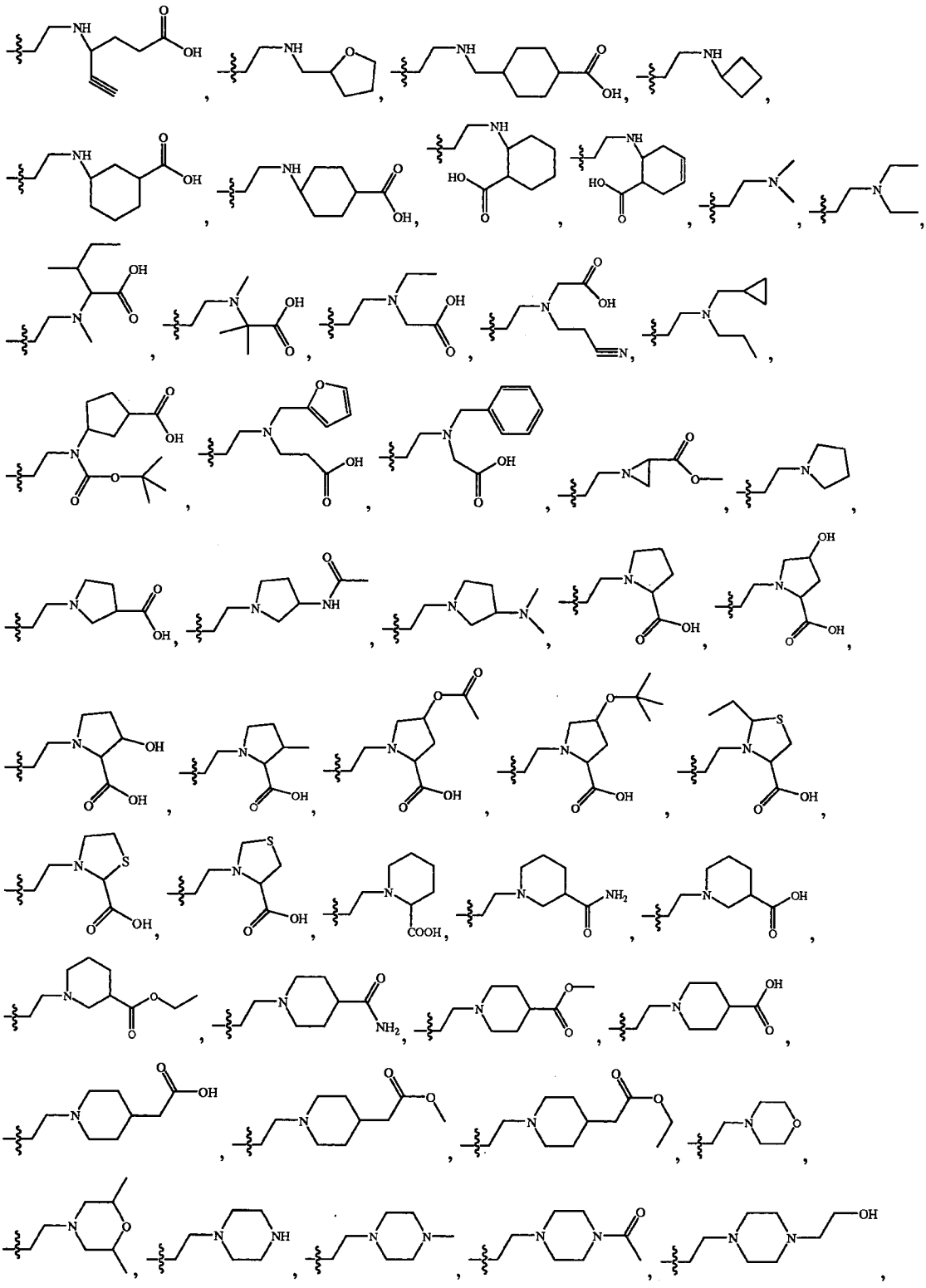
4. The compound of any one of claims 1-3, wherein R^2 if present, is halo, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or CO_2R^7 and R^7 is H or C_{1-6} alkyl.

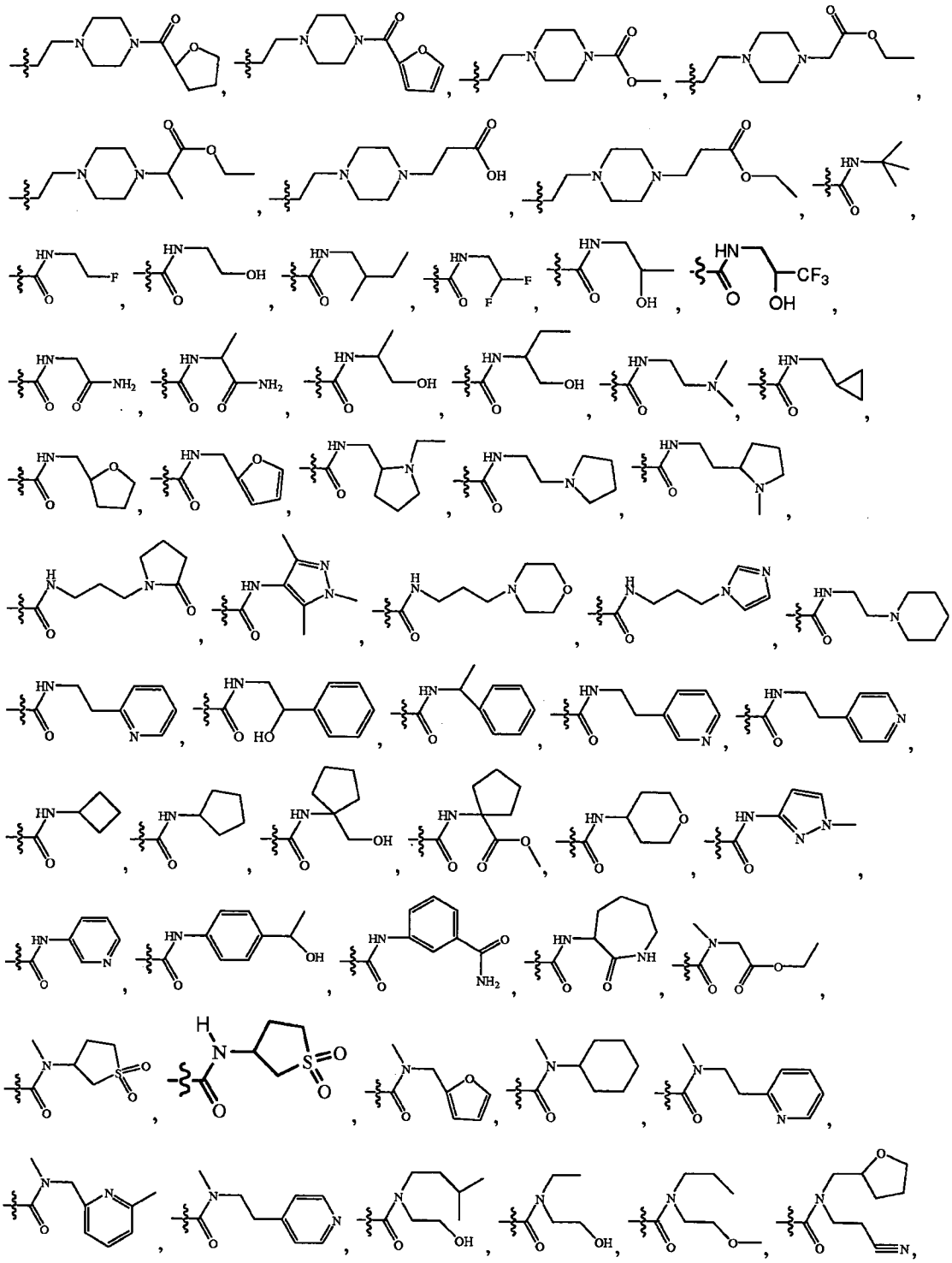
5. The compound of any one of claims 1-4, wherein R^3 is selected from the group consisting of

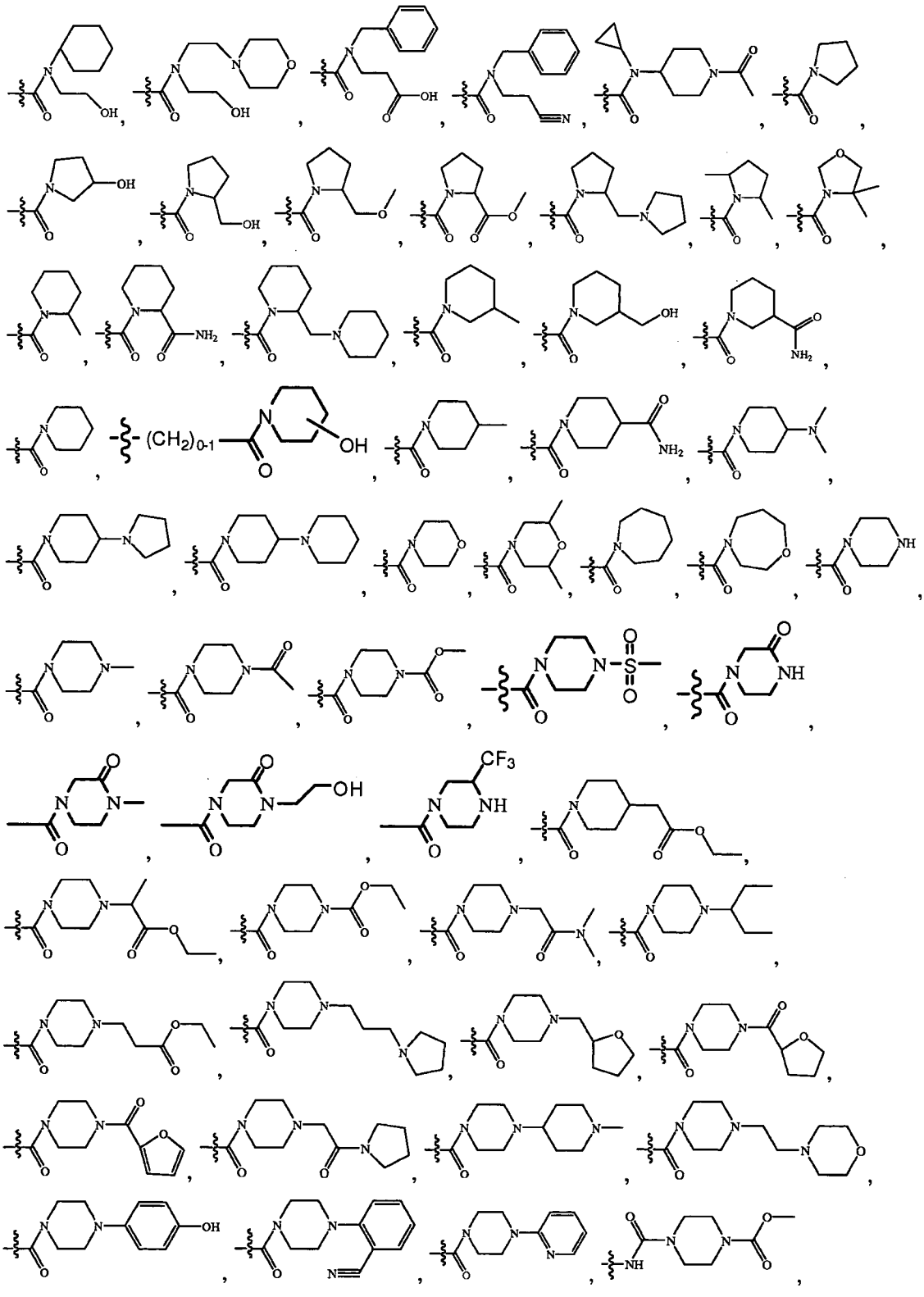


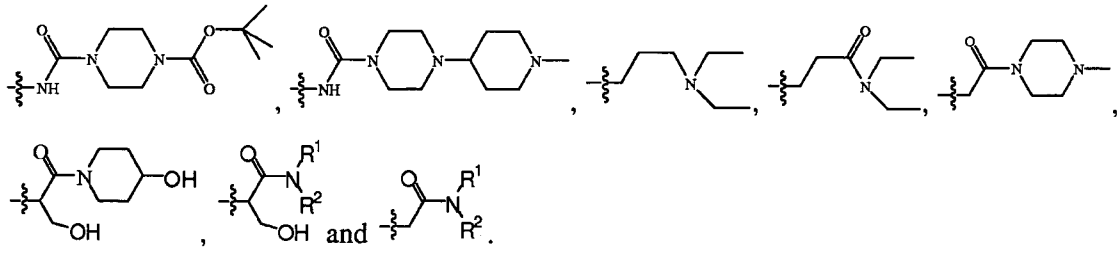




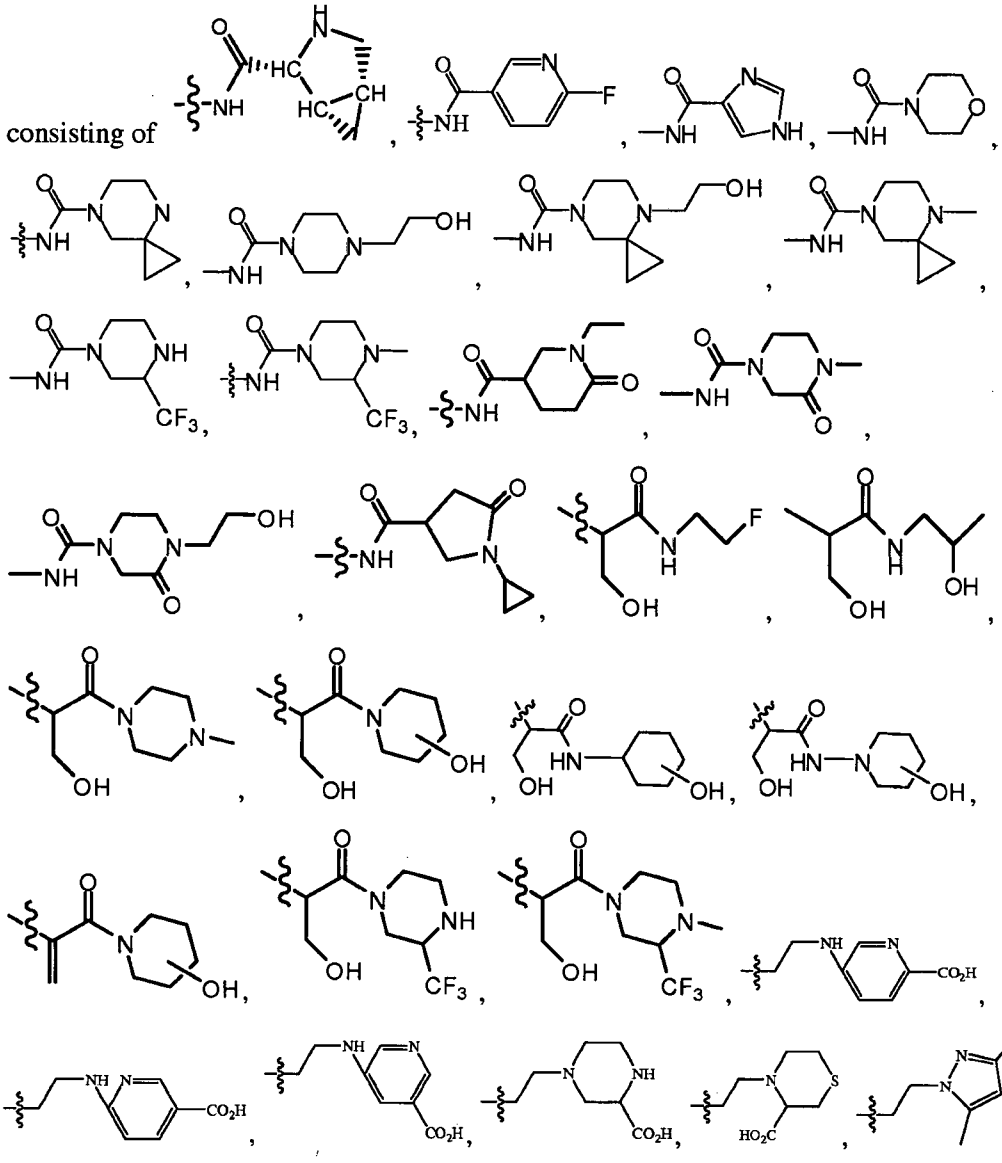


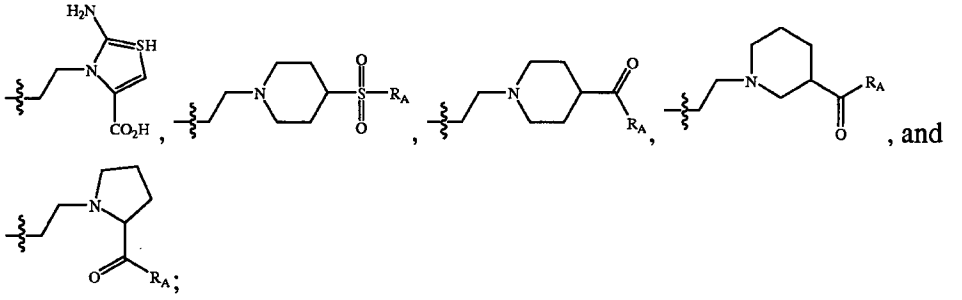






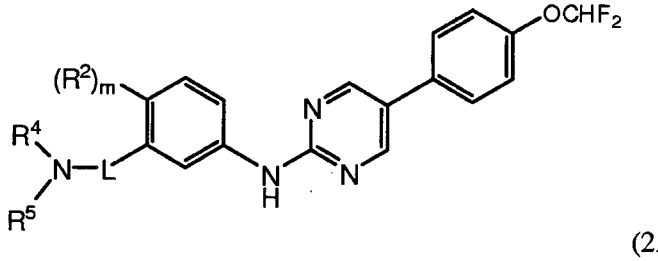
6. The compound of any one of claims 1-4, wherein R^3 is selected from the group consisting of



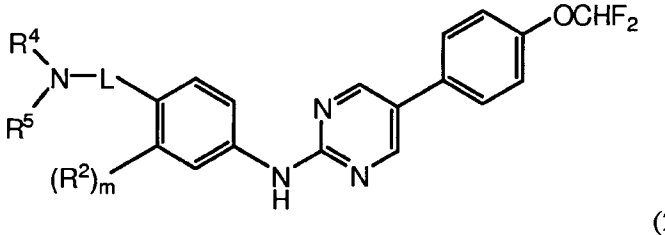


wherein R_A is $-NH_2$, $-NEt_2$ or $-NH(CH_2)_{1-6}OH$.

7. The compound of claim 1, wherein said compound is of Formula (2A) or (2B):



(2A)



(2B);

wherein R^4 and R^5 together with N form a 5-6 membered heterocyclic ring optionally containing NR^{16}, O, S, =O or a double bond; wherein said heterocyclic ring is optionally substituted with 1-2 R^{11} groups;

R^{11} is R^8, $(CR_2)_kOR^7$, CO_2R^7, $(CR_2)_k$–C(O)-$(CR_2)_k$-R^8, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ or $(CR_2)_kNRS(O)_{1-2}R^8$;

R^{16} is H, R^8, $-(CR_2)_{1-4}CO_2R^7$, $(CR_2)_k$–C(O)-$(CR_2)_k$-R^8, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_{1-4}NRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ or $(CR_2)_kNRS(O)_{1-2}R^8$;

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

R^6 is an optionally substituted C_{3-7} cycloalkyl, C_6 aryl, or a 5-6 membered heteroaryl or 5-7 membered heterocyclic ring;

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

k is 0-4.

8. The compound of claim 7, wherein R^4 and R^5 together with N form an optionally substituted piperidinyl, piperazinyl or morpholinyl.

9. The compound of claim 7 or 8, wherein L is –X-C(O), -$(CR_2)_{1-4}$ or -$O(CR_2)_{1-4}$;

X is $(CR_2)_{0-1}$ or [C(R)(CR_2OR)]; and

R is H or C_{1-6} alkyl.

10. The compound of claim 9, wherein L is $(CR_2)_{1-2}$.

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

N-(4-(2-(diethylamino)ethoxy)phenyl)-5-(4-(trifluoromethoxy)phenyl) pyrimidin-2-amine;

N-(4-(2-(diethylamino)ethoxy)phenyl)-5-(4-(difluoromethoxy)phenyl) pyrimidin-2-amine;

1-(2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy) ethyl)piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl) piperidine-4-carboxylic acid;

1-(4-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl) piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl) piperidine-4-carboxylic acid;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1-methylpiperidine-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2R,5R)-N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)piperidine-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-5-oxopyrrolidine-2-carboxamide;

(R)-N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-5-oxopyrrolidine-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-6-oxopiperidine-3-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-6-fluoropyridine-3-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1H-imidazole-5-carboxamide;

N-(2-methyl-5-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-5-oxopyrrolidine-2-carboxamide;

(S)-N-(2-methyl-5-(5-(4-(trifluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-5-oxopyrrolidine-2-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1-cyclopropyl-5-oxopyrrolidine-3-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-1-ethyl-6-oxopiperidine-3-carboxamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-N-(2-fluoroethyl)-3-hydroxypropanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-(2-hydroxypropyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((R)-2-hydroxypropyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((R)-2-hydroxypropyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((S)-2-hydroxypropyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((S)-2-hydroxypropyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((S)-2-hydroxypropyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-(4-hydroxycyclohexyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1r,4r)-4-hydroxycyclohexyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1r,4R)-4-hydroxycyclohexyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1r,4R)-4-hydroxycyclohexyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1s,4S)-4-hydroxycyclohexyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1s,4S)-4-hydroxycyclohexyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1s,4s)-4-hydroxycyclohexyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(3-hydroxypiperidin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((S)-3-hydroxypiperidin-1-yl)propan-1-one;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((S)-3-hydroxypiperidin-1-yl)propan-1-one;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((S)-3-hydroxypiperidin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((R)-3-hydroxypiperidin-1-yl)propan-1-one;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((R)-3-hydroxypiperidin-1-yl)propan-1-one;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-((R)-3-hydroxypiperidin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-(2-hydroxycyclopentyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1R,2R)-2-hydroxycyclopentyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2R)-2-hydroxycyclopentyl)propanamide;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2S)-2-hydroxycyclopentyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1R,2R)-2-hydroxycyclopentyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2S)-2-hydroxycyclopentyl)propanamide;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2R)-2-hydroxycyclopentyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2S)-2-hydroxycyclopentyl)propanamide;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-N-((1S,2R)-2-hydroxycyclopentyl)propanamide;

2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(4-hydroxypiperidin-1-yl)prop-2-en-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(4-hydroxypiperidin-1-yl)ethanone;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-methylpiperazin-1-yl)propan-1-one;

(R)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-methylpiperazin-1-yl)propan-1-one;

(S)-2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(4-methylpiperazin-1-yl)propan-1-one;

2-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-3-hydroxy-1-(3-(trifluoromethyl)piperazin-1-yl)propan-1-one;

2-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-1-(3-(trifluoromethyl)-4-methylpiperazin-1-yl)-3-hydroxypropan-1-one;

N1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)piperidine-1,4-dicarboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methylpiperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methanesulfonyl-piperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-acetylpiperazine-1-carboxamide;

1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-(1,3-dimethyl-1H-pyrazol-5-yl)urea;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)morpholine-4-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-(2-hydroxyethyl)piperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4,7-diazaspiro[2.5]octane-7-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-4,7-diazaspiro[2.5]octane-7-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-(2-hydroxyethy)-4,7-diazaspiro[2.5]octane-7-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-3-(trifluoromethyl)piperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-3-(trifluoromethyl)piperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-methyl-3-oxopiperazine-1-carboxamide;

N-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenyl)-4-(2-hydroxyethyl)-3-oxopiperazine-1-carboxamide;

1-(2-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenoxy) ethyl)piperidine-4-carboxylic acid;

1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl) piperidine-4-carboxylic acid;

1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzyl) piperidine-4-carboxylic acid;

1-(2-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-fluorophenoxy)ethyl)piperidine-4-carboxylic acid;

1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylphenethyl)piperidine-4-carboxylic acid;

4-(4-(5-(4-(Difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-1-methylpiperazin-2-one;

4-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-1-(2-hydroxyethyl)piperazin-2-one;

4-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl) piperazin-2-one;

(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)(3-(trifluoromethyl)piperazin-1-yl)methanone;

Methyl 1-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenethyl)piperidine-4-carboxylate;

1-(5-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-hydroxyphenethyl)piperidine-4-carboxylic acid;

1-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)ethyl)piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-methylbenzyl)piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-fluorobenzyl)piperidine-4-carboxylic acid;

1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)-2-hydroxybenzyl)piperidine-4-carboxylic acid;

4-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-1-(piperidin-4-yl)piperazin-2-one;

Isopropyl 4-(4-(3-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)benzoyl)-2-oxopiperazin-1-yl)piperidine-1-carboxylate;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)tetrahydro-2H-pyran-4-carboxamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-1-ethyl-6-oxopiperidine-3-carboxamide;

1-cyclopropyl-N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-5-oxopyrrolidine-3-carboxamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-3,5-dimethylisoxazole-4-carboxamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)isoxazole-5-carboxamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-2-(3-methylisoxazol-5-yl)acetamide;

N-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)-2-(tetrahydro-2H-pyran-4-yl)acetamide; and

N3-(1-(4-(5-(4-(difluoromethoxy)phenyl)pyrimidin-2-ylamino)phenyl)-2-hydroxyethyl)piperidine-1,3-dicarboxamide.

12. A pharmaceutical composition comprising a therapeutically effective amount of any one of claims 1-11 and a pharmaceutically acceptable carrier.

13. The use of a compound of any one of claims 1-11, or a pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent, for the manufacture of a medicament for treating a condition mediated by PDGFRα, PDGFRβ and/or c-

kit, wherein said condition is asthma, atopic dermatitis, urticaria, irritable bowel syndrome (IBS), or a fibrotic disease.

14. The use of claim 13, wherein said fibrotic disease is scleroderma, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), primary pulmonary hypertension (PPH), primary pulmonary arterial hypertension (PPAH), idiopathic arterial hypertension (IPAH), liver fibrosis, renal fibrosis and cardiac fibrosis.

15. The use of claim 13, wherein the second therapeutic agent is an anti-fibrotic agent, pirfenidone, tacrolimus, 5-chloro-2- {(1E)-3-[2-(4-methoxybenzoyl)-4-methyl-1H-pyrrol-1-yl]prop-1-en-1-yl}-*N*-(methylsulfonyl)benzamide, an anti-inflammatory agent, a corticosteroid, a cromolyn, a leukotriene antagonist, an IgE blocker, a bronchodilator, a β_2-agonist, xanthines, an anticholinergic, or a chemotherapeutic agent.

16. The use of claim 13, wherein said compound of any one of claims 1-11 is administered prior to, simultaneously with, or after the second therapeutic agent.

17. A method for modulating kinase activity comprising administering to a cell or tissue system or to a mammalian subject, a therapeutically effective amount of a compound of any one of claims 1-11 or a pharmaceutically acceptable salt thereof, wherein said kinase is c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-raf or b-raf kinases; thereby modulating said kinase activity.

18. The method of claim 17, wherein said kinase is c-kit, PDGFRα or PDGFRβ.

19. The method of claim 17, wherein the compound of any one of claims 1-11 directly contacts c-kit, PDGFRα or PDGFRβ *in vitro* or *in vivo*.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/073573

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/42 C07D401/12 C07D403/12 C07D413/12 A61K31/505
A61K31/506 A61P1/00 A61P7/04 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/038669 A (IRM LLC; NOVARTIS AG [CH]; MOLTENI VALENTINA [US]; LI XIAOLIN [US]; CH) 5 April 2007 (2007-04-05) claims 1-3,5,8,9,22,23,42-44,57,68,72,84,85; table 1; compounds 221-227,228-236, ...	1-19
A	ROSSIGNOL ET AL: "Synthesis of aminopyrimidylindoles structurally related to meridianins" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 63, no. 41, 1 August 2007 (2007-08-01), pages 10169-10176, XP022226165 ISSN: 0040-4020 Scheme 1: compound 13	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2008	16/01/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/073573

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007038669 A	05-04-2007	AU 2006297089 A1	05-04-2007
		CA 2622494 A1	05-04-2007
		EP 1928236 A2	11-06-2008
		KR 20080048041 A	30-05-2008

COMPUESTOS DE 5-(4-(HALO-ALCOXI)-FENIL)-PIRIMIDIN-2-AMINA Y COMPOSICIONES COMO INHIBIDORES DE CINASA

Referencia Cruzada a las Solicitudes Relacionadas

Esta solicitud reivindica el beneficio de la Solicitud Provisional de los Estados Unidos de Norteamérica con Número de Serie 60/957,260, presentada el 22 de Agosto de 2007, la cual se incorpora a la presente como referencia en su totalidad.

Campo Técnico

La invención se refiere a inhibidores de cinasa de proteína, y a métodos para utilizar estos compuestos. De una manera más particular, la invención se refiere a inhibidores de c-kit y PDGFR, y a la utilización de los mismos para el tratamiento y la prevención de los trastornos mediados por c-kit y PDGFR.

Técnica Antecedente

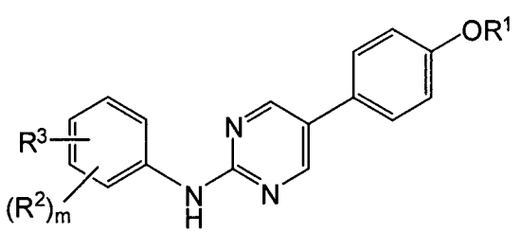
Las cinasas de proteína representan una gran familia de proteínas, que tienen un papel central en la regulación de una amplia variedad de procesos celulares, y en el mantenimiento del control sobre la función celular. Una lista parcial, no limitante, de estas cinasas, incluye: cinasas de tirosina receptoras, tales como la cinasa receptora del factor de crecimiento derivado de plaquetas (PDGFR), la cinasa receptora para el factor de células totipotentes, c-kit, el receptor del factor de crecimiento nervioso, trkB, el receptor del factor de crecimiento de fibroblastos, FGFR3; cinasas de tirosina no receptoras, tales como Abl y la cinasa de fusión BCR-Abl, Fes, Lck, y

Syk; y cinasas de serina/treonina tales como b-RAF, las cinasas MAP (por ejemplo, MKK6), y SAPK2ß. Se ha observado una actividad aberrante de la cinasa en muchos estados de enfermedad, incluyendo trastornos proliferativos benignos y malignos, así como en las enfermedades resultantes de una activación inapropiada de los sistemas inmune y nervioso.

Descripción de la Invención

La invención proporciona compuestos y composiciones farmacéuticas de los mismos, que pueden ser útiles como inhibidores de la cinasa de proteína.

En un aspecto, la invención proporciona compuestos de la Fórmula (1):



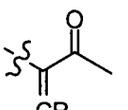
(1)

o una sal farmacéuticamente aceptable del mismo;

R^1 es un halo-alquilo que tiene de 1 a 6 átomos de flúor;

R^2 es 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; halógeno, ciano, nitro, $(CR_2)_kOR^7$, $(CR_2)_kO(CR_2)_{1-4}R^7$, $(CR_2)_kSR^7$, $(CR_2)_kNR^9R^{10}$, $(CR_2)_kC(O)O_{0-1}R^7$, $OC(O)R^7$, $(CR_2)_kC(S)R^7$, $(CR_2)_kC(O)NR^9R^{10}$, $(CR_2)_kC(O)NR(CR_2)_{0-}$

$_6C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^9R^{10}$, $(CR_2)_kS(O)_{1-2}R^8$, $(CR_2)_kNRS(O)_{1-2}R^8$ o $(CR_2)_kR^6$; o cualesquiera dos grupos R^2 adyacentes pueden formar juntos un anillo de arilo o heteroarilo carbocíclico, heterocíclico, de 5 a 8 miembros, opcionalmente sustituido;

R^3 es $-L-NR^4R^5$, $-X-NR-C(O)R^8$ o $-X-NR-C(O)NR^4R^5$ en donde L es $-X-C(O)$, $-X-OC(O)$, $-(CR_2)_j$, $-SO_{0-2}(CR_2)_j$, $-O(CR_2)_{1-4}$, o  ; y X es $(CR_2)_j$ o $[C(R)-(CR_2OR)]$;

R^4, R^5, R^9 y R^{10} son independientemente 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, alcoxilo, ciano, carboxilo o R^6; $(CR_2)_kCN$, $(CR_2)_{1-6}NR^7R^8$, $(CR_2)_{1-6}OR^7$, $(CR_2)_kC(O)O_{0-1}R^7$, $(CR_2)_kC(O)NR^7R^8$ o $(CR_2)_k-R^6$;

R^6 es un cicloalquilo de 3 a 7 átomos de carbono opcionalmente sustituido, arilo de 6 átomos de carbono, o un anillo de heteroarilo de 5 a 6 miembros o heterocíclico de 5 a 7 miembros;

R^7 y R^8 son independientemente $(CR_2)_k-R^6$ o 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, amido, hidroxilo, alcoxilo, ciano, carboxilo o R^6; o R^7 es H;

de una manera alternativa, R^4 y R^5 junto con N en cada NR^4R^5,

R^7 y R^8 junto con N en NR^7R^8, o R^9 y R^{10} junto con N en NR^9R^{10}, pueden formar un anillo heterocíclico de 4 a 7 miembros opcionalmente sustituido con 1 a 3 grupos R^{11};

R^{11} es R^8, $(CR_2)_k–OR^7$, CO_2R^7, $(CR_2)_k–C(O)-(CR_2)_k-R^8$, $(CR_2)_kC(O)NR^7R^8$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^8$, $(CR_2)_kS(O)_{1-2}R^8$ o $(CR_2)_kNRS(O)_{1-2}R^8$;

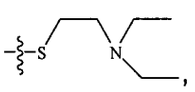
cada R es H o alquilo de 1 a 6 átomos de carbono;

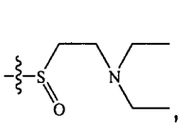
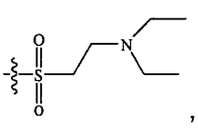
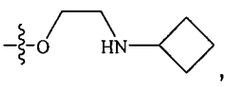
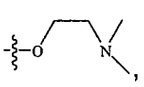
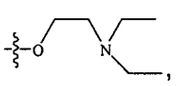
cada k es de 0 a 6; y

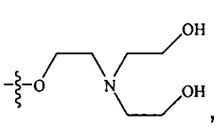
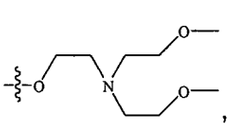
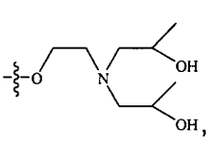
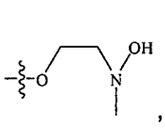
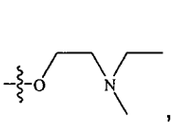
j y **m** son independientemente de 0 a 4;

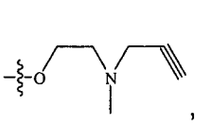
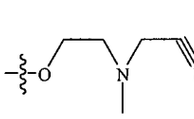
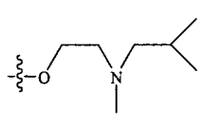
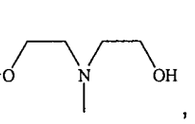
en el entendido de que R^1 no es trifluoro-metoxilo cuando R^3 es $C(O)NH_2$, $C(O)NR^{12}R^{13}$ o $SO_2NH(CH_2)_{2-3}NR^{14}R^{15}$; en donde R^{12} y R^{13} forman juntos piperazinilo, y R^{14} y R^{15} forman juntos morfolinilo.

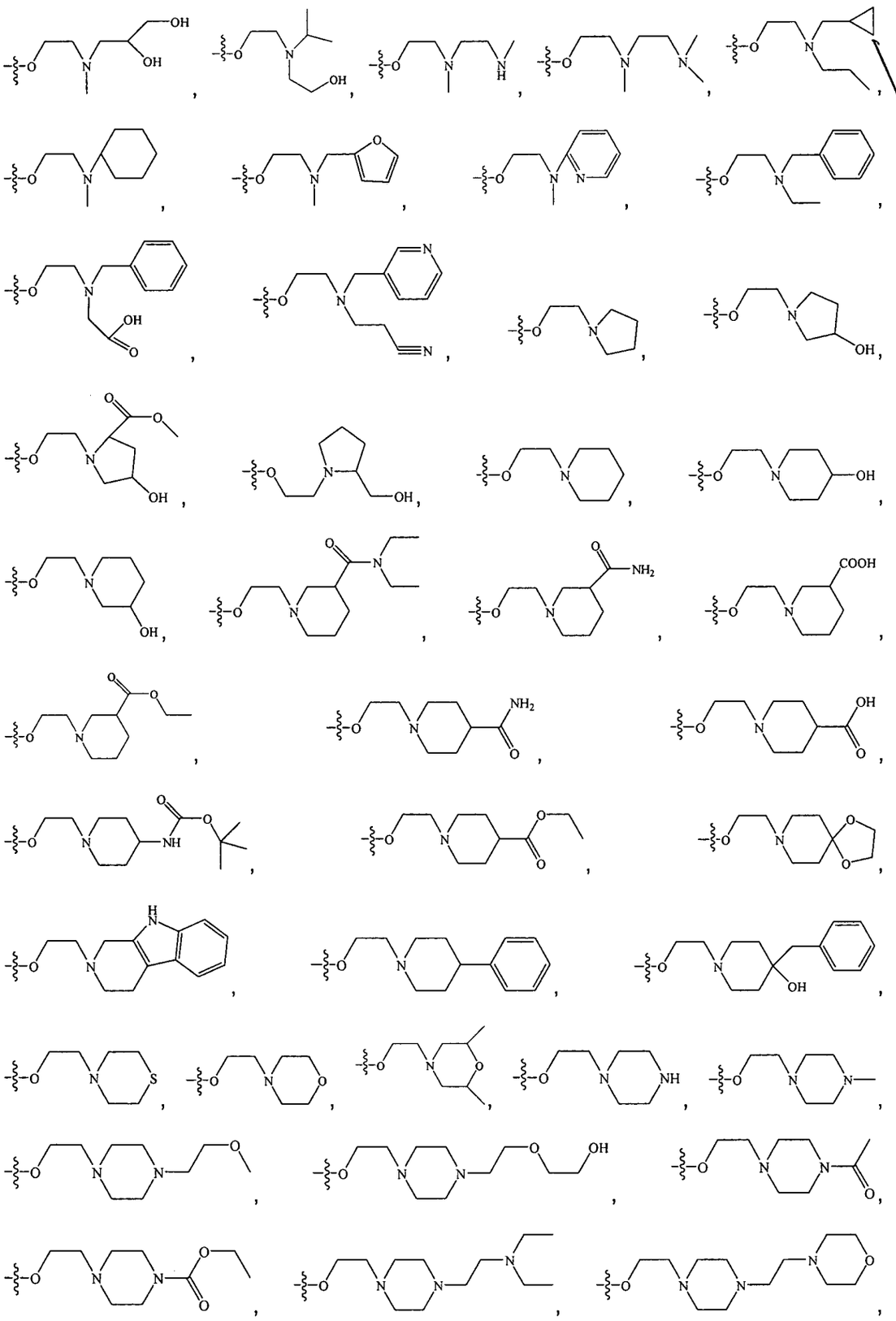
En la fórmula (1) anterior, R^1 puede ser $OCHF_2$, OCF_3, OCH_2CF_3 u OCF_2CH_2, OCH_2CF_3. En los ejemplos particulares, R^1 es $OCHF_2$.

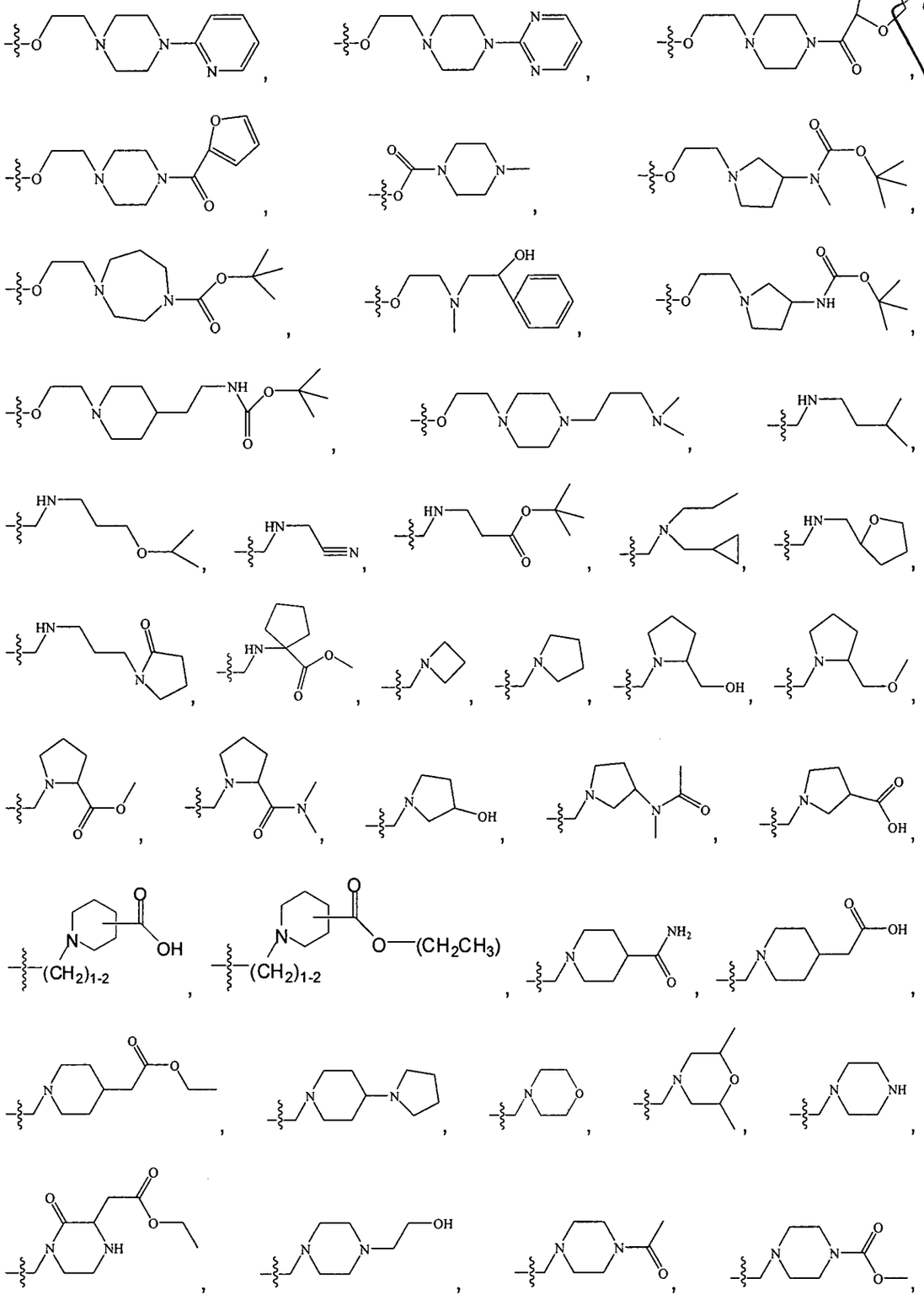
En algunos ejemplos, R^3 en la fórmula (1) anterior se selecciona a partir del grupo que consiste en  ,

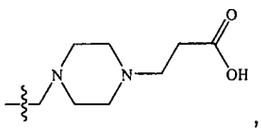
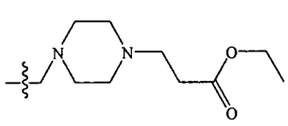
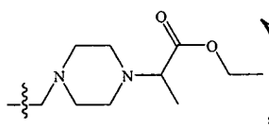
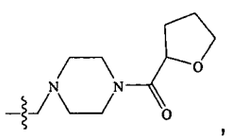
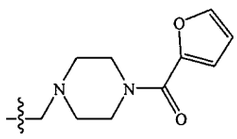
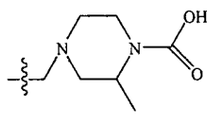
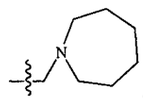
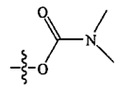
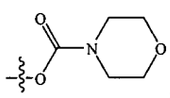
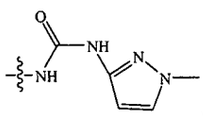
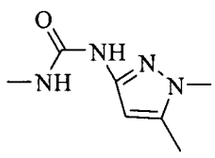
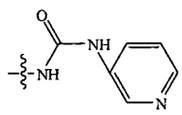
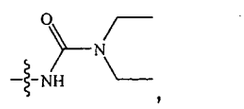
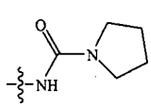
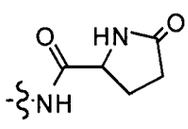
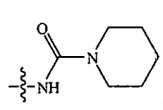
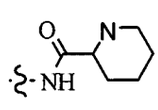
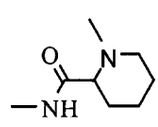
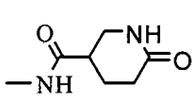
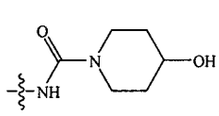
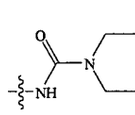
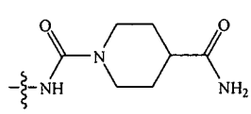
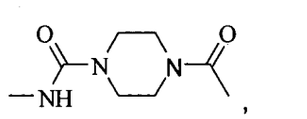
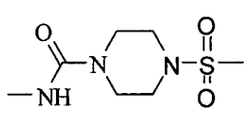
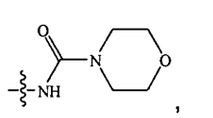
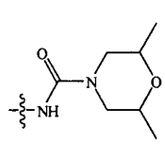
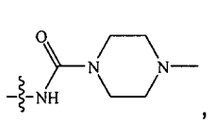
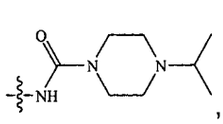
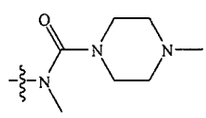
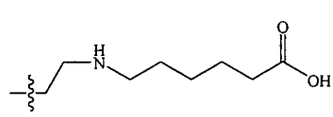
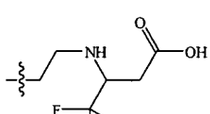
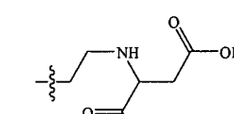
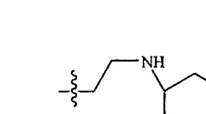
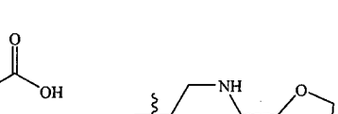
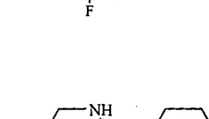
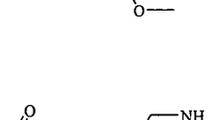
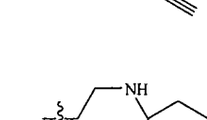
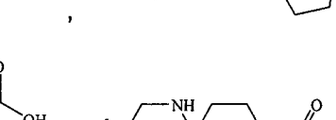
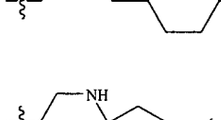
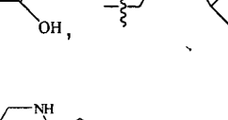
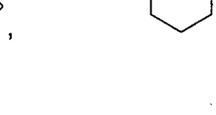
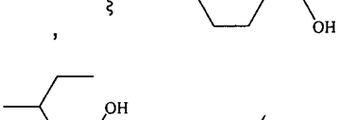
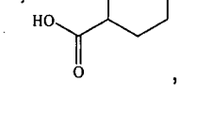
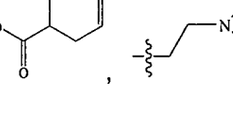
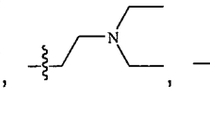
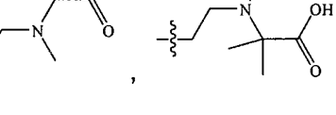
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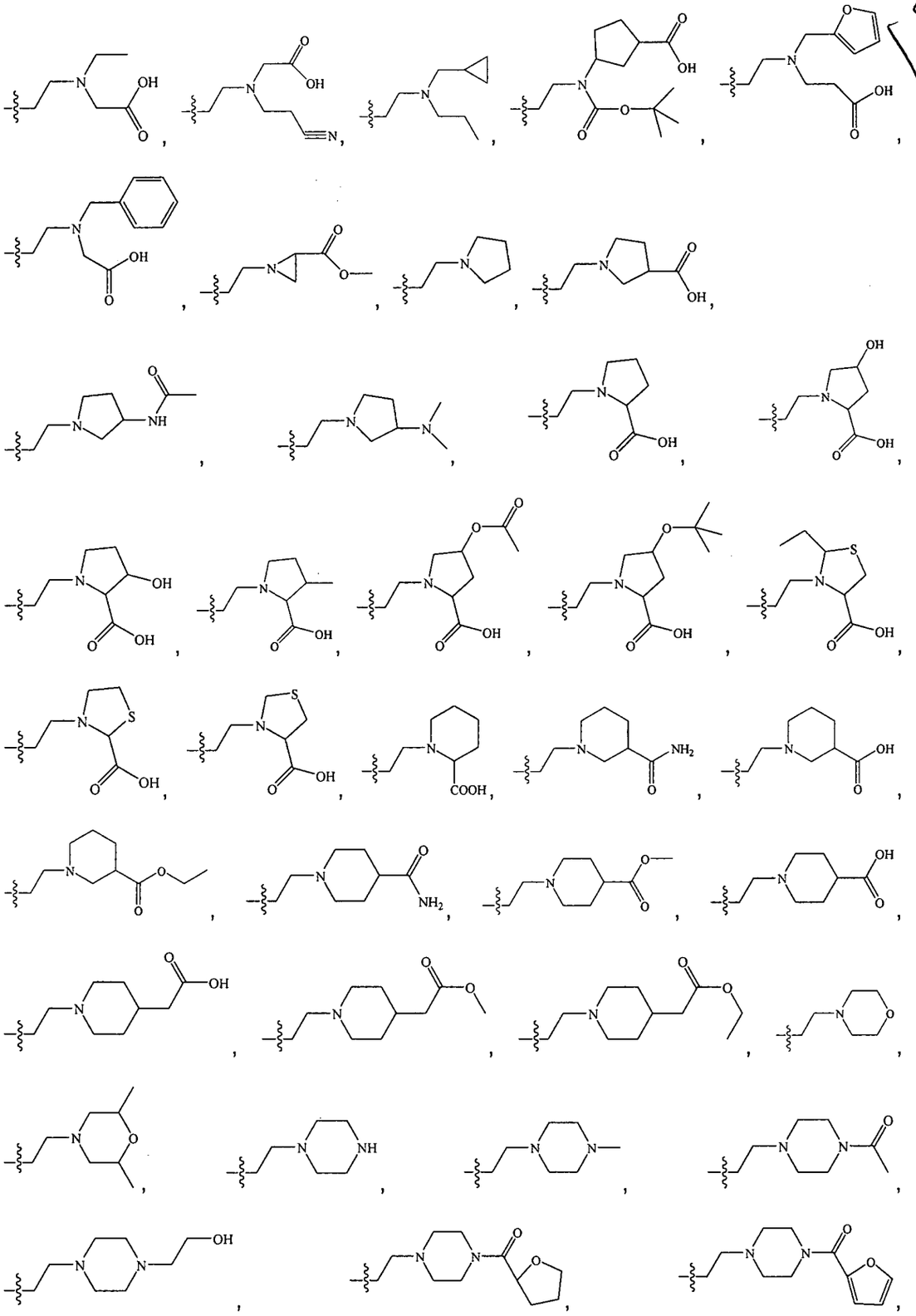
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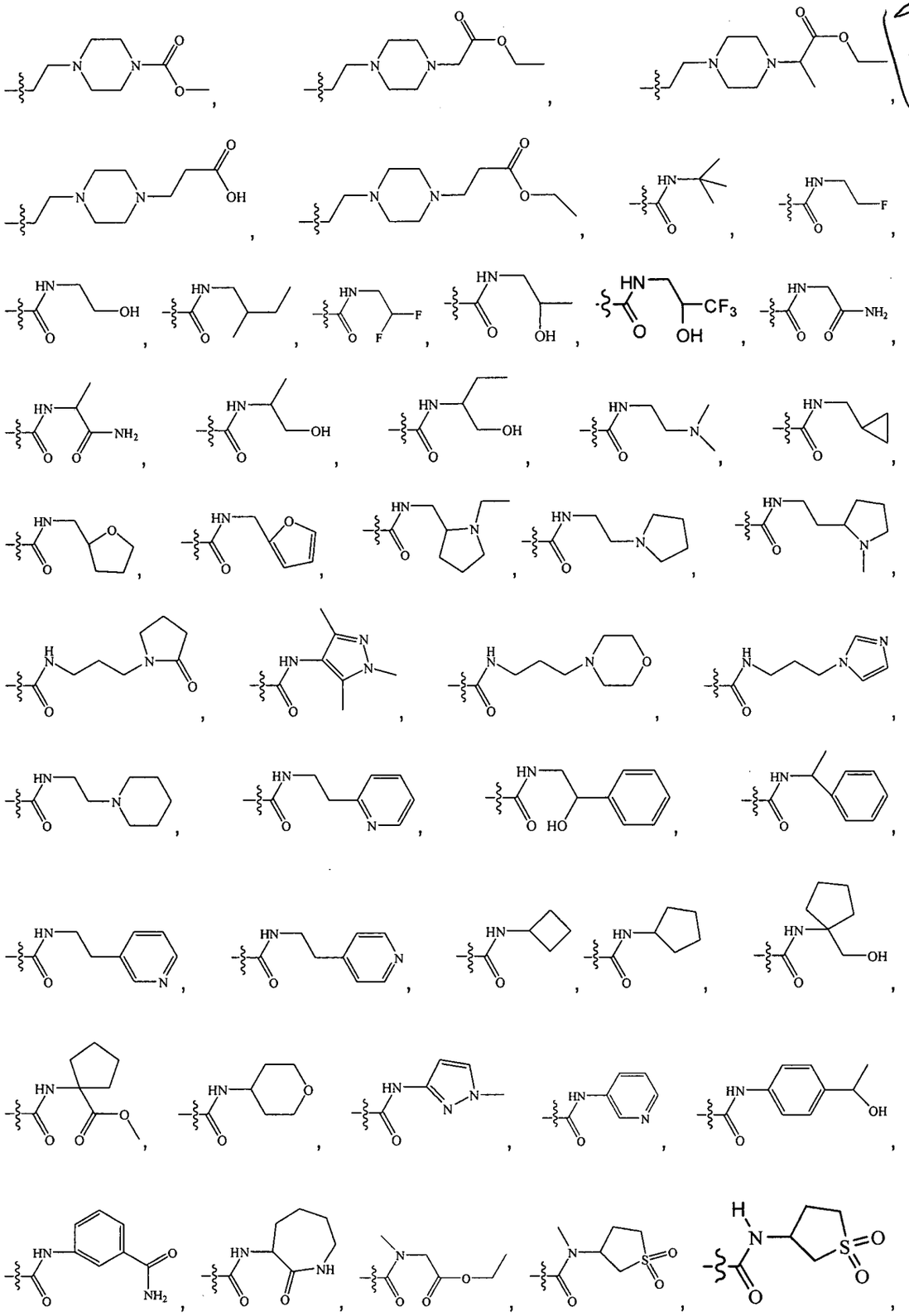
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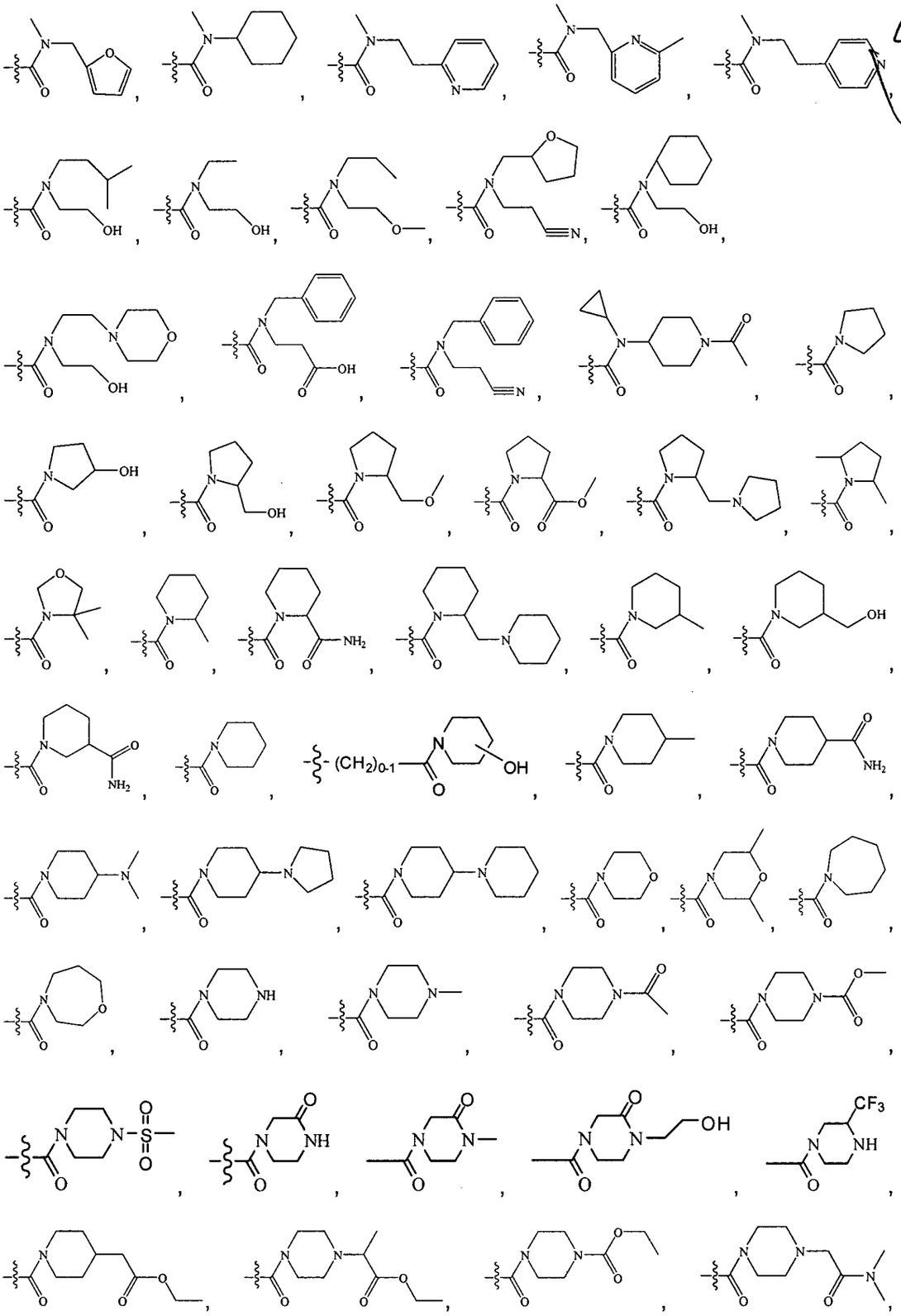
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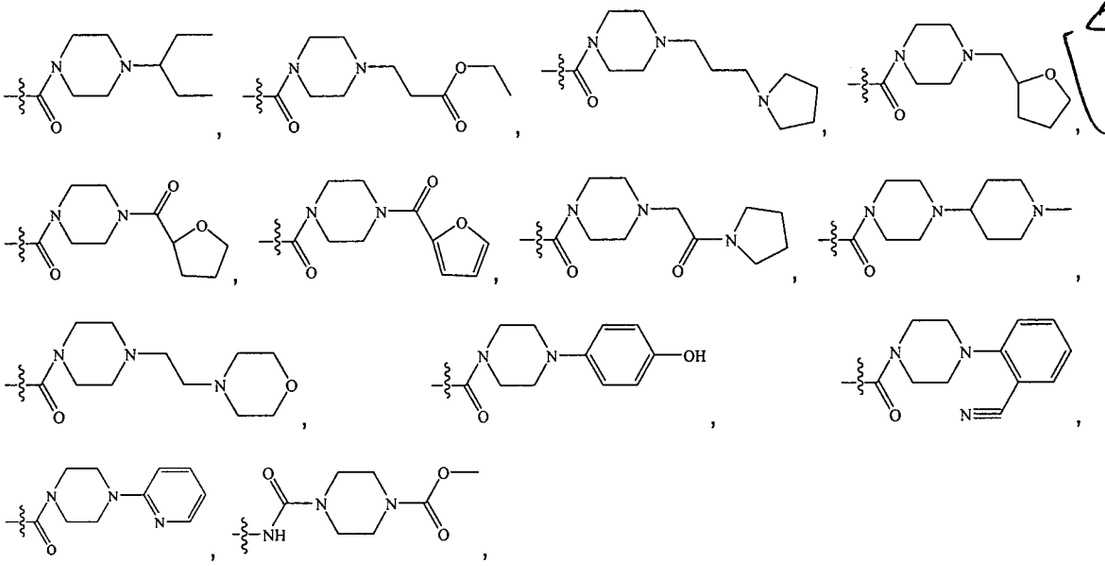
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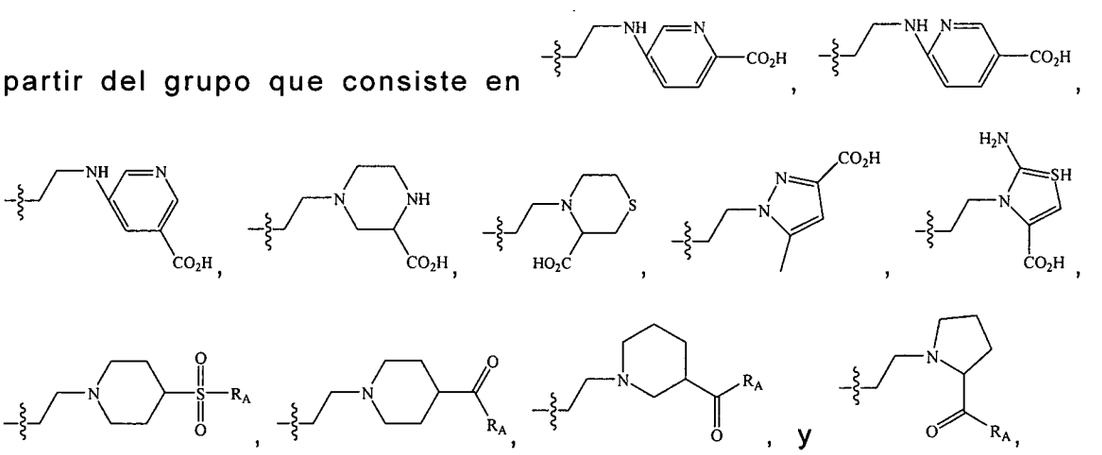






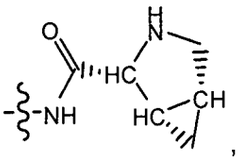
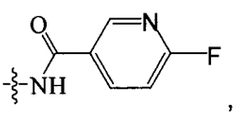
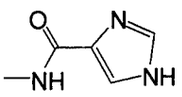
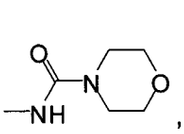
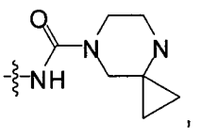
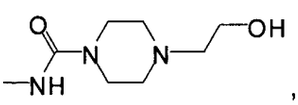
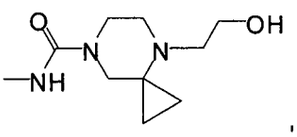
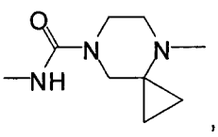
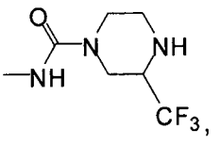
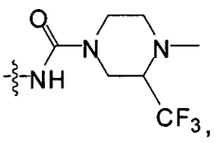
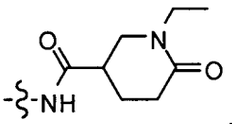
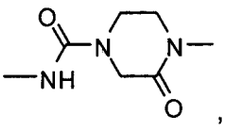
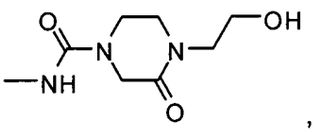
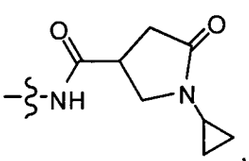
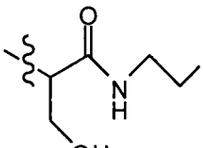
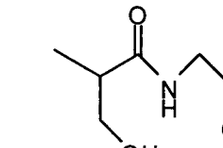
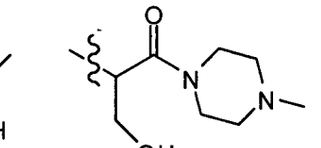
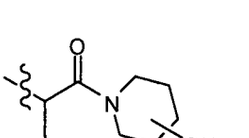
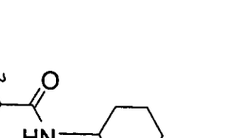
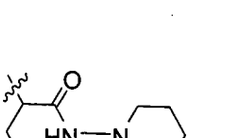
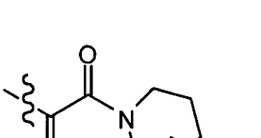
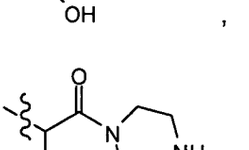
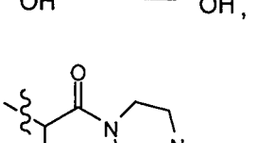
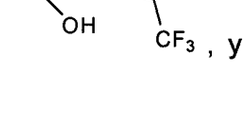
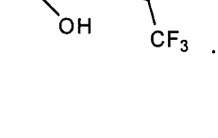


En otros ejemplos, R^3 en la fórmula (1) anterior se selecciona a partir del grupo que consiste en

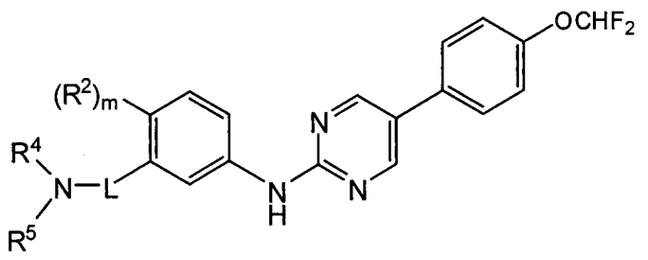


en donde R_A se selecciona a partir de $-NH_2$, $-NEt_2$, y -NH

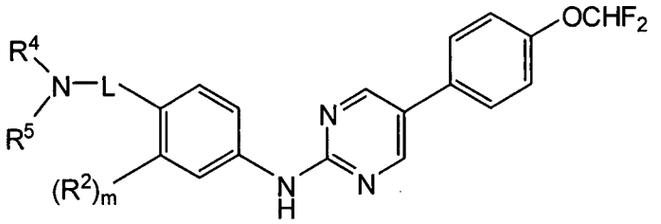
$(CH_2)_{1-6}OH$.

En todavía otros ejemplos, R^3 en la fórmula (1) anterior se selecciona a partir del grupo que consiste en  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , y  .

En una modalidad, los compuestos tienen la fórmula (2A) o (2B):



(2A)



(2B);

en donde R^4 y R^5 junto con N forman un anillo heterocíclico de 5 a 6 miembros que opcionalmente contiene NR^{16}, O, S, =O o un doble enlace; en donde este anillo heterocíclico está opcionalmente sustituido con 1 a 2 grupos R^{11};

R^{16} es H, R^8, $-(CR_2)_{1-4}CO_2R^7$, $(CR_2)_k-C(O)-(CR_2)_k-R^8$, $(CR_2)_kC(O)NR^7R^8$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_{1-4}NRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^8$, $(CR_2)_kS(O)_{1-2}R^8$ o $(CR_2)_kNRS(O)_{1-2}R^8$; y

R^4, R^5, R^7, R^8, R^{11}, R y **k** son como se definen en la fórmula (1).

En las fórmulas (2A) o (2B) anteriores, R^4 y R^5 junto con N en NR^4R^5 pueden formar un piperidinilo, piperazinilo o morfilinilo opcionalmente sustituido. En algunos ejemplos, L es –X-C(O), $-(CR_2)_{1-4}$ u $-O(CR_2)_{1-4}$; en donde X es $(CR_2)_{0-1}$ o [C(R)-(CR_2OR)]. En

otros ejemplos, L es $(CR_2)_{1-2}$.

En la fórmula (1) anterior, (2A) o (2B), R^2 si está presente, es halógeno, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, hidroxilo o CO_2R^7, y R^7 es H o alquilo de 1 a 6 átomos de carbono.

En una modalidad, la presente invención proporciona un compuesto seleccionado a partir del grupo que consiste en:

N-(4-(2-(dietil-amino)-etoxi)-fenil)-5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-amina;

N-(4-(2-(dietil-amino)-etoxi)-fenil)-5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-amina;

ácido 1-(2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1-metil-piperidin-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-azabiciclo-[3.1.0]-hexan-2-carboxamida;

(1S,2R,5R)-N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-azabiciclo-[3.1.0]-hexan-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-piperidin-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-5-oxo-pirrolidin-2-carboxamida;

(R)-N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-5-oxo-pirrolidin-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-6-oxo-piperidin-3-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-6-fluoro-piridin-3-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1H-imidazol-5-carboxamida;

N-(2-metil-5-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-5-oxo-pirrolidin-2-carboxamida;

(S)-N-(2-metil-5-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-5-oxo-pirrolidin-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1-ciclopropil-5-oxo-pirrolidin-3-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1-etil-6-oxo-piperidin-3-carboxamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-N-(2-fluoro-etil)-3-hidroxi-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-hidroxi-piperidin-1-il)-propan-1-ona;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-

fenil)-3-hidroxi-1-(4-hidroxi-piperidin-1-il)-propan-1-ona;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-hidroxi-piperidin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-(2-hidroxi-propil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((R)-2-hidroxi-propil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((R)-2-hidroxi-propil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((S)-2-hidroxi-propil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((S)-2-hidroxi-propil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((S)-2-hidroxi-propil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-(4-hidroxi-ciclohexil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,4R)-4-hidroxi-ciclohexil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,4R)-4-hidroxi-ciclohexil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,4R)-4-hidroxi-ciclohexil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,4S)-4-hidroxi-ciclohexil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,4S)-4-hidroxi-ciclohexil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,4S)-4-hidroxi-ciclohexil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(3-hidroxi-piperidin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((S)-3-hidroxi-piperidin-1-il)-propan-1-ona;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((S)-3-hidroxi-piperidin-1-il)-propan-1-ona;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((S)-3-hidroxi-piperidin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((R)-3-hidroxi-piperidin-1-il)-propan-1-ona;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((R)-3-hidroxi-piperidin-1-il)-propan-1-ona;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((R)-3-hidroxi-piperidin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-(2-hidroxi-ciclopentil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,2R)-2-hidroxi-ciclopentil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2R)-2-hidroxi-ciclopentil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-

hidroxi-N-((1S,2S)-2-hidroxi-ciclopentil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,2R)-2-hidroxi-ciclopentil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2S)-2-hidroxi-ciclopentil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2R)-2-hidroxi-ciclopentil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2S)-2-hidroxi-ciclopentil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2R)-2-hidroxi-ciclopentil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(4-hidroxi-piperidin-1-il)-prop-2-en-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(4-hidroxi-piperidin-1-il)-etanona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-metil-piperazin-1-il)-propan-1-ona;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-metil-piperazin-1-il)-propan-1-ona;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-metil-piperazin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(3-(trifluoro-metil)-piperazin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(3-(trifluoro-metil)-4-metil-piperazin-1-il)-3-hidroxi-propan-1-ona;

N1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-piperidin-1,4-dicarboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metan-sulfonil-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-acetil-piperazin-1-carboxamida;

1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-(1,3-dimetil-1H-pirazol-5-il)-urea;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)morfolin-4-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(2-hidroxi-etil)-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-4,7-diazaespiro-[2.5]-octan-7-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(2-hidroxi-etil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-(trifluoro-metil)-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-3-(trifluoro-metil)-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-

fenil)-4-metil-3-oxopiperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(2-hidroxi-etil)-3-oxopiperazin-1-carboxamida;

ácido 1-(2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxílico;

ácido 1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico;

ácido 1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico;

ácido 1-(2-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etil)-piperidin-4-carboxílico;

ácido 1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenetil)-piperidin-4-carboxílico;

4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-1-metil-piperazin-2-ona;

4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-1-(2-hidroxi-etil)-piperazin-2-ona;

4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-piperazin-2-ona;

(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-(3-(trifluoro-metil)-piperazin-1-il)-metanona;

1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxilato de metilo;

ácido 1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-hidroxi-fenetil)-piperidin-4-carboxílico;

ácido 1-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-etil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-bencil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-fluoro-bencil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-hidroxi-bencil)-piperidin-4-carboxílico;

4-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-1-(piperidin-4-il)-piperazin-2-ona;

4-(4-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-2-oxopiperazin-1-il)-piperidin-1-carboxilato de isopropilo;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-tetrahidro-2H-piran-4-carboxamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-1-etil-6-oxo-piperidin-3-carboxamida;

1-ciclopropil-N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-5-oxo-pirrolidin-3-carboxamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-3,5-dimetil-isoxazol-4-carboxamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-isoxazol-5-carboxamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-2-(3-metil-isoxazol-5-il)-acetamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-

2-hidroxi-etil)-2-(tetrahidro-2H-piran-4-il)-acetamida; y

N3-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-piperidin-1,3-dicarboxamida.

En otro aspecto, la presente invención proporciona composiciones farmacéuticas que comprenden una cantidad terapéuticamente efectiva de un compuesto que tiene la fórmula (1), (2A) o (2B), y un excipiente farmacéuticamente aceptable.

En todavía otro aspecto, la presente invención proporciona métodos para modular la actividad de la cinasa, los cuales comprenden administrar a un sistema o a un sujeto que lo necesite, una cantidad terapéuticamente efectiva del compuesto que tiene la fórmula (1), (2A) o (2B), o sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo, modulando de esta manera la actividad de la cinasa.

En una modalidad, la invención proporciona métodos para modular las cinasas c-kit, PDGFRα, PDGFRß, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFß, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2ß, BRK, Fms, KDR, c-raf o b-raf. En las modalidades particulares, la invención proporciona métodos para modular c-kit, PDGFRα o PDGFRß; y de una manera más particular, la invención proporciona métodos en donde un compuesto que tiene la fórmula (1), (2A) o (2B), o sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo, puede hacer contacto directamente con c-kit, PDGFRα o PDGFRß *in vitro* o *in vivo*.

La presente invención también proporciona métodos para el tratamiento de una enfermedad o condición en donde la modulación de la actividad de la cinasa pueda prevenir, inhibir, o disminuir la patología y/o sintomatología de la enfermedad o condición, los cuales comprenden administrar a un sujeto una cantidad terapéuticamente efectiva de un compuesto que tiene la fórmula (1), (2A) o (2B), o sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo, y opcionalmente en combinación con un segundo agente terapéutico. Los ejemplos de los agentes terapéuticos que se pueden utilizar en combinación con un compuesto de la invención incluyen, pero no se limitan a, un agente anti-fibrótico, pirfenidona, tacrolimus, un agente anti-inflamatorio, un corticosteroide, una cromolina, un antagonista de leucotrieno, un bloqueador de IgE, un broncodilatador, un agonista-$ß_2$, xantinas, un anticolinérgico, o un agente quimioterapéutico. Cuando se administra con un segundo agente terapéutico, el compuesto de la fórmula (1), (2A) o (2B), o las sales farmacéuticamente aceptables o composiciones farmacéuticas del mismo, se pueden administrar antes de, simultáneamente con, o después del segundo agente terapéutico.

En una modalidad, la invención proporciona métodos para el tratamiento de una enfermedad o condición modulada por las cinasas c-kit, PDGFRα, PDGFRß, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFß, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2ß, BRK, Fms, KDR, c-raf o b-raf. En los

ejemplos particulares, la invención proporciona métodos para el tratamiento de una enfermedad o condición modulada por PDGFRα, PDGFRß o c-kit. En algunos ejemplos, la invención proporciona métodos para el tratamiento de una enfermedad o condición modulada por c-kit.

Los ejemplos de las enfermedades o condiciones mediadas por cinasa que pueden ser mediadas utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, una enfermedad asociada con los mastocitos, un trastorno de alergia, síndrome de intestino irritable (IBS), una enfermedad fibrótica, un trastorno neoplásico, un trastorno inflamatorio, un trastorno autoinmune, una enfermedad del injerto contra el huésped, un síndrome metabólico, un trastorno relacionado con el sistema nervioso central, un trastorno neurodegenerativo, una condición de dolor, un trastorno de abuso de sustancias, un cáncer, una enfermedad cardiovascular, y una enfermedad priónica.

Los ejemplos de una enfermedad asociada con los mastocitos que se puede tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, trastornos alérgicos (incluyendo asma y dermatitis atópica), urticaria, acné y acnés por *Propionibacterium*, Fibrodisplasia ossificans progresiva (FOP), inflamación y destrucción de tejido inducida por exposición a armas químicas o biológicas (tales como ántrax y mostaza de azufre), fibrosis quística; enfermedad renal, trastornos inflamatorios de los músculos, VIH, diabetes tipo II, isquemia cerebral, mastocitosis,

dependencia de drogas y síntomas de abstinencia, trastornos del sistema nervioso central, prevención y minimización de pérdida del cabello, infecciones bacterianas, cistitis intersticial, enfermedades inflamatorias del intestino (por ejemplo, enfermedad de Crohn, colitis ulcerativa, colitis indeterminada, y colitis infecciosa), angiogénesis tumoral, enfermedades autoinmunes, enfermedades inflamatorias, esclerosis múltiple (MS), y pérdida ósea.

Los ejemplos de los trastornos de alergia que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, asma, dermatitis atópica, rinitis alérgica, sinusitis alérgica, síndrome anafiláctico, urticaria, angioedema, dermatitis alérgica por contacto, eritema nodosum, eritema multiforme, venulitis cutánea necrotizante, inflamación de la piel por mordedura de insecto, e infestación por parásitos succionadores de sangre.

El síndrome de intestino irritable (IBS) es un trastorno gastrointestinal funcional caracterizado por dolor abdominal y hábitos alterados del intestino. El dolor se alivia de una manera característica mediante la defecación, y puede estar asociado con una aumento o disminución en la frecuencia de la evacuación, alteraciones en la consistencia de las heces, estreñimiento o urgencia, una sensación de evacuación incompleta, paso de moco, o distensión abdominal.

Una enfermedad fibrótica, como se utiliza en la presente, abarca todas las condiciones relacionadas o asociadas con la

formación y depósito de componentes de matriz extracelular, en particular en los órganos internos, incluyendo los riñones, corazón, pulmones, hígado, piel, y articulaciones. Los ejemplos de las enfermedades fibróticas que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, esclerodermia, fibrosis pulmonar, fibrosis pulmonar idiopática (IPF), hipertensión pulmonar primaria (por ejemplo, hipertensión arterial pulmonar (PPAH)), fibrosis hepática, fibrosis renal, fibrosis cardíaca, cirrosis en hígado, fibrosis de médula ósea, hepatitis C (HCV) y esteatohepatitis no alcohólica (NASH).

Los ejemplos de los trastornos neoplásicos que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, mastocitosis, tumor estromal gastrointestinal, cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas, leucemia mielocítica aguda, leucemia linfocítica aguda, síndrome mielodisplásico, leucemia mielógena crónica, carcinoma colo-rectal, carcinoma gástrico, cáncer testicular, glioblastoma, y astrocitoma.

Los ejemplos de los trastornos inflamatorios que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, artritis reumatoide, conjuntivitis, espondilitis reumatoide, osteoartritis, y artritis gotosa.

Los ejemplos de los trastornos autoinmunes que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, esclerosis múltiple, soriasis,

enfermedad intestinal inflamatoria, enfermedad inflamatoria del intestino (IBD), colitis ulcerativa, enfermedad de Crohn, artritis reumatoide, poliartritis, esclerodermia local o sistémica, lupus eritematoso sistémico, lupus eritematoso discoide, lupus cutáneo, dermatomiositis, polimiositis, síndrome de Sjogren, panarteritis nodular, enteropatía autoinmune, y glomerulonefritis proliferativa.

Los ejemplos de las enfermedades del injerto contra el huésped que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, rechazo de injerto de trasplante de órgano, tal como trasplante de riñón, trasplante de páncreas, trasplante de hígado, trasplante de corazón, trasplante de pulmón, y trasplante de médula ósea.

Los ejemplos de síndrome metabólico que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, diabetes tipo I, diabetes tipo II, y obesidad.

Los ejemplos de los trastornos relacionados con el sistema nervioso central que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, depresión, trastorno distímico, trastorno ciclotímico, anorexia, bulimia, síndrome pre-menstrual, síndrome post-menopáusico, lentitud mental, pérdida de concentración, preocupación pesimista, agitación, auto-desprecio y libido reducida, un trastorno de ansiedad, un trastorno psiquiátrico, y esquizofrenia.

Los ejemplos de las condiciones de depresión que se pueden tratar utilizando los compuestos y composiciones de la invención

incluyen, pero no se limitan a, depresión bipolar, depresión severa o melancólica, depresión atípica, depresión refractaria, y depresión por temporada. Los ejemplos de los trastornos de ansiedad que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, ansiedad asociada con hiperventilación y arritmias cardíacas, trastornos fóbicos, trastorno obsesivo-compulsivo, trastorno de tensión post-traumática, trastorno de tensión aguda, y trastorno de ansiedad generalizada. Los ejemplos de los trastornos psiquiátricos que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, ataques de pánico, incluyendo psicosis, trastornos de desilusión, trastornos de conversión, fobias, manías, delirio, episodios disociativos, incluyendo amnesia disociativa, fuga disociativa, y comportamiento suicida disociativo, auto-menosprecio, comportamiento violento o agresivo, trauma, personalidad de línea límite, y psicosis aguda, tal como esquizofrenia, incluyendo esquizofrenia paranoide, esquizofrenia desorganizada, esquizofrenia catatónica, y esquizofrenia no diferenciada.

Los ejemplos de trastorno neurodegenerativo que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, osteoartritis, enfermedad de Alzheimer, enfermedad de Parkinson, enfermedad de Huntington, las enfermedades de priones, enfermedad de neuronas motoras (MND), y esclerosis lateral amiotrófica (ALS).

Los ejemplos de las condiciones de dolor que se pueden tratar

utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, dolor agudo, dolor post-operatorio, dolor crónico, dolor nociceptivo, dolor por cáncer, dolor neuropático, y síndrome de dolor psicogénico.

Los ejemplos de los trastornos por uso de sustancias que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, adicción a drogas, abuso de drogas, habituación a drogas, dependencia de drogas, síndrome de abstinencia, y sobredosis.

Los ejemplos de los cánceres que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, glioma, melanoma, tumor estromal gastrointestinal (GIST), cáncer pulmonar de células pequeñas, cáncer colo-rectal, y otros tumores sólidos.

Los ejemplos de las enfermedades cardiovasculares que se pueden tratar utilizando los compuestos y composiciones de la invención incluyen, pero no se limitan a, angina de pecho, infarto de miocardio, insuficiencia cardíaca congestiva, cardiomiopatía, hipertensión, estenosis arterial, y estenosis venosa.

De una manera más particular, los compuestos de la invención se pueden utilizar para el tratamiento y la prevención de asma, dermatitis atópica, urticaria, síndrome de intestino irritable (IBS), o una enfermedad fibrótica, incluyendo, pero no limitándose a, esclerodermia, fibrosis pulmonar, fibrosis pulmonar idiopática (IPF), hipertensión pulmonar primaria (PPH), hipertensión arterial pulmonar

primaria (PPAH), hipertensión arterial idiopática (IPAH), fibrosis hepática, fibrosis renal y fibrosis cardíaca.

Adicionalmente, la presente invención proporciona el uso de un compuesto que tiene la fórmula (1), (2A) o (2B), o una composición farmacéuticamente aceptable del mismo, y opcionalmente en combinación con un segundo agente terapéutico, para la fabricación de un medicamento para el tratamiento de una enfermedad o condición modulada por las cinasas c-kit, PDGFRα, PDGFRß, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFß, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2ß, BRK, Fms, KDR, c-raf o b-raf; y de una manera más particular, para la fabricación de un medicamento para el tratamiento de una enfermedad o condición modulada por PDGFRα, PDGFRß o c-kit.

En los métodos anteriores para utilizar los compuestos de la invención, un compuesto que tiene la fórmula (1), (2A) o (2B) se puede administrar a un sistema que comprenda células o tejidos. En otras modalidades, un compuesto que tiene la fórmula (1), (2A) o (2B) se puede administrar a un sujeto humano o animal.

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, $-OCH_2CH_2O-$, alquiltioles, tioalcoxilo, alquil-aminas, etc.).

"Arilo" se refiere a un anillo aromático monocíclico o bicíclico fusionado que contiene átomos de carbono. Por ejemplo, arilo puede ser fenilo o naftilo. "Arileno" significa un radical divalente derivado a partir de un grupo arilo.

"Hetero-arilo", 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. Los ejemplos de los hetero-arilos incluyen, pero no se limitan a, piridilo, indolilo, indazolilo, quinoxalinilo, quinolinilo, benzo-furanilo, benzo-piranilo, benzo-tiopiranilo, benzo-[1,3]-dioxol, imidazolilo, benzo-imidazolilo, pirimidinilo, furanilo, oxazolilo, isoxazolilo, triazolilo, tetrazolilo, pirazolilo, tienilo, 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 es un heteroátomo. Por

ejemplo, un anillo heterocíclico puede contener N, O, S, -N=, -S-, -S(O), -$S(O)_2$-, o -NR-, en donde R puede ser hidrógeno, alquilo de 1 a 4 átomos de carbono o un grupo protector. Los ejemplos de los anillos heterocíclicos incluyen, pero no se limitan a, morfolino, pirrolidinilo, pirrolidinil-2-ona, piperazinilo, piperidinilo, piperidinilona, 1,4-dioxa-8-aza-espiro-[4.5]-dec-8-ilo, etc.

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.

A menos que se indique de otra manera, cuando un sustituyente se considera como "opcionalmente sustituido," esto significa que el sustituyente es un grupo que puede estar sustituido con uno o más grupos individualmente e independientemente seleccionados a partir de, por ejemplo, un alquilo opcionalmente halogenado, alquenilo, alquinilo, alcoxilo, alquil-amina, tioalquilo, alquinilo, amida, amino, incluyendo los grupos amino mono- y di-sustituidos, arilo, ariloxilo, tioarilo, carbonilo, carbocíclico, ciano, cicloalquilo, halógeno, heteroalquilo, heteroalquenilo, heteroalquinilo, hetero-arilo, heterocíclico, hidroxilo, isocianato, isotiocianato, mercapto, nitro, O-carbamilo, N-carbamilo, O-tiocarbamilo, N-tiocarbamilo, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxilo, O-carboxilo, perhalo-alquilo, perfluoro-alquilo, sililo, sulfonilo, tiocarbonilo, tiocianato, trihalometan-sulfonilo, y los compuestos protegidos de los mismos. Los grupos protectores que pueden formar los compuestos protegidos de los

sustituyentes anteriores son conocidos por los expertos en este campo, y se pueden encontrar en referencias tales como Greene y Wuts, Protective Groups in Organic Synthesis, 3ª Edición, John Wiley & Sons, Nueva York, NY, 1999, y Kocienski, Protective Groups, Thieme Verlag, Nueva York, NY, 1994, los cuales se incorporan a la presente como referencia en su totalidad.

Los términos "co-administración" o "administración combinada" o similares, como se utilizan en la presente, pretenden abarcar la administración de los agentes terapéuticos seleccionados a un solo paciente, y se pretende que incluya los regímenes de tratamiento en donde los agentes no necesariamente se administren por la misma vía de administración o al mismo tiempo.

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 ingrediente activos.

El término "cantidad terapéuticamente efectiva" significa la cantidad del compuesto objeto que provocará una respuesta biológica o médica en una célula, tejido, órgano, sistema, animal o humano, que esté siendo buscada por el investigador, veterinario, médico, u otro clínico.

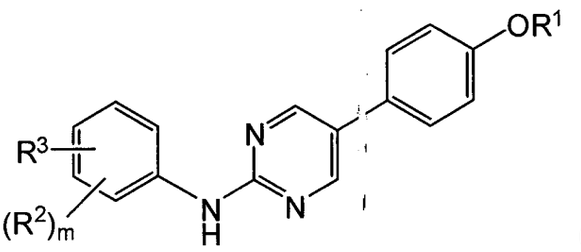
El término "administración" o "administrar" al sujeto el compuesto, significa proporcionar un compuesto de la invención y pro-fármacos del mismo a un sujeto que necesite tratamiento.

A menos que se informe de otra manera para esta invención, una cinasa seleccionada a partir de c-kit, PDGFRα, PDGFRß, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFß, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2ß, BRK, Fms, KDR, c-raf y b-raf se refiere las formas de tipo silvestre y mutantes (es decir, que tienen cambios de aminoácidos individuales o múltiples a partir de la secuencia de tipo silvestre).

Modos para Llevar a Cabo la Invención

La presente invención proporciona compuestos y composiciones farmacéuticas de los mismos, los cuales pueden ser útiles como inhibidores de cinasa de proteína.

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



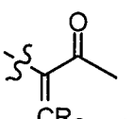
(1)

o una sal farmacéuticamente aceptable del mismo;

R^1 es un halo-alquilo que tiene de 1 a 6 átomos de flúor;

R^2 es 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; halógeno, ciano, nitro, $(CR_2)_kOR^7$, $(CR_2)_kO(CR_2)_{1-4}R^7$, $(CR_2)_kSR^7$, $(CR_2)_kNR^9R^{10}$, $(CR_2)_kC(O)O_{0-1}R^7$, $OC(O)R^7$, $(CR_2)_kC(S)R^7$, $(CR_2)_kC(O)NR^9R^{10}$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^9R^{10}$, $(CR_2)_kS(O)_{1-2}R^8$, $(CR_2)_kNRS(O)_{1-2}R^8$ o $(CR_2)_kR^6$; o cualesquiera dos grupos R^2 adyacentes pueden formar juntos un anillo de arilo o heteroarilo carbocíclico, heterocíclico, de 5 a 8 miembros, opcionalmente sustituido;

R^3 es -L-NR^4R^5, -X-NR-C(O)R^8 o -X-NR-C(O)NR^4R^5 en donde L

es –X-C(O), -X-OC(O), -$(CR_2)_j$, -$SC_{0-2}(CR_2)_j$, -$O(CR_2)_{1-4}$, o  ; y X es $(CR_2)_j$ o [C(R)-(CR_2OR)];

R^4, R^5, R^9 y R^{10} son independientemente 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, alcoxilo, ciano, carboxilo o R^6; $(CR_2)_kCN$, $(CR_2)_{1-6}NR^7R^8$, $(CR_2)_{1-6}OR^7$, $(CR_2)_kC(O)O_{0-1}R^7$, $(CR_2)_kC(O)NR^7R^8$ o $(CR_2)_k$-R^6;

R^6 es un cicloalquilo de 3 a 7 átomos de carbono opcionalmente sustituido, arilo de 6 átomos de carbono, o un anillo de heteroarilo de 5 a 6 miembros o heterocíclico de 5 a 7 miembros;

R^7 y R^8 son independientemente $(CR_2)_k$-R^6 o 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, amido, hidroxilo, alcoxilo, ciano, carboxilo o R^6; o R^7 es H;

de una manera alternativa, R^4 y R^5 junto con N en cada NR^4R^5, R^7 y R^8 junto con N en NR^7R^8, o R^9 y R^{10} junto con N en NR^9R^{10} pueden formar un anillo heterocíclico de 4 a 7 miembros opcionalmente sustituido con 1 a 3 grupos R^{11};

R^{11} es R^8, $(CR_2)_k$–OR^7, CO_2R^7, $(CR_2)_k$–C(O)-$(CR_2)_k$-R^8, $(CR_2)_kC(O)NR^7R^8$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^8$, $(CR_2)_kS(O)_{1-2}R^8$ o $(CR_2)_kNRS(O)_{1-2}R^8$;

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

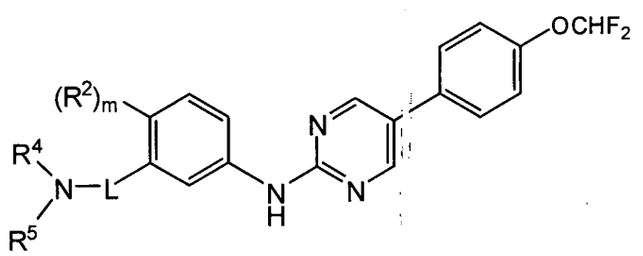
cada k es de 0 a 6; y

j y **m** son independientemente de 0 a 4;

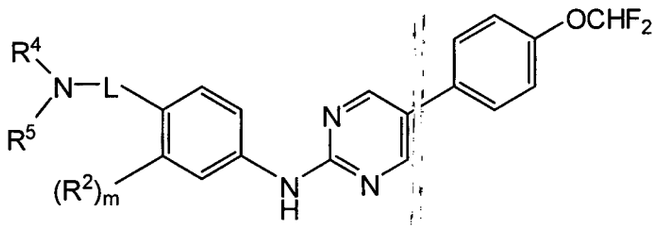
en el entendido de que R^1 no es trifluoro-metoxilo cuando R^3 es $C(O)NH_2$, $C(O)NR^{12}R^{13}$ o $SO_2NH(CH_2)_{2-3}NR^{14}R^{15}$; en donde R^{12} y R^{13} forman juntos piperazinilo, y R^{14} y R^{15} forman juntos morfolinilo.

En una modalidad, los compuestos tienen la fórmula (2A) o

(2B):



(2A)



(2B);

en donde R^4 y R^5 junto con N forman un anillo heterocíclico de 5 a 6 miembros que opcionalmente contiene NR^{16}, O, S, =O o un doble enlace; en donde este anillo heterocíclico está opcionalmente sustituido con 1 a 2 grupos R^{11};

R^{16} es H, R^8, $-(CR_2)_{1-4}CO_2R^7$, $(CR_2)_k-C(O)-(CR_2)_k-R^8$, $(CR_2)_kC(O)NR^7R^8$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_{1-4}NRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^8$, $(CR_2)_kS(O)_{1-2}R^8$ o $(CR_2)_kNRS(O)_{1-2}R^8$; y

R^4, R^5, R^7, R^8, R^{11}, R y **k** son como se definen en la fórmula (1).

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 y diaestereómeros puros. La invención abarca además los posibles tautómeros de los compuestos de la invención.

La presente invención también incluye todas las variaciones isotópicas adecuadas de los compuestos de la invención, o sales farmacéuticamente aceptables de los mismos. Una variación isotópica de un compuesto de la invención o de una sal farmacéuticamente aceptable del mismo se define como una en donde cuando menos un átomo es reemplazado por un átomo que tiene el mismo número atómico pero una masa atómica diferente de la masa atómica usualmente encontrada en la naturaleza. Los ejemplos de los isótopos que se pueden incorporar en los compuestos de la invención y las sales farmacéuticamente aceptables de los mismos incluyen, pero no se limitan a, isótopos de hidrógeno, carbono, nitrógeno y oxígeno, tales como as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F, ^{36}Cl y ^{123}I. Ciertas variaciones isotópicas de los compuestos de la invención y las sales farmacéuticamente aceptables de los mismos, por ejemplo, aquéllos en donde se incorpora un isótopo radioactivo tal como ^{3}H o ^{14}C, son útiles en los estudios de distribución del fármaco y/o el sustrato en el tejido.

En los ejemplos particulares, los isótopos de ^{2}H, ^{3}H y ^{14}C se pueden utilizar por su facilidad de preparación y detectabilidad. En otros ejemplos, la sustitución con isótopos, tales como ^{2}H, puede proporcionar ciertas ventajas terapéuticas que resultan de la mayor

estabilidad metabólica, tales como una mayor vida media *in vivo*, o requerimientos de dosificación reducida. Las variaciones isotópicas de los compuestos de la invención o las sales farmacéuticamente aceptables de los mismos, en términos generales se pueden preparar mediante procedimientos convencionales utilizando las variaciones isotópicas apropiadas de los reactivos adecuados. Las variaciones isotópicas de los compuestos tienen el potencial para cambiar el destino metabólico de un compuesto y/o para crear pequeños cambios en las propiedades físicas, tales como la hidrofobicidad, y similares. La variación isotópica tiene el potencial para mejorar la eficacia y la seguridad, para mejorar la bidisponibilidad y la vida media, para alterar el enlace de proteína, para cambiar la biodistribución, para aumentar la proporción de metabolitos activos, y/o para disminuir la formación de metabolitos reactivos o tóxicos.

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.

Los compuestos que tienen la fórmula (1), (2A) o (2B) 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. El valor IC_{50} en estos experimentos se da como la concentración del compuesto de prueba en cuestión que da como resultado un conteo celular que es el 50 por ciento más bajo que el obtenido utilizando el control sin inhibidor. En general, los compuestos de la invención tienen valores IC_{50} de 1 nM a 10 µM. En algunos ejemplos, los compuestos de la invención tienen valores IC_{50} de 0.01 µM a 5 µM. En otros ejemplos, los compuestos de la invención tienen valores IC_{50} de 0.01 µM a 1 µM, o más en particular de 1 nM a 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. Las fórmulas (1), (2A) y (2B) 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 una o más de las siguientes cinasas a 10 µM: cinasas c-kit, PDGFRα, PDGFRß, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFß, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2ß, BRK, Fms, KDR, c-raf o b-raf.

Los compuestos de la invención también se pueden utilizar para el tratamiento de una condición o enfermedad mediada por cinasa, tal como las enfermedades mediadas por las cinasas c-kit, PDGFRα, PDGFRß, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFß, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2ß, BRK, Fms, KDR, c-raf o b-raf.

De una manera más particular, los compuestos de la invención se pueden utilizar para el tratamiento y la prevención de asma, dermatitis atópica, urticaria, síndrome de intestino irritable (IBS), o una enfermedad fibrótica, incluyendo, pero no limitándose a, esclerodermia, fibrosis pulmonar, fibrosis pulmonar idiopática (IPF), hipertensión pulmonar primaria (PPH), hipertensión arterial pulmonar primaria (PPAH), hipertensión arterial idiopática (IPAH), fibrosis hepática, fibrosis renal y fibrosis cardíaca.

Farmacología y Utilidad

Los compuestos de la invención se rastrean contra el panel de cinasa (de tipo silvestre y/o mutaciones de la misma), y pueden modular la actividad de cuando menos un miembro del panel de cinasa. Como tales, los compuestos de la invención pueden ser útiles para el tratamiento de enfermedades o trastornos en donde las cinasas contribuyan a la patología y/o sintomatología de la enfermedad. Los ejemplos de las cinasas que pueden ser inhibidas por los compuestos y composiciones descritas en la presente, y contra las cuales pueden ser útiles los métodos descritos en la presente incluyen, pero no se limitan a, las cinasas c-kit, PDGFRα,

PDGFRß, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFß, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2ß, BRK, Fms, KDR, c-raf o b-raf.

c-Kit

Los mastocitos son elementos de tejido derivados a partir de un subconjunto particular de células totipotentes hematopoiéticas que expresan los antígenos CD34, c-kit y CD13. Los mastocitos se caracterizan por su heterogeneidad, no solamente con respecto a la localización y estructura del tejido, sino también a los niveles funcionales e histoquímicos. Los progenitores de mastocitos inmaduros circulan en la corriente sanguínea y se diferencian en diferentes tejidos. Estos procesos de diferenciación y proliferación están bajo la influencia de las citoquinas, siendo una de importancia el Factor de Células Totipotentes (SCF), también denominado como el ligando Kit, Factor Steel, o Factor de Crecimiento de Mastocitos. El receptor del Factor de Células Totipotentes es codificado por el proto-oncogén, c-kit, que se expresa en las células progenitoras hematopoiéticas, en los mastocitos, en las células germinales, en las células intersticiales de Cajal (ICC), y en algunos tumores humanos, y también es expresado por las células no hematopoiéticas.

Las cinasas de tirosina son proteínas de tipo receptoras o de tipo no receptoras, las cuales transfieren el fosfato terminal de ATP a los residuos de tirosina de las proteínas, activando o inactivando de esta manera las sendas de trasducción de señales. El receptor del Factor de Células Totipotentes, c-kit, es una cinasa de proteína

tirosina receptora transmembrana Tipo III que inicia las cascadas de transducción de señales de crecimiento y proliferación celular en respuesta al enlace del Factor de Células Totipotentes. El ligamiento del receptor c-kit con el Factor de Células Totipotentes induce su dimerización seguida por su transforilación, conduciendo al reclutamiento y a la activación de diferentes sustratos intracitoplásmicos. Estos sustratos activados inducen múltiples sendas de señalización intracelular responsables de la proliferación y activación celular. Se sabe que estas proteínas están involucradas en muchos mecanismos celulares, que en caso de interrumpirse, conducen a trastornos, tales como una proliferación y migración celular anormal, así como inflamación. Los compuestos de la presente invención pueden inhibir los procesos celulares que involucran al Factor de Células Totipotentes, tales como inhibir la autofosforilación del receptor del Factor de Células Totipotentes y la activación de la cinasa MAPK estimulada por el Factor de Células Totipotentes (cinasa de proteína activada por mitógeno).

La actividad de la cinasa de proteína tirosina receptora c-kit está regulada en las células normales, y es importante la actividad funcional normal del producto genético c-kit para el mantenimiento de una hematopoiesis, melanogénesis, genetogénesis, y crecimiento y diferenciación normales de los mastocitos. En adición a su importancia en las actividades fisiológicas celulares normales, c-kit tiene un papel en los aspectos biológicos de ciertos cánceres humanos, y la actividad mal regulada de la cinasa c-kit está

implicada en la patogénesis de los cánceres humanos, y en ciertos tipos de tumores. Se puede presentar una proliferación de crecimiento de células tumorales mediado por c-kit mediante una mutación específica del polipéptido c-kit que da como resultado una activación independiente del ligando, o mediante el estímulo autócrino del receptor. En el primer caso, las mutaciones que causan la activación constitutiva de la actividad de la cinasa c-kit en ausencia de enlace del Factor de Células Totipotentes, están implicadas en los cánceres humanos malignos, incluyendo tumores de células germinales, tumores de mastocitos, tumores estromales gastrointestinales, cáncer pulmonar de células pequeñas, melanoma, cáncer de mama, leucemia mielógena aguda, neuroblastoma, y mastocitosis.

Los mastocitos presentes en los tejidos de los pacientes están implicados en, o contribuyen a, la génesis de enfermedades tales como enfermedades autoinmunes (esclerosis múltiple, artritis reumatoide, enfermedades inflamatorias del intestino (IBD)), enfermedades alérgicas, angiogénesis tumoral, enfermedades inflamatorias, y cistitis intersticial. Las enfermedades alérgicas incluyen, pero no se limitan a, rinitis alérgica, sinusitis alérgica, síndrome anafiláctico, urticaria, angioedema, dermatitis atópica, dermatitis alérgica por contacto, eritema nodosum, eritema multiforme, venulitis necrotizante cutánea, inflamación de la piel por mordedura de insecto, y asma. El asma se caracteriza por obstrucción del flujo de aire, híper-respuesta bronquial e inflamación

de las vías respiratorias, e incluye asma bronquial y asma alérgico.

En estas enfermedades, los mastocitos participan en la destrucción de los tejidos mediante la liberación de un cóctel de diferentes proteasas y mediadores, tales como histamina, proteasas neutras, mediadores derivados de lípido (prostaglandinas, tromboxanos y leucotrienos), y diferentes citoquinas (IL-1, IL-2, IL-3, IL-4, IL-5, IL- 6, IL-8, TNF-A, GM-CSF, MIP-LA, MIP-Ib, MIP-2 e IFN-y). La activación de los mastocitos induce diversas respuestas efectoras, tales como secreción de mediadores alérgicos, proteasas, quimiocinas tales como MCP-1 y RANTES, leucotrienos, prostaglandinas, neurotrofinas, la inducción de la transcripción del gen de citoquina (IL-4, IL-5, IL-6, IL-13, TNFA y GM-CSF). Estos mediadores contribuyen a crear el fenotipo asmático por sus efectos sobre las células endoteliales, las células de músculo liso, y los fibroblastos, y sobre la matriz extracelular, y mediante el reclutamiento de otras células inflamatorias.

Los mastocitos pueden tener un papel en el asma, como es sugerido por el tratamiento con anticuerpo monoclonal anti-IgE humanizado. El objetivo principal de la terapia anti-IgE es dirigirse específicamente a la IgE, con el resultado de inactivar la anti-IgE libre y detener la producción adicional de IgE. En adición, debido a que los niveles de IgE son un importante regulador del nivel de expresión del receptor de IgE, FceRI, un objetivo de esta terapia es reducir la expresión de FceRI en los mastocitos y en los basófilos, y, como consecuencia, disminuir la capacidad de estas células para

activarse. La capacidad de la terapia anti-IgE para reducir la expresión de FceRI se ha demostrado en basófilos. La disminución de la expresión de FceRI en los basófilos está asociada con una disminución en la capacidad de los basófilos para secretar mediadores después de su activación.

Los inhibidores de c-kit también se pueden utilizar en el tratamiento de diabetes mellitus no dependiente de insulina (NLDDM), también conocida como diabetes tipo II, una enfermedad crónica que aparece cuando la insulina es ineficiente para promover la absorción de glucosa por parte de las células, dando como resultado mayores niveles de glucosa en la sangre. Esta enfermedad afecta a aproximadamente 100 millones de personas en todo el mundo, el 75 por ciento de las cuales son obesas en el momento del diagnóstico. Durante muchos años, el fracaso de la regulación de la absorción de glucosa conduce al desarrollo de diabetes Tipo II, y se necesita regular el nivel de glucosa en sangre con productos medicinales. Finalmente, el nivel de glucosa en sangre mal regulado es responsable de daños a los vasos sanguíneos, al riñón, y a los ojos, así como de enfermedades cardiovasculares. Estos daños de tejido contribuyen a la mortalidad en los diabéticos.

En adición, la activación de los mastocitos por diferentes estímulos, tales como tensión, trauma, infección, así como de los neurotransmisores, puede participar en la exacerbación del desequilibrio químico que provoca trastornos del sistema nervioso central. De una manera más específica, la desgranulación de los

mastocitos es estimulada por los neurotransmisores comunes, tales como neurotensina, somatostatina, sustancia P, y acetil-colina, por los factores de crecimiento o de sobrevivencia, notoriamente tal como el NGF; los mastocitos TGFßL involucrados en la respuesta a estos estímulos pueden ser los mastocitos cerebrales, pero también otros mastocitos que liberen el contenido de sus gránulos hacia la corriente sanguínea, que finalmente alcanzan las neuronas sensoriales, motoras, o cerebrales. El teñido de los mastocitos cerebrales es un tipo de teñido de CTMC, pero muestran el patrón secretor de MMC, implicando que constituyen un subconjunto particular de mastocitos que presentan especificidades.

En seguida de la activación de los mastocitos, los gránulos liberados liberan diferentes factores capaces de modular y alterar la neurotransmisión y la sobrevivencia de las neuronas. Entre estos factores, la serotonina es importante, debido a que se ha observado un incremento en el nivel de serotonina libre en los pacientes deprimidos. De una manera alternativa, la repentina elevación de serotonina puede ser seguida por un período de agotamiento de serotonina, conduciendo a dolor y a migraña. Como una consecuencia, se cree que los mastocitos exacerban de una manera autócrina o parácrina la mala regulación de la neurotransmisión. Por ejemplo, la liberación de neurotransmisores, tales como la serotonina, inducida por ansiedad o por tensión, activa los mastocitos, los cuales a su vez liberan el contenido de sus gránulos, contribuyendo adicionalmente al desequilibrio químico en el cerebro,

conduciendo a trastornos del sistema nervioso central.

Otros mediadores liberados por los mastocitos se pueden categorizar en vasoactivos, nociceptivos, pro-inflamatorios, y otros neurotransmisores. Tomados juntos, estos factores son capaces de inducir una gran alteración en la actividad de las neuronas, ya sea sensoriales, motoras, o neuronas del sistema nervioso central. En adición, los pacientes afligidos con mastocitosis están más inclinados a desarrollar trastornos del sistema nervioso central que la población normal. Esto se puede explicar por la presencia de mutaciones activadoras en el receptor c-kit, que inducen la desgranulación de los mastocitos y una explosión de factores que contribuyen al desequilibrio químico y a la alteración de la neurotransmisión.

En algunos casos, los mastocitos activados también pueden participar en la destrucción de los tejidos neuronales mediante la liberación de un cóctel de diferentes proteasas y mediadores categorizados en tres grupos: mediadores asociados con gránulos preformados (histamina, proteoglicanos, y proteasas neutras), mediadores derivados de lípidos (prostaglandinas, tromboxanos, y leucotrienos), y diferentes citoquinas (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-A, GM-CSF, MIP-LA, MIP-Ib, MIP-2 e IFN-y). La liberación por parte de los mastocitos activados de mediadores (TNF-A, histamina, leucotrienos, prostaglandinas, etc.), así como de proteasas, puede: i) inducir inflamación y vasodilatación, y ii) participar en el proceso de destrucción del tejido neuronal. La

inhibición de la actividad de c-kit reduce la proliferación celular, agotando los mastocitos responsables de las enfermedades y/o condiciones, sugiriendo de esta manera un papel para el uso de inhibidores de c-kit en el tratamiento de enfermedades y/o condiciones dependientes de c-kit, tales como trastornos del sistema nervioso central.

También se han identificado mastocitos que están involucrados en, o que contribuyen a, la dependencia de drogas y los síntomas de abstinencia. La dependencia de drogas es el resultado de un fenómeno denominado como tolerancia, que es la necesidad de aumentar la dosis de la droga para mantener su efecto total, y de dependencia física, que es la habituación del cuerpo a una droga. Cuando se interrumpe la ingestión de una droga, el individuo puede experimentar un síndrome de abstinencia desagradable.

La activación de los mastocitos por diferentes drogas, incluyendo, pero no limitándose a, derivados salicílicos, derivados de morfina, opioides, heroína, anfetaminas, alcohol, nicotina, analgésicos, anestésicos, y ansiolíticos, da como resultado la desgranulación de los mastocitos, los cuales participan en la exacerbación del desequilibrio químico responsable de la habituación a drogas y del síndrome de abstinencia. En seguida de la activación de los mastocitos, los gránulos liberados liberan diferentes factores capaces de modular y alterar la neurotransmisión. Entre estos factores está la morfina, que se enlaza o se almacena en los gránulos de los mastocitos. El humo del tabaco también induce la

liberación de mediadores desde los mastocitos caninos, y modula la producción de prostaglandina, conduciendo a asma. En adición, los pacientes afligidos con mastocitosis están más inclinados a desarrollar trastornos por uso de sustancias que la población normal. Esto puede ser explicado por la presencia de mutaciones activadoras en el receptor c-kit, que inducen la desgranulación de los mastocitos y una explosión de factores que contribuyen al desequilibrio químico y a la alteración de la neurotransmisión.

En la actualidad no existe ningún tratamiento disponible que proporcione alivio y que ayude a los individuos a retirarse de los trastornos de abuso de sustancias. Los inhibidores de c-kit se pueden utilizar para el tratamiento de trastornos por abuso de sustancias, en particular adicción a drogas, abuso de drogas, habituación a drogas, dependencia de drogas, síndrome de abstinencia, y sobredosis, el cual comprende administrar un compuesto capaz de agotar los mastocitos de un ser humano que necesite dicho tratamiento.

c-Kit tiene una homología sustancial con el receptor del factor de crecimiento derivado de plaquetas y con el receptor de CSF-1 (c-Fms). Las investigaciones sobre diferentes líneas celulares eritroides y mieloides indican una expresión del gen c-Kit en las primeras etapas de diferenciación (Andre y colaboradores, *Oncogene* 1989 4: 1047-1049). Ciertos tumores, tales como las células de glioblastoma, de la misma manera exhiben una expresión pronunciada del gen c-Kit.

PDGF (Factor de crecimiento derivado de plaquetas)

El PDGF (Factor de crecimiento derivado de plaquetas) tiene un papel importante tanto en el crecimiento normal como también en la proliferación celular patológica. Los compuestos de la invención pueden inhibir la actividad del receptor del factor de crecimiento derivado de plaquetas (PDGFR), y se pueden utilizar como un agente para tratar trastornos proliferativos no malignos, tales como esclerodermia y otros trastornos fibróticos, ateroesclerosis, trombosis o soriasis. Los compuestos de la presente invención también se pueden utilizar como una sustancia inhibidora de tumor, por ejemplo en cáncer pulmonar de células pequeñas, gliomas, sarcomas, tumores de próstata, y tumores del colon, mama, y ovario.

En una modalidad, los compuestos de la invención se pueden utilizar para el tratamiento y la prevención de un trastorno o enfermedad fibrótica, una condición relacionada o asociada con la formación y el depósito de los componentes de matriz extracelular en los órganos internos, incluyendo los riñones, corazón, pulmones, hígado, piel, y articulaciones. Diversos estudios han implicado al PDGFR como un jugador central en las respuestas fibróticas a la lesión del tejido, por ejemplo:

i) el PDGF aumenta en los macrófagos alveolares de los pacientes con fibrosis pulmonar idiopática (IPF);

ii) el PDGFRβ es uno de los primeros genes aumentados después de la activación de las células estrelladas hepáticas para llegar a ser miofibroblastos, un paso central en el desarrollo de

fibrosis en el hígado;

iii) el PDGF y sus receptores son significativamente aumentados en esclerodermia, y de una manera similar, aumentan en el proceso de fibrogénesis renal;

iv) el PDGF se induce mediante lesión y/o mediante citoquinas pro-inflamatorias, o en una forma autocrina sobre los miofibroblastos que impulsan su proliferación, diferenciación, y migración. Estos miofibroblastos entonces secretan proteínas de matriz extracelular y colágeno, conduciendo a escarificación y daño progresivo de órganos. La secreción de TGFβ también contribuye de una manera significativa a la producción de colágeno durante la fibrogénesis;

v) un transgén de PDGF-C induce el desarrollo de fibrosis hepática en ratones, mientras que una versión negativa-dominante soluble de PDGFRβ previene la fibrosis hepática en ratas; y

vi) la administración de PDGF-B al riñón promovió los signos de fibrogénesis renal en ratas.

Los trastornos o enfermedades fibróticas que se pueden tratar utilizando los compuestos de la invención incluyen enfermedades pulmonares fibróticas, tales como fibrosis pulmonar (o enfermedad pulmonar intersticial o fibrosis pulmonar intersticial), fibrosis pulmonar idiopática, hipertensión pulmonar primaria, hipertensión arterial pulmonar idiopática, el elemento fibrótico de neumoconiosis (el cual está asociado con la exposición a los riesgos medio-ambientales, tales como fumar, asbestos, pelusa de algodón, polvo

de piedra, polvo de minas y otras partículas), sarcoidosis pulmonar, alveolitis fibrosante, el elemento fibrótico o hipertrófico de la fibrosis quística, enfermedad pulmonar obstructiva crónica, síndrome de insuficiencia respiratoria de adultos, y enfisema. Los compuestos de la invención también se pueden utilizar para el tratamiento y la prevención de enfermedades que tengan, como una manifestación, hipertrofia fibrótica de los riñones (fibrosis renal), del hígado (fibrosis hepática), corazón (fibrosis cardíaca), próstata (por ejemplo, hipertrofia prostática benigna (BPH)), pleura (por ejemplo, pleuritis, fibrosis pleural), páncreas, y de la piel y/o de los tejidos musculares, tales como esclerodermia, fascitis eosinofílica, lesiones discoides asociadas con lupus o lupus discoide o adhesiones quirúrgicas.

Otros trastornos o enfermedades fibróticas que se pueden tratar utilizando los compuestos de la invención incluyen, pero no se limitan a, esclerosis sistémica, enfermedad de tejido conectivo mixto, fibrodisplasia, enfermedad fibroquística, sarcoidosis, miositis (por ejemplo, polimiositis, polimiositis idiopática primaria, polimiositis de la infancia, dermatomiositis, dermatomiositis de la infancia, dermatomiositis idiopática primaria en adultos, miositis de cuerpos de inclusión, polimiositis o dermatomiositis asociada con tumores malignos); enfermedades que tienen, como una manifestación, hipertrofia de íntima vascular fibrótica, tal como vasculitis (incluyendo vasculitis de arteria coronaria), poliarteritis nodosa o arteritis temporal; enfermedades que tienen, como una manifestación, hipertrofia fibrótica del tejido nervioso tal como

cerebroesclerosis, esclerosis anular; esclerosis difusa y esclerosis lobar; y enfermedades que tienen, como una manifestación, hipertrofia fibrótica o fibrosis de la pared intestinal, tal como enfermedad inflamatoria del intestino, incluyendo enfermedad de Crohn.

Adicionalmente, los compuestos de la presente invención también pueden ser útiles para la protección de las células totipotentes, por ejemplo para combatir el efecto hemotóxico de los agentes quimioterapéuticos, tales como 5-fluoro-uracilo; y también pueden ser útiles para el tratamiento de asma e hipereosinofilia. Los compuestos de la invención se pueden utilizar en especial para el tratamiento de enfermedades que respondan a la inhibición de la cinasa receptora del factor de crecimiento derivado de plaquetas.

Los compuestos de la presente invención también pueden exhibir efectos útiles en el tratamiento de trastornos que se presenten como un resultado de trasplante, por ejemplo, trasplante alogénico, en especial rechazo de tejido, tal como bronquiolitis obliterativa (OB), es decir, un rechazo crónico de trasplantes alogénicos de pulmón. En contraste con los pacientes sin OB, aquéllos con OB con frecuencia muestran una concentración elevada del factor de crecimiento derivado de plaquetas en los fluidos del lavado broncoalveolar.

Los compuestos de la presente invención también pueden ser efectivos contra las enfermedades asociadas con la migración y proliferación de células de músculo liso vascular (en donde PDGF y

PDGFR también tienen con frecuencia un papel), tales como restenosis y ateroesclerosis. Estos efectos y las consecuencias de los mismos para la proliferación o migración de células de músculo liso vascular *in vitro* e *in vivo* se pueden demostrar mediante la administración de los compuestos de la presente invención, y también mediante la investigación de su efecto sobre el engrosamiento de la íntima vascular en seguida de lesión mecánica *in vivo*.

CSF1R (FMS)

La proteína codificada por este gen es el receptor para el factor estimulante de colonias 1, una citoquina que controla la producción, diferenciación, y función de los macrófagos. CSFR1 media la mayoría de, si no es que todos, los efectos biológicos de esta citoquina. La proteína codificada es un receptor transmembrana de cinasa de tirosina y miembro de la familia de cinasas de proteína tirosina receptoras de CSF1/PDGF. Las mutaciones en este gen se han asociado con una predisposición a la malignidad mieloide. (Véase, por ejemplo, Casas y colaboradores, *Leuk. Linphoma* 2003, 44: 1935-41).

Abl, Trk, Syk, Ras, Raf, MAPK, TGFβ, FGFR3, c-Src, SAPK, Lck, Fes, Csk

La cinasa de tirosina de Abelson (es decir, Abl, c-Abl) está involucrada en la regulación del ciclo celular, en la respuesta celular a la tensión genotóxica, y en la transmisión de información acerca del medio ambiente celular a través de la señalización de integrina.

Parece que la proteína Abl sirve a un papel complejo como un módulo celular que integra las señales desde diferentes fuentes extracelulares e intracelulares, y que tiene influencia sobre las decisiones con respecto al ciclo celular y a la apoptosis. La cinasa de tirosina de Abelson incluye los subtipos derivados, tales como la fusión quimérica (oncoproteína) BCR-Abl con una actividad de cinasa de tirosina mal regulada, o la v-Abl.

La proteína de fusión BCR-Abl es un resultado de una translocalización recíproca que fusiona el proto-oncogén Abl con el gen Bcr. Entonces, BCR-Abl es capaz de transformar las células-B a través del incremento de la actividad mitogénica. Este incremento da como resultado una reducción de la sensibilidad a la apoptosis, así como la alteración de la adhesión e inicio de las células progenitoras CML.

BCR-Abl es importante en la patogénesis del 95 por ciento de la leucemia mielógena crónica (CML) y del 10 por ciento de la leucemia linfocítica aguda. STI-571 (GLEEVEC®) es un inhibidor de la cinasa de tirosina oncogénica BCR-Abl, y se utiliza para el tratamiento de leucemia mieloide crónica (CML). Sin embargo, algunos pacientes en la etapa de crisis de explosión de leucemia mieloide crónica son resistentes al STI-571, debido a las mutaciones en la cinasa BCR-Abl. Se han reportado más de 22 mutaciones hasta la fecha, tales como G250E, E255V, T315I, F317L y M351T.

Los compuestos de la presente invención pueden inhibir la cinasa abl, por ejemplo la cinasa v-abl. Los compuestos de la

presente invención también pueden inhibir la cinasa BCR-Abl de tipo silvestre, y las mutaciones de la cinasa BCR-Abl, y por lo tanto, pueden ser adecuados para el tratamiento de cáncer y enfermedades tumorales positivas para Bcr-abl, tales como leucemias (en especial leucemia mieloide crónica y leucemia linfoblástica aguda, en donde se encuentran en especial los mecanismos de acción apoptóticos). Los compuestos de la presente invención también pueden ser efectivos contra las células totipotentes leucémicas, y pueden ser potencialmente útiles para la purificación de estas células *in vitro* después de remover estas células (por ejemplo, remoción de médula ósea), y para el reimplante de las células una vez que se han limpiado de las células de cáncer (por ejemplo, reimplante de células de médula ósea purificadas).

La familia trk de receptores de neurotrofina (trkA, trkB, trkC) promueve la sobrevivencia, el crecimiento, y la diferenciación de los tejidos neuronales y no neuronales. La proteína TrkB se expresa en las células de tipo neuroendocrino en el intestino delgado y en el colon, en las células alfa del páncreas, en los monocitos y macrófagos de los nodos linfáticos y del bazo, y en las capas granulares de la epidermis (Shibayama y Koizumi, 1996). La expresión de la proteína TrkB se ha asociado con un progreso desfavorable de los tumores de Wilms y de los neuroblastomas. Más aún, la TrkB se expresa en las células de próstata cancerosas, pero no en las células normales. La senda de señalización corriente abajo de los receptores de trk involucra la cascada de activación de MAPK

a través de los genes Shc, Ras activado, ERK-1, y ERK-2, y la senda de transducción de PLC-gamma (Sugimoto y colaboradores, 2001).

Syk es una cinasa de tirosina que tiene un papel importante en la desgranulación de los mastocitos y en la activación de los eosinófilos. De conformidad con lo anterior, la cinasa Syk está implicada en diferentes trastornos alérgicos, en particular asma. Se ha demostrado que Syk se enlaza con la cadena gamma fosforilada del receptor FcεR1 por medio de los dominios N-terminales SH2, y es importante para la señalización corriente abajo.

La senda de señalización Ras-Raf-MEK-ERK media la respuesta celular a las señales de crecimiento. Ras se muta hasta una forma oncogénica en aproximadamente el 15 por ciento del cáncer humano. La familia Raf pertenece a la cinasa de proteína serina/treonina, e incluye a tres miembros: A-Raf, B-Raf, y c-Raf (ó Raf-1). B-Raf puede tener un papel prominente en la formación de ciertos tumores sin requerimiento de un alelo Ras activado (*Nature*, 417: 949-954 (2002)). Se han detectado mutaciones de B-Raf en un gran porcentaje de melanomas malignos.

Los tratamientos médicos existentes para melanoma están limitados en su efectividad, en especial para los melanomas en etapa tardía. Los compuestos de la presente invención también inhiben los procesos celulares que involucran a la cinasa b-Raf, proporcionando una nueva oportunidad terapéutica para el tratamiento de los cánceres humanos, en especial para melanoma.

Las cinasas de proteína activadas por mitógeno (MAPKs) son

miembros de las sendas de transducción de señales conservadas que activan los factores de transcripción, los factores de traducción, y otras moléculas objetivo, en respuesta a una variedad de señales extracelulares. Las cinasas de proteína activadas por mitógeno son activadas por la fosforilación en un motivo de fosforilación doble que tiene la secuencia Thr-X-Tyr, mediante las cinasas de cinasa de proteína activada por mitógeno (MKKs). En los eucariotes superiores, se ha correlacionado el papel fisiológico de la señalización de las cinasas de proteína activadas por mitógeno, con los eventos celulares tales como proliferación, oncogénesis, desarrollo, y diferenciación. De conformidad con lo anterior, la capacidad para regular la transducción de señales por medio de estas sendas (en particular por medio de MKK4 y MKK6), podría conducir al desarrollo de tratamientos y terapias preventivas para las enfermedades humanas asociadas con la señalización de las cinasas de proteína activadas por mitógeno, tales como enfermedades inflamatorias, enfermedades autoinmunes, y cáncer.

Múltiples formas de la MAPK p38 (α, ß, γ, δ), cada una codificada por un gen separado, forman parte de una cascada de cinasa involucrada en la respuesta de las células a una variedad de estímulos, incluyendo tensión osmótica, luz ultravioleta, y eventos mediados por citoquina. Se piensa que estas cuatro isoformas de p38 regulan diferentes aspectos de la señalización intracelular. Su activación es parte de una cascada de eventos de señalización que conducen a la síntesis y producción de las citoquinas pro-

inflamatorias como TNFα. P38 funciona mediante la fosforilación de los sustratos corriente abajo que incluyen otras cinasas y factores de transcripción. Se ha demostrado que los agentes que inhiben la cinasa p38 bloquean la producción de citoquinas, incluyendo, pero no limitándose a, TNFα, IL-6, IL-8 e IL-1ß.

Se ha demostrado que los monocitos de sangre periférica (PBMCs) expresan y secretan citoquinas pro-inflamatorias cuando son estimuladas con lipopolisacáridos (LPS) *in vitro*. Los inhibidores de p38 bloquean eficientemente este efecto cuando los monocitos de sangre periférica son previamente tratados con estos compuestos antes del estímulo con lipopolisacáridos. Los inhibidores de p38 son eficaces en modelos animales de enfermedad inflamatoria. Los efectos destructivos de muchos estados de enfermedad son causados por la sobreproducción de citoquinas pro-inflamatorias. La capacidad de los inhibidores de p38 para regular esta sobreproducción los hace útiles como agentes modificadores de la enfermedad.

Se ha demostrado que las moléculas que bloquean la función de p38 son efectivas para inhibir la resorción ósea, inflamación, y otras patologías inmunes y basadas en la inflamación. Por consiguiente, un inhibidor de p38 seguro y efectivo proporcionaría un medio para tratar las enfermedades debilitantes que puedan ser reguladas mediante la modulación de la señalización de p38. Por consiguiente, los compuestos de la invención que inhiban la actividad de p38 son útiles para el tratamiento de inflamación,

osteoartritis, artritis reumatoide, cáncer, enfermedades autoinmunes, y para el tratamiento de otras enfermedades mediadas por citoquina.

El factor de crecimiento transformante-beta (TGFß) denota una súper-familia de proteínas que incluye, por ejemplo, TGFß1, TGFß2, y TGFß3, que son moduladores pleotrópicos de crecimiento y diferenciación celular, desarrollo embrionario y óseo, formación de matriz extracelular, hematopoiesis, respuestas inmunes e inflamatorias. Los miembros de la familia TGFß inician las sendas de señalización intracelular que conducen finalmente a la expresión de los genes que regulan el ciclo celular, controlan las respuestas proliferativas, o se relacionan con las proteínas de matriz extracelular que median la señalización de afuera hacia dentro, la adhesión celular, la migración, y la comunicación intercelular.

En consecuencia, los compuestos de la invención que sean inhibidores de la senda de señalización intracelular de TGFß, son productos terapéuticos útiles para las enfermedades fibroproliferativas, incluyendo trastornos de riñón asociados con una actividad mal regulada de TGFß y una fibrosis excesiva, incluyendo glomerulonefritis (GN), tal como glomerulonefritis proliferativa mesangial, glomerulonefritis inmune, y glomerulonefritis crescéntica. Otras condiciones renales incluyen nefropatía diabética, fibrosis intersticial renal, fibrosis renal en pacientes de trasplante que reciban ciclosporina, y nefropatía asociada con VIH. Los trastornos vasculares de colágeno incluyen esclerosis sistémica progresiva, plimiositis, esclerodermia, dermatomiositis, fascitis eosinofílica,

morfea, o aquéllos asociados con la presentación de síndrome de Raynaud. Las fibrosis pulmonares resultantes de la actividad excesiva de TGFß incluyen síndrome de insuficiencia respiratoria de adultos, enfermedad pulmonar obstructiva crónica (COPD), fibrosis pulmonar idiopática, y fibrosis pulmonar intersticial con frecuencia asociada con trastornos autoinmunes, tales como lupus eritematoso sistémico y esclerodermia, contacto químico, o alergias. Otro trastorno autoinmune asociado con las características fibroproliferativas es la artritis reumatoide. Las condiciones fibroproliferativas pueden estar asociadas con procedimientos quirúrgicos de los ojos. Estos procedimientos incluyen cirugía de unión retinal acompañando a vitreo-retinopatía proliferativa, extracción de catarata con implante de lente intraocular, y cirugía de drenaje posterior a glaucoma.

Se demostró que el receptor del factor de crecimiento de fibroblastos 3 ejerce un efecto regulador negativo sobre el crecimiento óseo y una inhibición de la proliferación de los condrocitos. La displasia tanatofórica es causada por diferentes mutaciones en el receptor del factor de crecimiento de fibroblastos 3. Una mutación, TDII FGFR3, tiene una actividad de cinasa de tirosina constitutiva que activa el factor de transcripción Stat1, conduciendo a la expresión de un inhibidor del ciclo celular, paro del crecimiento, y desarrollo óseo anormal (Su y colaboradores, *Nature* 1997, 386: 288-292). El FGFR3 también se expresa con frecuencia en los cánceres de tipo mieloma múltiple.

La cinasa c-Src transmite las señales oncogénicas de muchos receptores. Por ejemplo, la sobre-expresión del receptor de factor de crecimiento epidérmico o de HER2/neu en los tumores, conduce a la activación constitutiva de c-src, que es una característica para las células malignas, pero que está ausente de las células normales. Por otra parte, los ratones deficientes en la expresión de c-src exhiben un fenotipo osteopetrótico, indicando una participación clave de c-src en la función de los osteoclastos, y un posible involucramiento en los trastornos relacionados.

La familia de las cinasas de proteína ribosomal S6 humana consiste en cuando menos 8 miembros (RSK1, RSK2, RSK3, RSK4, MSK1, MSK2, p70S6K y p70S6Kb). Las cinasas de proteína de la proteína ribosomal S6 tienen funciones pleotrópicas importantes, y entre ellas está un papel clave en la regulación de la traducción del ARNm durante la biosíntesis de proteína (*Eur. J. Biochem*, Noviembre de 2000; 267 (21): 6321-30, *Exp Cell Res.*, 25 de Noviembre de 1999; 253 (1): 100-9, *Mol. Cell Endocrinol.* 1999; 151 (1-2): 65-77). También se ha implicado la fosforilación de la proteína ribosomal S6 mediante p70S6 en la regulación de la movilidad celular (*Immunol. Cell Biol.* Agosto de 2000; 78 (4): 447-51), y del crecimiento celular (*Prog. Nucleic Acid Res. Mol. Biol.*, 2000; 65: 101-27), y por consiguiente, puede ser importante en la metástasis tumoral, en la respuesta inmune, y en la reparación de tejido, así como en otras condiciones de enfermedad.

Las SAPKs (también llamadas "cinasas N-terminales jun" o

"JNKs"), son una familia de cinasas de proteína que representan el penúltimo paso en las sendas de transducción de señales que dan como resultado la activación del factor de transcripción c-jun y la expresión de los genes regulados por c-jun. En particular, c-jun está involucrado en la transcripción de los genes que codifican las proteínas involucradas en la reparación del ADN que sea dañado debido a agresiones genotóxicas. Los agentes que inhiban la actividad de SAPK en una célula, impiden la reparación del ADN, y sensibilizan a la célula a las modalidades terapéuticas de cáncer que actúan mediante la inducción de daño del ADN.

Lck tiene un papel en la señalización de células-T. Los ratones que carecen del gen Lck, tienen una nula capacidad para desarrollar timocitos. La función de Lck como un activador positivo de la señalización de células-T, sugiere que los inhibidores de Lck pueden ser útiles para el tratamiento de una enfermedad autoinmune, tal como artritis reumatoide.

Fes se expresa fuertemente en las células hematopoiéticas mieloides, y está implicado en las sendas de señalización tanto de diferenciación como de sobrevivencia en los leucocitos mieloides. CSK está implicado en los cánceres, en particular los cánceres colo-rectales y de mama.

De conformidad con lo anterior, la presente invención proporciona además un método para prevenir o tratar cualquiera de las enfermedades o trastornos descritos anteriormente, en un sujeto que necesite dicho tratamiento, cuyo método comprende administrar

a este sujeto una cantidad terapéuticamente efectiva (véase, "Administration and Pharmaceutical Compositions", más adelante) de un compuesto de la Fórmula (1), (2A), (2B) o (C), ó una sal farmacéuticamente aceptable del mismo. Para cualquiera de los usos anteriores, la dosificación requerida variará dependiendo del modo de administración, de la condición particular que se vaya a tratar, y del efecto deseado.

Administración y Composiciones Farmacéuticas

Una composición farmacéutica, como se utiliza en la presente, se refiere a una mezcla de un compuesto de la invención con otros componentes químicos, tales como vehículos, estabilizantes, diluyentes, agentes dispersantes, agentes de suspensión, agentes espesantes, y/o excipientes. La composición farmacéutica facilita la administración del compuesto a un organismo. Las composiciones farmacéuticas que contienen un compuesto de la invención se pueden administrar en cantidades terapéuticamente efectivas como composiciones farmacéuticas mediante cualquier forma y vía convencional conocida en la materia, incluyendo, pero no limitándose a: administración intravenosa, oral, rectal, en aerosol, parenteral, oftálmica, pulmonar, transdérmica, vaginal, ótica, nasal, y tópica.

Se puede administrar el compuesto de una manera local en lugar de sistémica, por ejemplo mediante la inyección del compuesto directamente en un órgano, con frecuencia en una formulación de depósito o de liberación sostenida. Adicionalmente, se puede administrar una composición farmacéutica que contenga un

compuesto de la invención en un sistema de suministro dirigido de fármacos, por ejemplo, en un liposoma recubierto con anticuerpo específico del órgano. Los liposomas se dirigirán y serán absorbidos selectivamente por el órgano. En adición, las composiciones farmacéuticas que contienen un compuesto de la invención se pueden proporcionar en la forma de una formulación de liberación rápida, en la forma de una formulación de liberación prolongada, o en la forma de una formulación de liberación intermedia.

Para administración oral, un compuesto de la invención se puede formular fácilmente mediante la combinación de los compuestos activos con vehículos o excipientes farmacéuticamente aceptables bien conocidos en la materia. Estos vehículos hacen posible que los compuestos descritos en la presente se formulen como tabletas, polvos, píldoras, grageas, cápsulas, líquidos, geles, jarabes, elíxires, pastas acuosas, suspensiones y similares, para ingestión oral por parte de un paciente que se vaya a tratar.

Las preparaciones farmacéuticas para uso oral se pueden obtener mediante la mezcla de uno o más excipientes sólidos con uno o más de los compuestos descritos en la presente, opcionalmente se muele la mezcla resultante, y se procesa la mezcla de gránulos, después de agregar auxiliares adecuados, si se desea, para obtener tabletas o núcleos de grageas. Los excipientes adecuados son, en particular, rellenos tales como azúcares, incluyendo lactosa, sacarosa, manitol, o sorbitol; preparaciones de celulosa tales como: por ejemplo, almidón de maíz, almidón de trigo,

almidón de arroz, almidón de papa, gelatina, goma de tragacanto, metil-celulosa, celulosa microcristalina, hidroxi-propil-metil-celulosa, carboxi-metil-celulosa de sodio; u otros, tales como: polivinil-pirrolidona (PVP o povidona) o fosfato de calcio. Si se desea, se pueden agregar agentes desintegrantes, tales como croscarmelosa de sodio reticulada, polivinil-pirrolidona, agar, o ácido algínico o una sal del mismo tal como alginato de sodio.

A los núcleos de grageas se les pueden proporcionar recubrimientos adecuados. Para este propósito, se pueden utilizar soluciones de azúcar concentradas, las cuales opcionalmente pueden contener goma arábiga, talco, polivinil-pirrolidona, gel de carbopol, polietilenglicol, y/o dióxido de titanio, soluciones de laca, y los solventes o mezclas de solventes orgánicos adecuados. Se pueden agregar materiales colorantes o pigmentos a las tabletas o a los recubrimientos de grageas para identificación o para caracterizar diferentes combinaciones de dosis del compuesto activo.

Las preparaciones farmacéuticas que se pueden utilizar oralmente incluyen cápsulas de ajuste a presión hechas de gelatina, así como cápsulas selladas blandas hechas de gelatina y un plastificante, tal como glicerol o sorbitol. Las cápsulas de ajuste a presión pueden contener los ingredientes activos en mezcla con rellenos tales como lactosa, aglutinantes tales como almidones, y/o lubricantes tales como talco o estearato de magnesio, y, opcionalmente, estabilizantes. En las cápsulas blandas, los compuestos activos se pueden disolver o suspender en líquidos

adecuados, tales como aceites grasos, parafina líquida, o polietilenglicoles líquidos. En adición, se pueden agregar estabilizantes.

Para administración bucal o sublingual, las composiciones pueden tomar la forma de tabletas, grageas, o geles formulados de una manera convencional. Las inyecciones parenterales pueden involucrar inyección de bolo o infusión continua. La composición farmacéutica de un compuesto de la invención puede estar en una forma adecuada para inyección parenteral como suspensiones, soluciones o emulsiones estériles en vehículos oleosos o acuosos, y pueden contener agentes de formulación, tales como agentes de suspensión, estabilizantes y/o dispersantes. Las formulaciones farmacéuticas para administración parenteral incluyen soluciones acuosas de los compuestos activos en una forma soluble en agua. Adicionalmente, las suspensiones de los compuestos activos se pueden preparar como suspensiones para inyección oleosas apropiadas. Los solventes o vehículos lipofílicos adecuados incluyen aceites grasos, tales como aceite de ajonjolí, o ésteres de ácidos grasos sintéticos, tales como oleato de etilo o triglicéridos, o liposomas. Las suspensiones para inyección acuosas pueden contener sustancias que aumenten la viscosidad de la suspensión, tales como carboxi-metil-celulosa de sodio, sorbitol, o dextrano. Opcionalmente, la suspensión también puede contener estabilizantes adecuados o agentes que aumenten la solubilidad de los compuestos para permitir la preparación de soluciones altamente concentradas.

De una manera alternativa, el ingrediente activo puede estar en forma de polvo para reconstituirse con un vehículo adecuado, por ejemplo, agua estéril libre de pirógeno, antes de usarse.

Los compuestos de la invención se pueden administrar tópicamente y se pueden formular en una variedad de composiciones tópicamente administrables, tales como soluciones, suspensiones, lociones, geles, pastas, barras medicadas, bálsamos, cremas, o ungüentos. Estos compuestos farmacéuticos pueden contener solubilizantes, estabilizantes, agentes mejoradores de la tonicidad, reguladores, y conservadores.

Las formulaciones adecuadas para administración transdérmica pueden emplear dispositivos de suministro transdérmico y parches de suministro transdérmico, y pueden ser emulsiones lipofílicas, o soluciones acuosas reguladas disueltas y/o dispersadas en un polímero o en un adhesivo. Estos parches se pueden construir para el suministro continuo, pulsátil, o sobre demanda de los agentes farmacéuticos. Todavía además, el suministro transdérmico de los compuestos de la invención se puede llevar a cabo por medio de parches iontoforéticos y similares. Adicionalmente, los parches transdérmicos pueden proporcionar el suministro controlado de los compuestos de la invención. La velocidad de absorción se puede hacer más lenta mediante la utilización de membranas de control de velocidad o mediante el atrape del compuesto dentro de una matriz polimérica o gel. Inversamente, se pueden utilizar mejoradores de absorción para aumentar la absorción. Un mejorador de absorción o

vehículo puede incluir solventes farmacéuticamente aceptables absorbibles para ayudar al paso a través de la piel. Por ejemplo, los dispositivos transdérmicos están en la forma de un parche que comprende un miembro de respaldo, un depósito que contiene el compuesto opcionalmente con vehículos, opcionalmente una barrera de control de velocidad para suministrar el compuesto a la piel del huésped a una velocidad controlada y previamente determinada durante un período de tiempo prolongado, y elementos para asegurar el dispositivo a la piel.

Para la administración mediante inhalación, los compuestos de la invención pueden estar en una forma como un aerosol, una niebla, o un polvo. Las composiciones farmacéuticas de los compuestos de la invención se pueden suministrar de una manera conveniente en la forma de una presentación de rocío en aerosol a partir de paquetes presurizados o de un nebulizador, con el uso de un propelente adecuado, por ejemplo, dicloro-difluoro-metano, tricloro-fluoro-metano, dicloro-tetrafluoro-etano, dióxido de carbono, u otro gas adecuado. En el caso de un aerosol presurizado, la unidad de dosificación se puede determinar proporcionando una válvula para suministrar una cantidad medida. Se pueden formular cápsulas y cartuchos, tales como, a manera de ejemplo solamente, gelatina para utilizarse en un inhalador o insuflador, conteniendo una mezcla en polvo del compuesto y una base de polvo adecuada, tal como lactosa o almidón.

Los compuestos de la invención también se pueden formular en

composiciones rectales, tales como enemas, geles rectales, espumas rectales, aerosoles rectales, supositorios, supositorios de jalea, o enemas de retención, que contienen bases para supositorio convencionales, tales como manteca de cacao u otros glicéridos, así como polímeros sintéticos, tales como polivinil-pirrolidona, PEG, y similares. En las formas de supositorio de las composiciones, primero se funde una cera de bajo punto de fusión, tal como, pero no limitándose a, una mezcla de glicéridos de ácidos grasos, opcionalmente en combinación con manteca de cacao.

Las composiciones farmacéuticas se pueden formular de una manera convencional utilizando uno o más vehículos fisiológicamente aceptables, que comprendan excipientes y auxiliares que faciliten el procesamiento de los compuestos activos en preparaciones que se puedan utilizar farmacéuticamente. La formulación apropiada depende de la vía de administración elegida. Se puede emplear cualquiera de las técnicas, vehículos, y excipientes bien conocidos como adecuados y como es entendido en este campo. Las composiciones farmacéuticas que comprenden un compuesto de la invención se pueden fabricar de una manera convencional, tal como, a manera de ejemplo solamente, por medio de procesos convencionales de mezcla, disolución, granulación, elaboración de grageas, levigación, emulsión, encapsulación, atrape, o compresión.

Las composiciones farmacéuticas incluirán cuando menos un vehículo, diluyente o excipiente farmacéuticamente aceptable, y un compuesto de la fórmula (1), (2A) o (2B) descrito en la presente

como un ingrediente activo en forma de ácido libre o de ácido libre, o en una forma de sal farmacéuticamente aceptable. En adición, los métodos y composiciones farmacéuticas descritas en la presente incluyen el uso de *N*-óxidos, formas cristalinas (también conocidas como polimorfas), así como metabolitos activos de estos compuestos que tengan el mismo tipo de actividad. En algunas situaciones, los compuestos pueden existir como tautómeros. Todos los tautómeros se incluyen dentro del alcance de los compuestos presentados en la presente. Adicionalmente, los compuestos descritos en la presente pueden existir en formas no solvatadas así como solvatadas, con solventes farmacéuticamente aceptables, tales como agua, etanol, y similares. Las formas solvatadas de los compuestos presentados en la presente también se consideran como dadas a conocer en la presente. En adición, las composiciones farmacéuticas pueden incluir otros agentes medicinales o farmacéuticos, vehículos, adyuvantes, tales como agentes conservadores, estabilizantes, humectantes o emulsionantes, promotores de solución, sales para regular la presión osmótica, y/o reguladores. En adición, las composiciones farmacéuticas también pueden contener otras sustancias terapéuticamente valiosas.

Los métodos para la preparación de las composiciones que comprenden los compuestos descritos en la presente incluyen la formulación de los compuestos con uno o más excipientes o vehículos inertes, farmacéuticamente aceptables, para formar un sólido, semi-sólido, o líquido. Las composiciones sólidas incluyen,

pero no se limitan a, polvos, tabletas, gránulos dispersables, cápsulas, pastillas, y supositorios. Las composiciones líquidas incluyen soluciones en donde se disuelve un compuesto, emulsiones que comprenden un compuesto, o una solución que contiene liposomas, micelios, o nanopartículas, las cuales comprenden un compuesto como se da a conocer en la presente. Las composiciones semi-sólidas incluyen, pero no se limitan a, geles, suspensiones y cremas. Las composiciones pueden estar en soluciones o suspensiones líquidas, en formas sólidas adecuadas para solución o suspensión en un líquido antes de usarse, o como emulsiones. Estas composiciones también pueden contener cantidades menores de sustancias auxiliares no tóxicas, tales como agentes humectantes o emulsionantes, agentes reguladores del pH, etc.

Se puede encontrar un resumen de las composiciones farmacéuticas descritas en la presente por ejemplo, en *Remington: The Science and Practice of Pharmacy*, 19a. Edición (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pensilvania 1975; Liberman, H.A. y Lachman, L., Editores, *Pharmaceutical Dosage Forms*, Marcel Decker, Nueva York, N.Y., 1980; y *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7a. Edición (Lippincott Williams & Wilkins, 1999), incorporados a la presente como referencia en su totalidad.

Métodos de Administración y Métodos de Tratamiento

Las composiciones que contienen los compuestos descritos en

la presente se pueden administrar para tratamientos profilácticos y/o terapéuticos. En las aplicaciones terapéuticas, las composiciones se administran a un paciente que ya esté sufriendo de una enfermedad o condición, en una cantidad suficiente para curar o cuando menos detener parcialmente los síntomas de la enfermedad o condición. Se considera bien dentro de la experiencia de la técnica la determinación de las cantidades terapéuticamente efectivas mediante experimentación de rutina (incluyendo, pero no limitándose a, un estudio clínico de escala de dosis).

Los compuestos de la invención se pueden utilizar en combinación con un segundo agente terapéutico. Por ejemplo, si uno de los efectos secundarios experimentados por un paciente al recibir uno de los compuestos en la presente es inflamación, los compuestos de la invención se pueden administrar dentro de una combinación con un agente anti inflamatorio. La efectividad terapéutica de un compuesto descrito en la presente también se puede mejorar mediante la administración de un adyuvante. Cuando los compuestos de la invención se administran en conjunto con otras terapias, las dosificaciones de los compuestos co-administrados variarán dependiendo del tipo de co-fármaco empleado, del fármaco específico empleado, de la enfermedad o condición que se esté tratando, etc. En adición, cuando se co-administran con uno o más agentes biológicamente activos, los compuestos de la invención se pueden administrar ya sea simultáneamente con los agentes biológicamente activos, o bien en secuencia. La administración de un

compuesto de la invención en combinación con un segundo agente terapéutico puede tener un efecto aditivo o sinérgico.

En algunos ejemplos, los compuestos de la invención se pueden utilizar en combinación con un agente anti-fibrótico; por ejemplo, un agente que interfiera con, o module, el progreso de una enfermedad fibrótica tal como esclerodermia, fibrosis pulmonar, fibrosis pulmonar idiopática (IPF), hipertensión pulmonar primaria (PPH), hipertensión arterial pulmonar primaria (PPAH), hipertensión arterial idiopática (IPAH), fibrosis hepática, fibrosis renal y fibrosis cardíaca. Los ejemplos de los agentes anti-fibróticos que se pueden utilizar en combinación con un compuesto de la invención incluyen, pero no se limitan a, pirfenidona (Nakazoto y colaboradores, Eur. J. Pharmacol. 446: 177-185 (2002), tacrolimus (Nagano y colaboradores, Eur. Respir. J. 27: 460-469 (2006) o 5-cloro-2- {(1E)-3-[2-(4-metoxi-benzoil)-4-metil-1H-pirrol-1-il]-prop-1-en-1-il}-*N*-(metil-sulfonil)-benzamida (SMP-534) (Sugaru y colaboradores, Am. J. Nephrology 26: 50-58 (2006)). Los compuestos de la invención también se pueden utilizar en combinación con un agente anti-inflamatorio, incluyendo, pero no limitándose a, corticosteroides y cromolinas, antagonistas de leucotrieno, y bloqueadores de IgE tales como omalizumab. En otros ejemplos, los compuestos de la invención se pueden utilizar en combinación con un medicamento para el tratamiento de asma; por ejemplo, broncodilatadores tales como agonistas-$ß_2$, xantinas (por ejemplo. metil-xantinas) y anticolinérgicos; y un agente anti-inflamatorio como se describe

anteriormente.

Los compuestos de la invención también se pueden utilizar en combinación con un agente quimioterapéutico para tratar un trastorno proliferativo celular, incluyendo, pero no limitándose a, linfoma, osteosarcoma, melanoma, o un tumor de mama, renal, de próstata, colo-rectal, de tiroides, de ovario, pancreático, neuronal, de pulmón, uterino o gastrointestinal. Los ejemplos de los agentes quimioterapéuticos que se pueden utilizar en las composiciones y métodos de la invención incluyen, pero no se limitan a, antraciclinas, agentes alquilantes (por ejemplo, mitomicina C), sulfonatos de alquilo, aziridinas, etileniminas, metil-melaminas, mostazas de nitrógeno, nitrosoureas, antibióticos, antimetabolitos, análogos de ácido fólico (por ejemplo, inhibidores de reductasa de dihidrofolato, tales como metotrexato), análogos de purina, análogos de pirimidina, enzimas, podofilotoxinas, agentes que contienen platino, interferones, e interleucinas. Los ejemplos particulares de los agentes quimioterapéuticos conocidos que se pueden utilizar en las composiciones y métodos de la invención incluyen, pero no se limitan a, busulfano, improsulfano, piposulfano, benzodepa, carbocuona, meturedepa, uredepa, altretamina, trietilen-melamina, trietilen-fosforamida, trietilen-tiofosforamida, trimetilol-melamina, clorambucil, clornafazina, ciclofosfamida, estramustina, ifosfamida, mecloretamina, clorhidrato de óxido de mecloretamina, melfalano, novembiquina, fenesterina, prednimustina, trofosfamida, mostaza de uracilo, carmustina, clorozotocina, fotemustina, lomustina, nimustina,

ranimustina, dacarbazina, manomustina, mitobronitol, mitolactol, pipobromano, aclacinomicinas, actinomicina F(1), antramicina, azaserina, bleomicina, cactinomicina, carubicina, carzinofilina, cromomicina, dactinomicina, daunorrubicina, daunomicina, 6-diazo-5-oxo-1-norleucina, doxorrubicina, epirrubicina, mitomicina C, ácido micofenólico, nogalamicina, olivomicina, peplomicina, plicamicina, porfiromicina, puromicina, estreptonigrina, estreptozocina, tubercidina, ubenimex, zinostatina, zorubicina, denopterina, metotrexato, pteropterina, trimetrexato, fludarabina, 6-mercapto-purina, tiamiprina, tioguanina, ancitabina, azacitidina, 6-azauridina, carmofur, citarabina, didesoxiuridina, doxifluridina, enocitabina, floxuridina, fluoro-uracilo, tegafur, L-asparaginasa, pulmozima, aceglatona, glicósido de aldofosfamida, ácido aminolevulínico, amsacrina, bestrabucil, bisantreno, carboplatina, cisplatina, defofamida, demecolcina, diazicuona, elfornitina, acetato de eliptinio, etoglucida, etoposida, flutamida, nitrato de galio, hidroxiurea, interferón-alfa, interferón-beta, interferón-gamma, interleucina-2, lentinano, lonidamina, mitoguazona, mitoxantrona, mopidamol, nitracrina, pentostatina, fenamet, pirarrubicina, ácido podofilínico, 2-etil-hidrazida, procarbazina, razoxano, sizofirano, espiro-germanio, paclitaxel, tamoxifeno, teniposida, ácido tenuazónico, triazicuona, 2,2',2"-tricloro-trietil-amina, uretano, vinblastina, vincristina, y vindesina.

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 solos o bien en combinación con uno o más agentes terapéuticos. Una cantidad terapéuticamente efectiva puede variar ampliamente dependiendo de la severidad de la enfermedad, la edad, y la salud general del sujeto, la potencia del compuesto utilizado, y de otros factores. En general, se indica que se obtienen resultados satisfactorios sistémicamente en dosificaciones diarias de aproximadamente 0.03 a 2.5 miligramos/kilogramo de peso corporal. Una dosificación diaria indicada en el mamífero superior, por ejemplo, en seres humanos, está en el intervalo 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 administración oral comprenden de aproximadamente 1 a 50 miligramos de ingrediente activo.

La toxicidad y la eficacia terapéutica de estos regímenes terapéuticos se pueden determinar mediante procedimientos farmacéuticos convencionales en cultivos celulares o en animales experimentales, incluyendo, pero no limitándose a, para determinar la LD_{50} (la dosis letal para el 50 por ciento de la población) y la ED_{50} (la dosis terapéuticamente efectiva en el 50 por ciento de la población). La proporción de dosis entre los efectos tóxicos y terapéuticos, es el índice terapéutico, y se puede expresar como la proporción entre la LD_{50} y la ED_{50}. Los datos obtenidos a partir de los ensayos de cultivos celulares y de los estudios con animales se

pueden utilizar para la formulación de un intervalo de dosificaciones para utilizarse en seres humanos. La dosificación de estos compuestos de preferencia queda dentro de un intervalo de concentraciones circulantes que incluyen la ED_{50} con una toxicidad mínima. La dosificación puede variar dentro de este intervalo, dependiendo de la forma de dosificación empleada, y de la vía de administración utilizada.

Procesos para la Elaboración de los Compuestos de la Invención

Los procedimientos generales para preparar los compuestos de la invención se describen en los Ejemplos que se encuentran más adelante. En las reacciones descritas, se pueden proteger los grupos funcionales reactivos, por ejemplo los grupos hidroxilo, amino, imino, tio, o carboxilo, en donde éstos se deseen en el producto final, para evitar su participación indeseada en las reacciones. Se pueden utilizar los grupos protectores convencionales de acuerdo con la práctica estándar, por ejemplo, véase T. W. Greene y P. G. M. Wuts en "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

Un compuesto de la invención se puede preparar como una sal de adición de ácido farmacéuticamente aceptable, mediante la reacción de la forma de base libre del compuesto con un ácido inorgánico u orgánico farmacéuticamente aceptable. De una manera alternativa, se puede preparar una sal de adición de base farmacéuticamente aceptable de un compuesto de la invención,

mediante la reacción de la forma de ácido libre del compuesto con una base inorgánica u orgánica farmacéuticamente aceptable. De una manera alternativa, las formas de sal de los compuestos de la invención se pueden preparar utilizando sales de los materiales de partida o de los intermediarios.

Las formas de ácido libre o de base libre de los compuestos de la invención, se pueden preparar a partir de la forma de sal de adición de base o de sal de adición de ácido correspondiente, respectivamente. Por ejemplo, un compuesto de la invención en una forma de sal de adición de ácido se puede convertir hasta la base libre correspondiente mediante su tratamiento con una base adecuada (por ejemplo, una solución de hidróxido de amonio, hidróxido de sodio, y similares). Un compuesto de la invención en una forma de sal de adición de base se puede convertir hasta el ácido libre correspondiente mediante su tratamiento con un ácido adecuado (por ejemplo, ácido clorhídrico, etc.).

Los compuestos de la invención en una forma no oxidada, se pueden preparar a partir de los N-óxidos de los compuestos de la invención mediante su 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, 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

los expertos ordinarios en este campo (por ejemplo, para mayores detalles, véase Saulnier y colaboradores, (1994), *Bioorganic and Medicinal Chemistry Letters*, Volumen 4, página 1985). Por ejemplo, se pueden preparar los pro-fármacos apropiados mediante la reacción de un compuesto no derivado de la invención con un agente carbamilante adecuado (por ejemplo, 1,1-aciloxi-alquil-carbano-clorhidato, carbonato de *para*-nitro-fenilo, o similares).

Los derivados protegidos de los compuestos de la invención se pueden hacer por medios conocidos por los expertos ordinarios en la materia. Una descripción detallada de las técnicas aplicables a la creación de grupos protectores y su remoción se puede encontrar en T. W. Greene "*Protective Groups in Organic Chemistry*", 3ª Edición, John Wiley and Sons, Inc. 1999.

Los compuestos de la presente invención se pueden preparar de una manera conveniente, o se pueden formar durante el proceso de la invención, como solvatos (por ejemplo, hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar de una manera conveniente mediante recristalización a partir de una mezcla de solventes acuosos/orgánicos, utilizando solventes orgánicos tales como dioxina, tetrahidrofurano, o metanol.

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, separar los diaestereómeros, y recuperar 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 propiedades físicas distintas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidad, reactividad, etc.), y se pueden separar fácilmente aprovechando la ventaja de estas diferencias. Los diaestereómeros se pueden separar mediante cromatografía, o mediante técnicas de separación/ resolución, basándose en las diferencias en la solubilidad. Entonces se recupera el enantiómero ópticamente puro, junto con el agente de resolución, por cualquier medio práctico que no dé como resultado la racemización. Una descripción más detallada de las técnicas aplicables a la resolución de los estereoisómeros de los compuestos a partir de su mezcla racémica se puede encontrar en Jean Jacques, Andre Collet, Samuel H. Wilen, "*Enantiomers, Racemates and Resolutions*", John Wiley and Sons, Inc. 1981.

En resumen, los compuestos que tienen la Fórmula (1), (2A), o (2B), se pueden hacer mediante un proceso que involucra:

(a) los procedimientos generales descritos en los Ejemplos (que se encuentran más adelante); y

(b) opcionalmente convertir un compuesto de la invención en una sal farmacéuticamente aceptable;

(c) opcionalmente convertir una forma de sal de un compuesto de la invención hasta una forma que no sea de sal;

(d) opcionalmente convertir una forma no oxidada de un compuesto de la invención en un N-óxido farmacéuticamente aceptable;

(e) opcionalmente convertir una forma de N-óxido de un compuesto de la invención hasta su forma no oxidada;

(f) opcionalmente resolver un isómero individual de un compuesto de la invención a partir de una mezcla de isómeros;

(g) opcionalmente convertir un compuesto no derivado de la invención en un derivado de pro-fármaco farmacéuticamente aceptable; y

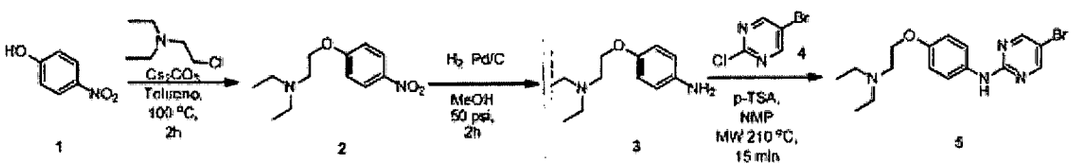
(h) opcionalmente convertir un derivado de pro-fármaco de un compuesto de la invención hasta su forma no derivada.

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 este campo, o como se da a conocer en los Ejemplos que se encuentran 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 similarmente se pueden emplear otros métodos bien conocidos.

Los siguientes ejemplos se ofrecen para ilustrar, pero no para limitar, la invención.

Preparación de Intermediarios

Síntesis de (5-bromo-pirimidin-2-il)-[4-(2-dietil-amino-etoxi)-fenil-amina **5**



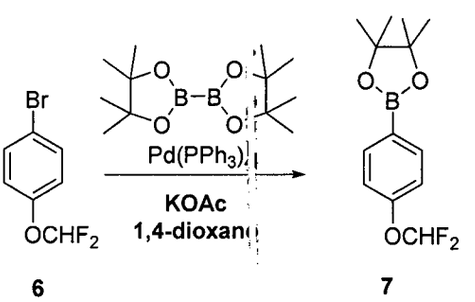
A una solución del 4-nitro-fenol **1** (36.0 milimoles) en tolueno (40 mililitros) se le agrega carbonato de cesio (53.8 milimoles) y clorhidrato de (2-cloro-etil)-dietil-amina (28.7 milimoles). La mezcla de reacción se calienta a 100°C durante 2 horas, y entonces se enfría a temperatura ambiente. El sólido se filtra al vacío y se lava con tolueno tibio. El filtrado se concentra para proporcionar la dietil-[2-(4-nitro-fenoxi)-etil]-amina **2** y se utiliza en el siguiente paso sin mayor purificación. ^{1}H RMN (400MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 6.86-6.84 (m, 2H), 4.05 (t, J = 4.0 Hz, 2H), 2.81 (t, J = 4.0 Hz), 2.55 (q, J = 8.0 Hz, 4H), 0.98 (t, J = 8.0 Hz, 6H). MS (m/z) $(M+1)^+$: 239.3.

A una solución de la dietil-[2-(4-nitro-fenoxi)-etil]-amina **2** (14.0 milimoles) en metanol (20 mililitros) en un frasco de presión Parr, se le agrega Pd (al 10 por ciento sobre carbón, 50 por ciento húmedo, 10 por ciento en peso). La suspensión se agita a 50 psi (3.5 kg/cm^2) de H_2 durante 2 horas. La mezcla de reacción se filtra a través de Celite. El solvente se remueve y el residuo se disuelve en metanol (20 mililitros) y se trata con HCl (1 equivalente de una solución 4N en dioxano), para proporcionar la 4-(2-dietil-amino-etoxi)-fenil-amina **3** como la sal de clorhidrato. ^{1}H RMN (400MHz, *d6*-DMSO) δ 6.98-

6.91 (m, 4H), 4.30 (t, J = 4.0 Hz, 2H), 3.47 (t, J = 4.0 Hz), 3.20 (m, 4H), 1.24 (t, J = 8.0 Hz, 6H). MS (m/z) $(M+1)^+$: 209.3.

Un matraz seco cargado con la 4-(2-dietil-amino-etoxi)-fenil-amina **3** (6.1 milimoles), p-TSA (6.1 milimoles), y 5-bromo-2-cloro-pirimidina **4** (6.1 milimoles) en NMP (5 mililitros), se calienta en un horno de microondas a 210°C durante 15 minutos. La mezcla de reacción se diluye con agua y se extrae con EtOAc (70 mililitros, 5 veces). La capa orgánica se lava con agua, salmuera, se seca sobre Na_2SO_4, y se concentra. La purificación mediante cromatografía en sílice (DCM : metanol : NH_4OH = 95 : 5 : 0.1) proporciona la 5-bromo-pirimidin-2-il)-[4-(2-dietil-amino-etoxi)-fenil-amina **5**. ^1H RMN (400MHz, $CDCl_3$) δ 8.37 (s, 2H), 7.43-7.40 (m, 2H), 7.02 (s, 1H), 6.91-6.89 (m, 2H), 4.06 (t, J = 4.0 Hz, 2H), 2.90 (t, J = 4.0 Hz, 2H), 2.67 (q, J = 8.0 Hz, 4H), 1.09 (t, J = 8.0 Hz, 6H). MS (m/z) $(M+1)^+$: 366.1.

<u>Síntesis de 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7**</u>

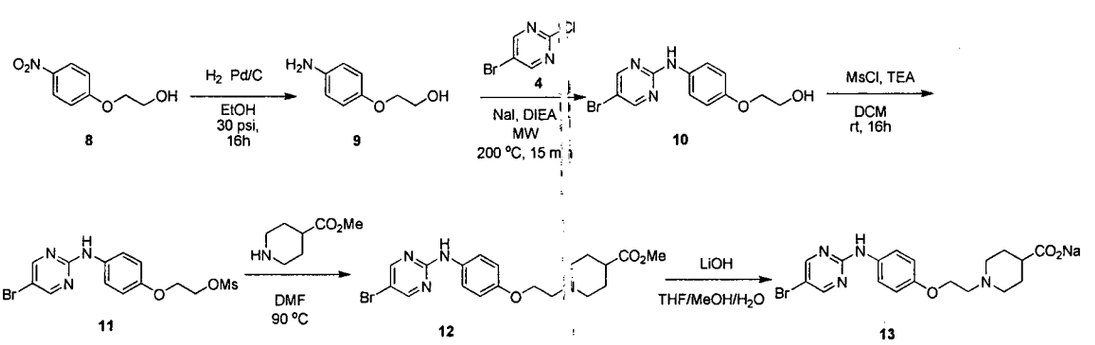


6 **7**

El bromo-4-(difluoro-metoxi)-benceno **6** (2.23 gramos, 10 milimoles), acetato de potasio (30.0 milimoles), 4,4,5,5-tetrametil-2-

(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (11.0 milimoles), y $Pd(PPh_3)_4$ (0.5 milimoles) se agregan a un matraz Schlenk de 40 mililitros equipado con una barra de agitación. El matraz se evacua y se vuelve a llenar con nitrógeno varias veces. Se agrega 1,4-dioxano (10 mililitros) mediante una jeringa. El matraz Schlenk se sella y se calienta a 150°C durante 20 minutos en un horno de microondas. Después de que se completa la reacción, el solvente se remueve al vacío. El residuo se disuelve en diclorometano (200 mililitros) y se lava con agua. La fase orgánica se seca con Na_2SO_4 anhidro, se filtra, y se concentra, para proporcionar un producto crudo. La purificación mediante cromatografía en columna de gel de sílice (EtOAc : hexanos, gradiente a partir del 0 por ciento al 20 por ciento) proporciona el 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7**. ^1H RMN (400MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.48 (t, J = 73.6 Hz, 1H), 1.27 (s, 12H). MS (m/z) $(M+1)^+$: 271.1.

<u>Síntesis de 1-(2-(4-(5-bromo-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxilato de sodio **13**</u>



El 2-(4-nitro-fenoxi)-etanol **8** (109 milimoles) y Pd/C (al 10 por ciento en peso) se suspenden en EtOH (50 mililitros) y se dejan absorber a 30 psi (1.4 kg/cm^2) de hidrógeno en un agitador Parr. La mezcla se agita a temperatura ambiente durante 16 horas. Después de la filtración y de la concentración, se obtiene el 2-(4-amino-fenoxi)-etanol **9** como un sólido color rosado claro, y se utiliza en el siguiente paso sin purificación. MS (m/z) $(M+1)^+$: 154.1.

Una mezcla del 2-(4-amino-fenoxi)-etanol **9** (70 milimoles), 5-bromo-2-cloro-pirimidina **4** (70 milimoles), yoduro de sodio (70 milimoles), y di-isopropil-etil-amina (140 milimoles), se calienta a 200°C durante 15 minutos en un horno de microondas. La mezcla de reacción se vierte en agua (300 mililitros). Después de la filtración, el sólido se lava con una mezcla de H_2O : metanol = 1:1 (100 mililitros), y se seca al vacío durante 12 horas, para dar el producto **10** como un sólido acanelado, el cual se utiliza en el siguiente paso sin purificación. MS (m/z) $(M+1)^+$: 310.2, 312.2.

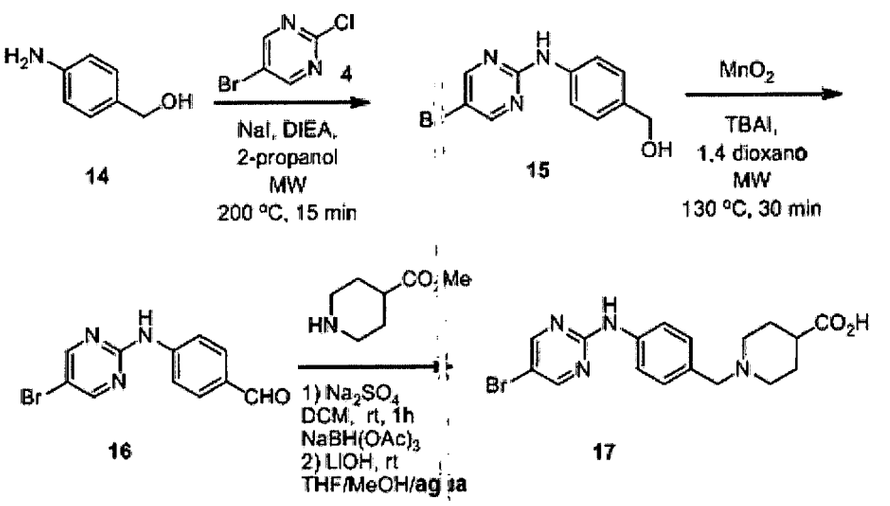
El 2-(4-(5-bromo-pirimidin-2-il-amino)-fenoxi)-etanol **10** (26.6 milimoles) se disuelve en dicloro-metano (50 mililitros), seguido por la adición de MsCl (32 milimoles). El recipiente de reacción se enfría en un baño de agua helada, y se agrega lentamente trietil-amina (53.3 milimoles). La mezcla se agita a temperatura ambiente durante 16 horas. El solvente se remueve y el residuo se tritura con agua (300 mililitros). El sólido se filtra y se seca al vacío durante 12 horas para dar el 2-(4-(5-bromo-pirimidin-2-il-amino)-fenoxi)-etil-metan-sulfonato **11** como un sólido grisáceo. ^{1}H RMN (400MHz, *d6*-DMSO) δ

9.71 (s, 1H), 8.54 (s, 2H), 7.59 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H), 4.52 (m, 2H), 4.22 (m, 2H), 3.24 (s, 3H). MS (m/z) $(M+1)^+$: 388.0, 340.0.

El 2-(4-(5-bromo-pirimidin-2-il-amino)-fenoxi)-etil-metan-sulfonato **11** (1.55 milimoles) e isonipecotato de metilo (3.10 milimoles) se disuelven en N,N-dimetil-formamida (5 mililitros) y se agita a 90°C durante 12 horas. Después de que se completa la reacción, se agrega Na_2CO_3 2M (20 mililitros), y la mezcla resultante se extrae con EtOAc (50 mililitros). La capa orgánica se separa y se concentra para dar el 1-(2-(4-(5-bromo-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxilato de metilo crudo **12**. MS (m/z) $(M+1)^+$: 435.1, 437.1.

El crudo **12** se suspende en una solución de tetrahidrofurano/ MeOH/H_2O (3:2:1, 10 mililitros) con LiOH acuoso 6N (9.3 milimoles) y se agita a temperatura ambiente durante 2 horas. El solvente se remueve al vacío para dar una solución acuosa. A la solución acuosa anterior, se le agrega NaOH 1N (2.0 mililitros), y el precipitado se filtra y se seca para proporcionar el 1-(2-(4-(5-bromo-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxilato de sodio **13**. ^1H RMN (400MHz, *d6*-DMSO) δ 9.67 (s, 1H), 8.52 (s, 2H), 7.54 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.01 (t, J = 6.0 Hz, 2H), 2.83 (m, 2H), 2.61 (m, 2H), 1.98 (m, 2H), 1.60-1.81 (m, 3H), 1.42-1.58 (m, 2H). MS (m/z) $(M+1)^+$: 421.1, 423.1.

<u>Síntesis del ácido 1-(4-(5-bromo-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico **17**</u>



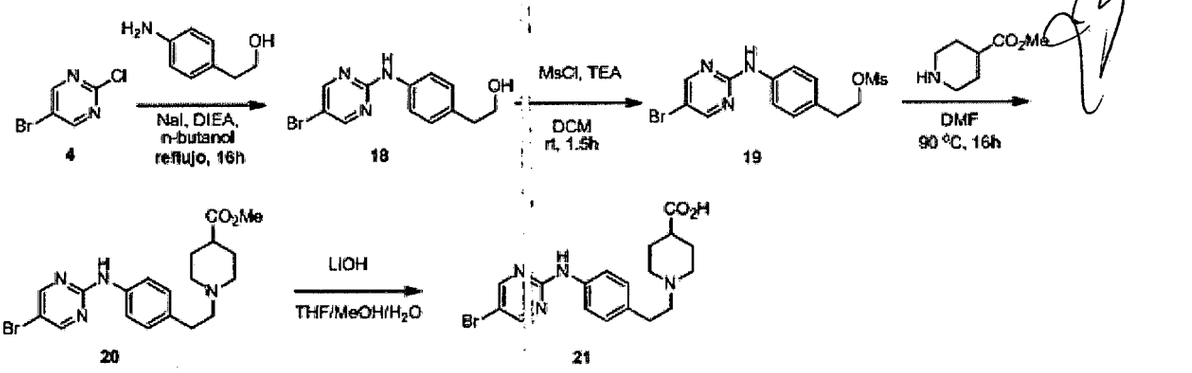
A una solución del alcohol 4-amino-bencílico **14** (8.12 milimoles) y 5-bromo-2-cloro-pirimidina **4** (9.74 milimoles) en 2-propanol (20 mililitros), se le agregan yoduro de sodio (8.12 milimoles) y di-isopropil-etil-amina (16.2 milimoles). La mezcla de reacción se calienta en el horno de microondas a 200°C durante 15 minutos. La purificación mediante cromatografía en gel de sílice con hexano : EtOAc = 7 : 3 proporciona el [4-(5-bromo-pirimidin-2-il-amino)-fenil]-metanol **15**. ^{1}H RMN (400MHz, $CDCl_3$) δ 8.36 (s, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H) 7.07 (bs, 1H), 4.60 (s, 2H). MS (m/z) $(M+1)^+$: 280.3, 282.3.

A una solución del [4-(5-bromo-pirimidin-2-il-amino)-fenil]-metanol **15** (0.94 milimoles) en dioxano (2 mililitros), se le agregan óxido de manganeso (IV) (4.7 milimoles) y TBAI (0.06 milimoles). La mezcla de reacción se calienta en un horno de microondas a 130°C durante 30 minutos. La purificación mediante cromatografía en gel de

sílice utilizando hexano : EtOAc = 1 : 1 proporciona el 4-[5-(4-metoxi-fenil)-pirimidin-2-il-amino]-benzaldehído **16**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 10.45 (s, 1H), 9.85 (s, 1H), 8.72 (s, 2H), 7.96 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H). MS (m/z) $(M+1)^+$: 278.0, 280.0.

Una mezcla del 4-(5-bromo-pirimidin-2-il-amino)-benzaldehído **16** (5.0 milimoles), metil-éster del ácido isonipecótico (10 milimoles), y Na_2SO_4 (exceso) en dicloro-metano : metanol : sulfóxido de dimetilo (4 : 1 : 0.2, volumen/volumen, 26 mililitros), se agita a temperatura ambiente durante 1 hora. Entonces se agrega $NaBH(OAc)_3$ (15.0 milimoles) y se agita durante 12 horas. La mezcla de reacción se apaga con HCl 1N (1 mililitro). Después de la filtración, todos los solventes se remueven al vacío. Al residuo se le agregan LiOH 6N (2.5 mililitros) y tetrahidrofurano : metanol : agua (3 : 2 : 1, 6 mililitros). La mezcla se agita durante 1 hora y se apaga mediante HCl 12N (5 mililitros). Después de la concentración, se agrega EtOH : MeCN (1 : 1, volumen/volumen, 100 mililitros). El sólido inorgánico se filtra. El filtrado amarillo se concentra y se filtra para dar la sal de HCl del ácido 1-(4-(5-bromo-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico **17** como un precipitado sólido amarillo. ^{1}H RMN (400MHz, *d6*-DMSO) δ 10.07 (s, 1H), 8.63 (s, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 4.17 (s, 2H), 3.10-3.40 (m, 2H), 2.89 (m, 2H), 1.67-2.06 (m, 5H). MS (m/z) $(M+1)^+$: 391.1, 393.1.

<u>Síntesis del ácido 1-(4-(5-bromo-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico **21**</u>



Una mezcla de 2-(4-amino-fenil)-etanol (0.72 moles), 5-bromo-2-cloro-pirimidina **4** (0.72 moles), yoduro de sodio (0.72 moles), y di-isopropil-etil-amina (1.45 moles) en *n*-butanol (400 mililitros) se calienta a reflujo durante 16 horas. La reacción se enfría a temperatura ambiente y la mezcla se diluye con agua. El sólido amarillo claro que se precipita se filtra para dar el 2-(4-(5-bromo-pirimidin-2-il-amino)-fenil)-etanol **18**. ^{1}H RMN (300MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.52 (s, 2H), 7.55 (m, 2H), 7.09 (d, 2H), 4.64 (m, 1H), 3.52 (m, 2H), 2.65 (m, 2H). MS (m/z) $(M+1)^+$: 294.1, 296.1.

A una solución del 2-(4-(5-bromo-pirimidin-2-il-amino)-fenil)-etanol **18** (6.22 milimoles) en dicloro-metano (30 mililitros) se le agregan trietil-amina (9.33 milimoles) y cloruro de metan-sulfonilo (7.47 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 1.5 horas. La reacción se diluye con H_2O (10 mililitros) y se lava con una solución de Na_2CO_3 (10 mililitros, 3 veces). La capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se concentra, para proporcionar el 4-(5-bromo-pirimidin-2-il-amino)-fenetil-metan-sulfonato **19**. ^{1}H RMN (400MHz, CD_2Cl_2) δ 8.36

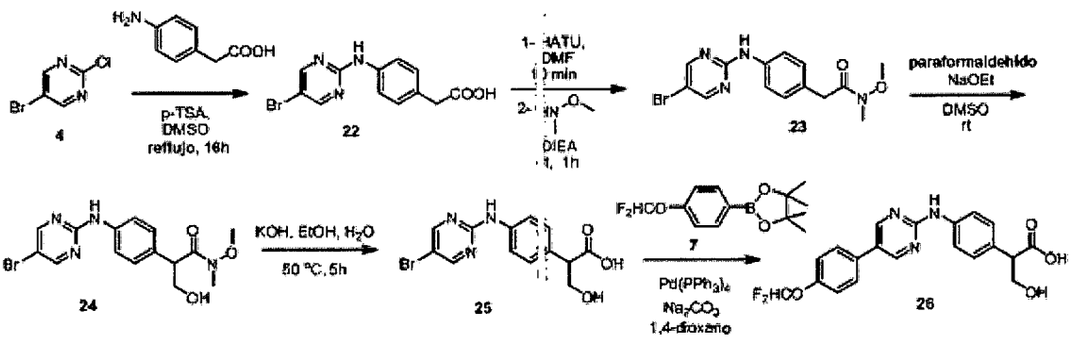
(s, 2H), 7.65 (bs, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 4.31 (t, J = 6.8 Hz, 2H), 2.91 (t, J = 6.8 Hz, 2H), 2.79 (s, 3H). MS (m/z) $(M+1)^+$: 372.0, 374.0.

La mezcla de reacción del 4-(5-bromo-pirimidin-2-il-amino)-fenetil-metan-sulfonato **19** (1.55 milimoles) e isonipecotato de metilo (3.10 milimoles) en N,N-dimetil-formamida (5 mililitros) se agita a 90°C durante 12 horas. Después de que se completa la reacción, se agrega Na_2CO_3 (2.0 M, 20 mililitros), y la mezcla resultante se extrae con EtOAc (50 mililitros). La capa orgánica se separa y se concentra para dar el 1-(4-(5-bromo-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxilato de metilo crudo **20**. MS (m/z) $(M+1)^+$:419.1.

El 1-(4-(5-bromo-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxilato de metilo crudo **20** se suspende en THF/MeOH/H_2O (3 : 2 : 1, 10 mililitros) y LiOH 6N (9.3 milimoles), y se agita a temperatura ambiente durante 2 horas. Después de la neutralización a un pH de 6 mediante la adición de HCl (1N), el solvente se remueve al vacío para dar un sólido, el cual se disuelve en tetrahidrofurano (20 mililitros). A la suspensión anterior, se le agrega un exceso de Na_2SO_4 y se filtra. El filtrado se concentra para proporcionar el ácido 1-(4-(5-bromo-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico **21**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.87 (s, 1H), 9.39 (bs, 1H), 8.59 (s, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 3.58-3.64 (m, 2H), 3.48-3.28 (m, 1H), 3.22-3.27 (m, 2H), 2.88-3.03 (m, 4H), 2.05-2.15 (m, 2H), 1.66-1.80 (m, 2H). MS (m/z) $(M+1)^+$: 405.1, 407.1.

Síntesis del ácido 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-

amino)-fenil)-3-hidroxi-propanoico **26**



El ácido 2-(4-amino-fenil)-acético (4.56 milimoles), 5-bromo-2-cloro-pirimidina **4** (3.26 milimoles), y p-TSA (0.842 milimoles) se calientan a reflujo en 1,4-dioxano (10 mililitros) y sulfóxido de dimetilo (2 mililitros) durante 16 horas. La mezcla se vierte sobre agua y se extrae con EtOAc. La concentración de la fase orgánica da el ácido 2-(4-(5-bromo-pirimidin-2-il-amino)-fenil)-acético **22** como un sólido amarillo. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.84 (s, 1H), 8.58 (s, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.50 (s, 2H). MS (m/z) $(M+1)^+$: 308.0, 310.0.

El ácido 2-(4-(5-bromo-pirimidin-2-il-amino)-fenil)-acético **22** (5.0 milimoles) y HATU (6.0 milimoles) se disuelven en dimetil-formamida seca (10 mililitros), y se agita durante 10 minutos. Entonces se agregan N,O-dimetil-hidroxilamina (7.5 milimoles) y di-isopropil-etil-amina (15.0 milimoles) a la solución. La mezcla de reacción se agita durante 1 hora a temperatura ambiente. Después de que se completa la reacción, la mezcla de reacción se agrega por

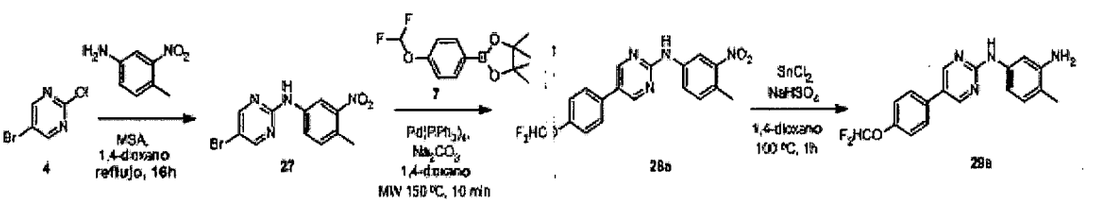
goteo a agua (100 mililitros). El precipitado se filtra y se seca para proporcionar la 2-(4-(5-bromo-pirimidin-2-il-amino)-fenil)-N-metoxi-N-metil-acetamida **23**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.82 (s, 1H), 8.58 (s, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 3.67 (s, 3H), 3.34 (s, 2H), 3.10 (s, 3H). MS (m/z) $(M+1)^+$: 351.0, 353.0.

La 2-(4-(5-bromo-pirimidin-2-il-amino)-fenil)-N-metoxi-N-metil-acetamida **23** (2.0 milimoles), paraformaldehído (6.0 milimoles), y etóxido de sodio (12.0 milimoles), se disuelven en sulfóxido de dimetilo (10 mililitros). La mezcla de reacción se agita a temperatura ambiente durante 1 hora. Entonces se agrega una solución de KOH (12.0 milimoles) en H_2O (5.0 mililitros) y EtOH (5.0 mililitros). La mezcla de reacción se calienta a 50°C durante 5 horas. Después de que se completa la reacción, la mezcla de reacción se lava con dicloro-metano (50 mililitros). La fase acuosa se acidifica a un pH de aproximadamente 5 y se extrae con dicloro-metano (50 mililitros, 2 veces). La capa orgánica se separa, se seca, y se concentra, para proporcionar el ácido 2-(4-(5-bromo-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoico **25**, el cual se utiliza en el siguiente paso sin mayor purificación. ^{1}H RMN (400MHz, *d6*-DMSO) δ 12.30 (bs, 1H), 9.84 (s, 1H), 8.57 (s, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 3.90 (t, J = 8.8 Hz, 1H), 3.49-3.61 (m, 2H), 3.35 (bs, 1H). MS (m/z) $(M+1)^+$: 338.0, 340.0.

A una solución del ácido 2-(4-(5-bromo-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoico **25** (0.5 milimoles) en 1,4-dioxano (2 mililitros), se le agrega el 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-

tetrametil-1,3,2-dioxaborolano **7** (0.5 milimoles), Na_2CO_3 (1.5 milimoles de una solución acuosa 3.0M), y $Pd(PPh_3)_4$ (0.025 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 150°C durante 10 minutos. La mezcla de reacción se diluye con agua (10 mililitros). La capa acuosa se lava con dicloro-metano (50 mililitros, 2 veces) y se acidifica a un pH de 5 utilizando HCl acuoso (1 N). La mezcla resultante se extrae con dicloro-metano (50 mililitros, 2 veces). La capa orgánica se separa, se seca sobre Na_2SO_4 y se concentra, para proporcionar el ácido 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoico crudo **26,** el cual se utiliza sin mayor purificación. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.65 (s, 1H), 8.79 (s, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.60-3.70 (m, 2H), 3.50-3.58 (m, 2H), 3.20-3.26 (m, 2H). MS (m/z) $(M+1)^+$: 402.1.

<u>Síntesis de la N1-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il)-4-metil-bencen-1,3-diamina **29a**</u>



La 5-bromo-2-cloro-pirimidina **4** (50 milimoles), 4-metil-3-nitro-anilina (60 milimoles), y ácido metil-sulfónico (15 milimoles), se calientan a reflujo en 1,4-dioxano (100 mililitros) durante 16 horas.

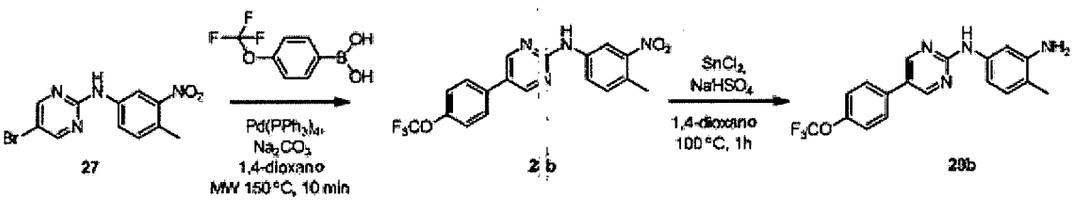
La mezcla se vierte en agua, se filtra, y se seca al vacío para dar la 5-bromo-N-(4-metil-3-nitro-fenil)-pirimidin-2-amina **27** como un sólido amarillo. ^{1}H RMN (400MHz, *d6*-DMSO) δ 10.25 (s, 1H), 8.68 (s, 2H), 8.49 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 2.4, 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 2.46 (s, 3H). MS (m/z) $(M+1)^+$: 309.0, 311.0.

A una solución de la 5-bromo-N-(4-metil-3-nitro-fenil)-pirimidin-2-amina **27** (0.5 milimoles) en 1,4-dioxano (2.0 mililitros) se le agregan el 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7** (0.5 milimoles), Na_2CO_3 (1.5 milimoles de una solución acuosa 3.0M), y $Pd(PPh_3)_4$ (0.025 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta en el horno de microondas a 150°C durante 10 minutos. La mezcla de reacción se diluye con agua (10 mililitros) y se extrae con dicloro-metano (50 mililitros, 2 veces). La capa orgánica se separa, se seca sobre Na_2SO_4 y se concentra. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona la 4-(difluoro-metoxi)-fenil)-N-(4-metil-3-nitro-fenil)-pirimidin-2-amina **28a**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 10.23 (s, 1H), 8.92 (s, 2H), 8.66 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 2.4, 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 74.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 2.47 (s, 3H). MS (m/z) $(M+1)^+$: 373.1.

Una suspensión de la 5-(4-(difluoro-metoxi)-fenil)-N-(4-metil-3-nitro-fenil)-pirimidin-2-amina **28a** (1.5 milimoles) y $SnCl_2 \cdot 2H_2O$ (4.5 milimoles) en $NaHSO_4$ 1N (50 mililitros) y 1,4-dioxano (50 mililitros),

se calienta a 100°C durante 1 hora. El solvente se remueve al vacío y el residuo se disuelve en NaOH al 5 por ciento, y se extrae con dicloro-metano (50 mililitros, 3 veces). La capa orgánica se lava con NaOH al 5 por ciento (50 mililitros, 1 vez), agua (50 mililitros, 1 vez), salmuera, se seca sobre Na_2SO_4 y se concentra, para proporcionar la N1-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il)-4-metil-bencen-1,3-diamina **29a,** la cual se utiliza sin mayor purificación. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.44 (s, 1H), 8.76 (s, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.30 (t, J = 74.4 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 6.90 (dd, J = 2.0, 8.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 4.95 (bs, 2H), 2.02 (s, 3H). MS (m/z) $(M+1)^+$: 343.1.

<u>Síntesis de la 4-metil-N1-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il)-bencen-1,3-diamina **29b**</u>



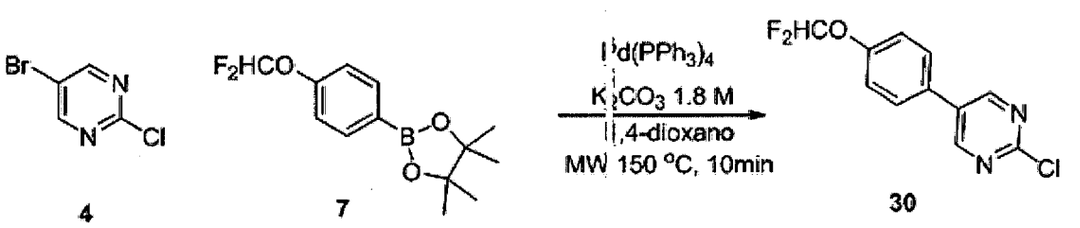
27 **28** **29b**

A una solución de la 5-bromo-N-(4-metil-3-nitro-fenil)-pirimidin-2-amina **27** (9.7 milimoles) en 1,4-dioxano (29 mililitros), se le agrega el ácido 4-(trifluoro-metoxi)-fenil-borónico (10.7 milimoles), Na_2CO_3 (29.2 milimoles de una solución acuosa 1.8 M), y $Pd(PPh_3)_4$ (1.46 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 100°C durante 12

horas. La mezcla de reacción se diluye con agua (20 mililitros) y se extrae con EtOAc (50 mililitros, 2 veces). La capa orgánica se separa, se seca sobre Na_2SO_4 y se concentra. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona la N-(4-metil-3-nitro-fenil)-5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-amina **28b**. MS (m/z) $(M+1)^+$: 390.1.

La N-(4-metil-3-nitro-fenil)-5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-amina **28b** (7.53 milimoles) y $SnCl_2 \cdot 2H_2O$ (33.2 milimoles) se suspenden en HCl 6N (40 mililitros). La mezcla se calienta a 100°C durante 3 horas. El recipiente de reacción se enfría en un baño de agua helada, y se agrega NaOH al 5 por ciento. La capa orgánica se extrae con EtOAc (50 mililitros, 3 veces), se lava con salmuera (50 mililitros, 1 vez), se seca sobre Na_2SO_4 y se concentra, para proporcionar la 4-metil-N1-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il)-bencen-1,3-diamina **29b**, la cual se utiliza sin mayor purificación. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.54 (s, 1H), 8.84 (s, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 2.4 Hz, 1H), 6.94 (dd, J = 2.0 y 8.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.83 (bs, 2H), 2.07 (s, 3H). MS (m/z) $(M+1)^+$: 361.1.

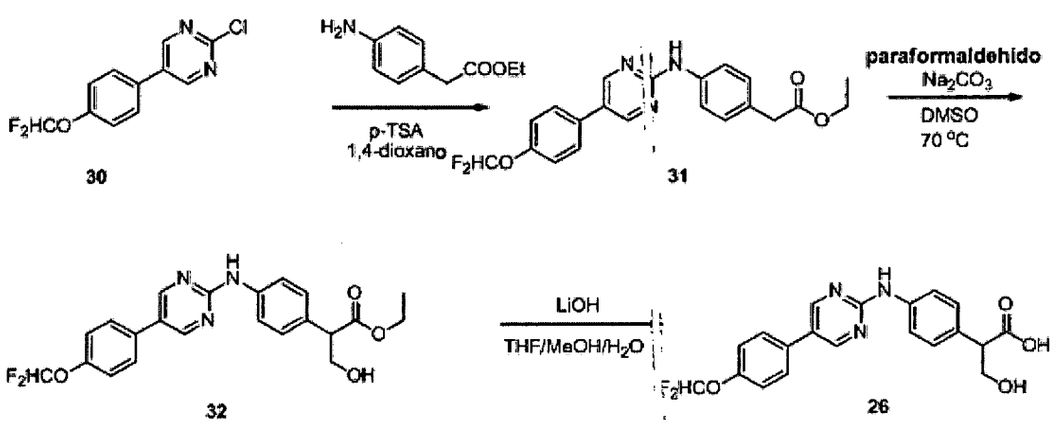
<u>Síntesis de la 2-cloro-5-(4-(difluoro-metoxi)-fenil)-pirimidina **30**</u>



4 **7** **30**

A una solución de la 5-bromo-2-cloro-pirimidina **4** (7.4 milimoles) en 1,4-dioxano (1.5 mililitros), se le agrega el 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7** (8.9 milimoles), K_2CO_3 acuoso 1.8M (16.2 milimoles), y $Pd(PPh_3)_4$ (0.38 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 150°C durante 10 minutos bajo microondas. Después de este tiempo, la mezcla de reacción se diluye con una solución saturada de NH_4Cl y se extrae con dicloro-metano (50 mililitros, 3 veces). La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4 y se concentra. La purificación mediante cromatografía en gel de sílice corta utilizando una mezcla de hexano : EtOAc = 3 : 1 proporciona la 2-cloro-5-(4-(difluoro-metoxi)-fenil)-pirimidina **30**. ^1H RMN (400MHz, $CDCl_3$) δ 8.73 (s, 2H), 7.47-7.52 (m, 2H), 7.20-7.24 (m, 2H), 6.52 (t, J = 72 Hz, 1H). MS (m/z) $(M+1)^+$: 257.0.

<u>Síntesis del ácido 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoico **26**</u>



Una mezcla del 2-(4-amino-fenil)-acetato de etilo (8 milimoles), 2-cloro-5-(4-(difluoro-metoxi)-fenil)-pirimidina **30** (4 milimoles), y p-TSA (2 milimoles) en 1,4-dioxano (4 mililitros), se calientan a reflujo durante 4 horas. La mezcla se vierte sobre HCl 1N. El sólido se filtra, se lava con HCl 1N, y se seca, para proporcionar el 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-acetato de etilo **31** como un sólido amarillo. ^{1}H RMN (400MHz, $CDCl_3$) δ 8.57 (s, 2H), 7.92 (s, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 9.1 Hz, 2H), 6.49 (t, J = 73.5 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.54 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H). MS (m/z) $(M+1)^+$: 400.1.

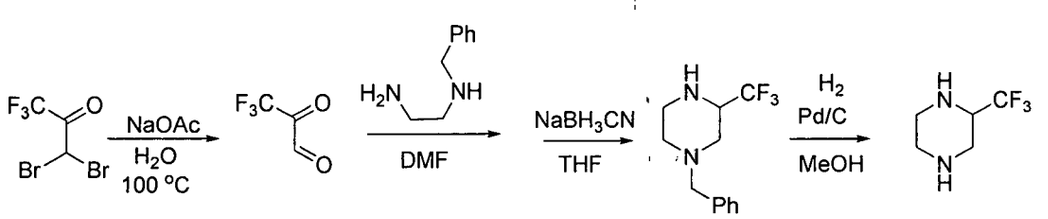
El 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-acetato de etilo **31** (1 milimol) y paraformaldehído (5 milimoles) se disuelven en sulfóxido de dimetilo seco (0.2 a 0.5M), y se calientan a 70°C en la presencia de Na_2CO_3 (5 milimoles) durante 2 a 6 horas, hasta que se logre una conversión mayor del 50 por ciento mediante monitoreo mediante LC/MS. La mezcla se diluye con EtOAc y se lava con agua. Después de la concentración, el residuo se purifica mediante cromatografía en gel de sílice para proporcionar el 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoato de etilo **32**. MS (m/z) $(M+1)^+$: 432.1.

A una solución del 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoato de etilo **32** (1 milimol) en tetrahidrofurano : metanol : agua (3 : 2 : 1, volumen/volumen), se le agrega LiOH 6N (3 milimoles). La mezcla de reacción se agita a

temperatura ambiente durante 1 hora hasta que se considera completa mediante LC/MS, y se diluye con agua. La capa acuosa se lava con dicloro-metano (30 mililitros, 2 veces), y se acidifica a un pH = 5 utilizando HCl acuoso 1N. La mezcla resultante se extrae con dicloro-metano (50 mililitros, 3 veces). La capa orgánica se separa, se seca sobre Na_2SO_4 y se concentra, para proporcionar un producto crudo, el cual, sobre la cristalización a partir de agua, proporciona el ácido 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoico **26** como un sólido grisáceo. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.65 (s, 1H), 8.79 (s, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.60-3.70 (m, 2H), 3.50-3.58 (m, 2H), 3.20-3.26 (m, 2H). MS (m/z) $(M+1)^+$: 402.1.

La separación mediante HPLC quiral utilizando una columna (R,R)-WelkO-1 y hexano : etanol : metanol = 75 : 12.5 : 12.5, con dietil-amina al 0.1 por ciento como gradiente, proporciona los dos enantiómeros **26a** (primer pico eluido) y **26b** (segundo pico eluido). Al enantiómero **26a** se le asigna arbitrariamente la configuración R, mientras que al enantiómero **26b** se le asigna arbitrariamente la configuración S.

<u>Síntesis de la 2-(trifluoro-metil)-piperazina **35a**</u>



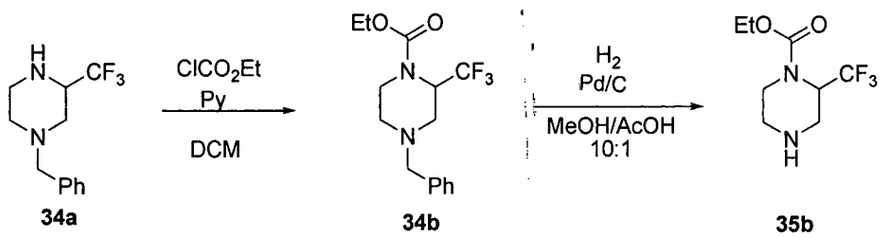
32 **33** **34a** **35a**

Una mezcla de la 3,3-dibromo-1,1,1-trifluoro-propan-2-ona **32** (38.4 milimoles) y NaOAc (153.7 milimoles) en H_2O (50 mililitros) se calienta a 100°C durante 12 horas. La extracción de la mezcla acuosa con EtOAc (50 mililitros, 2 veces) y la concentración de la fase orgánica proporciona un aceite crudo. Al residuo anterior se le agrega dimetil-formamida (30 mililitros), y la solución se enfría a 0°C. Entonces se agrega una solución de N1-bencil-etan-1,2-diamina (2.3 mililitros) en N,N-dimetil-formamida (15 mililitros). La mezcla de reacción resultante se agita a temperatura ambiente durante 12 horas. El solvente se remueve al vacío, para proporcionar un residuo, el cual se disuelve en tetrahidrofurano (15 mililitros) y regulador de citrato (30 mililitros), seguido por la adición de $NaBH_3CN$ 1M (25 mililitros). La mezcla se agita a temperatura ambiente durante 12 horas. El solvente orgánico se remueve al vacío, y el residuo resultante se basifica a un pH = 8 mediante la adición de NaOH 1N. La extracción de la solución acuosa con dicloro-metano (50 mililitros, 2 veces), y la concentración de la fase orgánica proporcionan un aceite crudo, el cual se purifica mediante cromatografía en gel de sílice utilizando hexano : EtOAc = 3 : 1, para proporcionar la 1-bencil-3-(trifluoro-metil)-piperazina **34a**. ^{1}H RMN (400MHz, *d*2-DCM) δ 7.37-7.25 (m, 5H), 3.57(d, 2H), 3.35-3.45 (m, 1H), 3.05-3.10 (m, 1H), 2.87-3.00 (m, 2H), 2.74-2.80 (m, 1H), 2.10-2.18 (m, 2H), 1.74 (s, 1H). MS (m/z) (M+1)$^+$: 245.1.

La 1-bencil-3-(trifluoro-metil)-piperazina **34a** (4.1 milimoles) se disuelve en metanol (50 mililitros), seguido por la adición de AcOH

(2.0 mililitros) y el 5 por ciento molar de Pd/C. El matraz se carga con un globo de hidrógeno, y se agita durante 12 horas. La mezcla se filtra sobre Celite, y el filtrado se concentra para proporcionar la 2-(trifluoro-metil)-piperazina **35a**, la cual se utiliza sin mayor purificación. MS (m/z) $(M+1)^+$: 155.1.

Síntesis del 2-(trifluoro-metil)-piperazin-1-carboxilato de etilo **35b**



34a **34b** **35b**

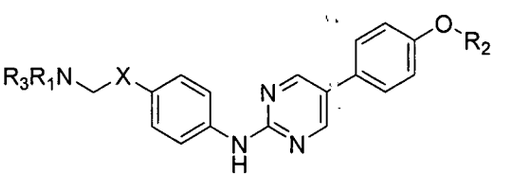
A una solución de la 1-bencil-3-(trifluoro-metil)-piperazina **34a** (1.0 milimoles) y piridina (1.1 milimoles) en dicloro-metano (5 mililitros), se le agrega cloro-formato de etilo (1.1 milimoles). La mezcla resultante se agita a temperatura ambiente durante 1 hora. Después de que se completa la reacción, la mezcla de reacción se diluye con dicloro-metano (15 mililitros) y se lava con agua. La capa orgánica se separa, se seca sobre Na_2SO_4, se filtra, y se concentra para proporcionar el 4-bencil-2-(trifluoro-metil)-piperazin-1-carboxilato de etilo **34b**, el cual se utiliza sin purificación. MS (m/z) $(M+1)^+$: 317.1.

El 4-bencil-2-(trifluoro-metil)-piperazin-1-carboxilato de etilo **34b** (1.0 milimoles) se disuelve en metanol (10 mililitros), seguido por la adición de AcOH (1.0 mililitros) y el 5 por ciento molar de

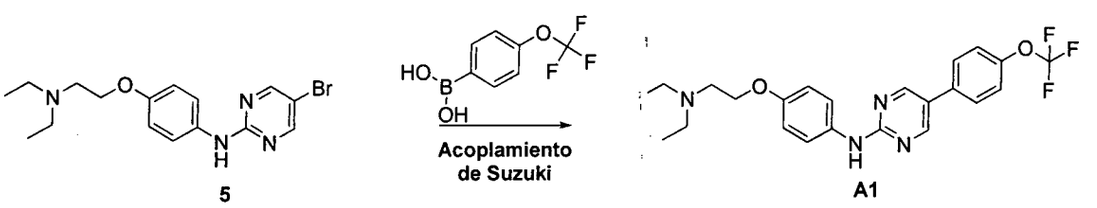
Pd/C. El matraz se carga con un globo de hidrógeno y se agita durante 12 horas. La mezcla se filtra sobre Celite y el filtrado se concentra para proporcionar el 1-carboxilato de 2-(trifluoro-metil)-piperazina **35b**, el cual se utiliza sin mayor purificación. MS (m/z) $(M+1)^+$: 227.1.

Preparación de los Compuestos Finales

Compuestos Tipo A



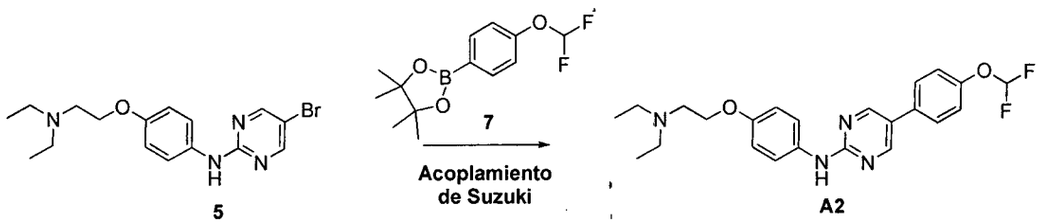
Ejemplo **A1**: N-(4-(2-(dietil-amino)-etoxi)-fenil)-5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-amina



5 A1

A una solución de la (5-bromo-pirimidin-2-il)-[4-(2-dietil-amino-etoxi)-fenil-amina **5** (0.5 milimoles) en 1,4-dioxano (2.0 mililitros) se le agregan ácido 4-(trifluoro-metoxi)-fenil-borónico (0.5 milimoles), Na_2CO_3 3M (1.5 milimoles), y $Pd(PPh_3)_4$ (0.025 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 150°C durante 10 minutos. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona la N-(4-(2-(dietil-amino)-etoxi)-fenil)-5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-amina **A1**. MS (m/z) $(M+1)^+$: 447.2.

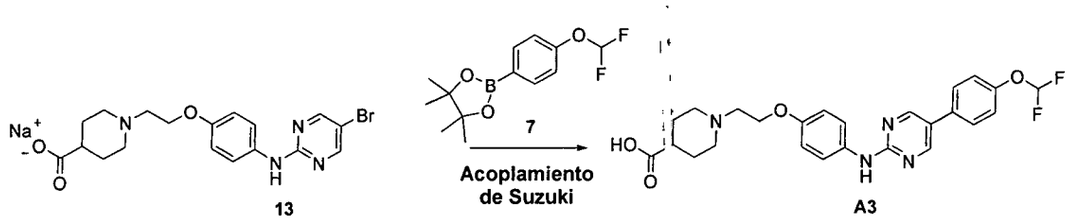
Ejemplo **A2**: N-(4-(2-(dietil-amino)-etoxi)-fenil)-5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-amina



5 **A2**

A una solución de la (5-bromo-pirimidin-2-il)-[4-(2-dietil-amino-etoxi)-fenil-amina **5** (0.5 milimoles) en 1,4-dioxano (2.0 mililitros), se le agregan el 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7** (0.5 milimoles), Na_2CO_3 3M (1.5 milimoles), y $Pd(PPh_3)_4$ (0.025 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 150°C durante 10 minutos. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona la N-(4-(2-(dietil-amino)-etoxi)-fenil)-5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-amina **A2**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.68 (s, 1H), 8.78 (s, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 9.2 Hz, 2H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 1H), 4.28 (t, J = 4.8 Hz, 2H), 3.51 (m, 2H), 3.23 (m, 4H), 1.24 (t, J = 7.2, 6H). MS (m/z) $(M+1)^+$: 429.2.

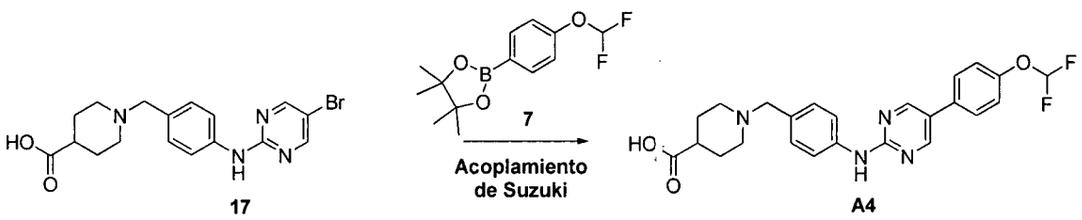
Ejemplo **A3**: Ácido 1-(2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxílico



13 **A3**

A una solución de. 1-(2-(4-(5-bromo-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxilato de sodio **13** (0.05 milimoles) en 1,4-dioxano (1.0 mililitros), se le agregan 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7** (0.05 milimoles), Na_2CO_3 3M (0.15 milimoles), y $Pd(PPh_3)_4$ (0.0025 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 150°C durante 10 minutos. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona el ácido 1-(2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxílico **A3**. ^1H RMN (400MHz, *d6*-DMSO) δ 9.68 (s, 1H), 8.78 (s, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 9.2 Hz, 2H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 1H), 4.28 (t, J = 4.8 Hz, 2H), 3.51 (m, 2H), 3.23 (m, 4H), 1.24 (t, J = 7.2, 6H). MS (m/z) $(M+1)^+$: 485.2.

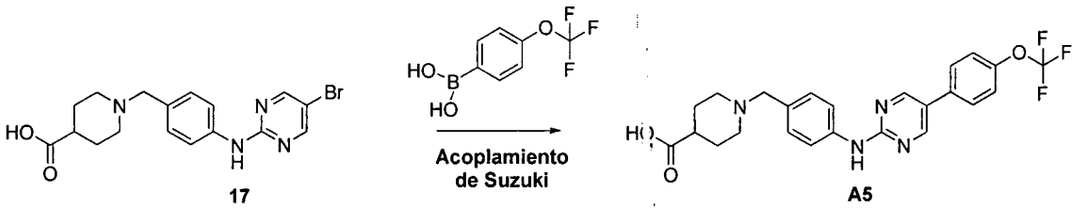
Ejemplo **A4**: Ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico



A una solución del ácido 1-(4-(5-bromo-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico **17** (0.05 milimoles) en 1,4-dioxano (1.0 mililitros), se le agregan 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7** (0.05 milimoles), Na_2CO_3 3M (0.15 milimoles), y $Pd(PPh_3)_4$ (0.0025 milimoles). La reacción se evacua y

se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 150°C durante 10 minutos. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona el ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico **A4**. ^{1}H RMN (400MHz, *d4*-MeOH) δ 8.64 (s, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.78 (t, J = 74.0 Hz, 1H), 4.11 (s, 2H), 3.31 (m, 2H), 2.92 (m, 2H), 2.36 (m, 1H), 2.02 (m, 2H), 1.81 (m, 2H). MS (m/z) $(M+1)^+$: 455.2.

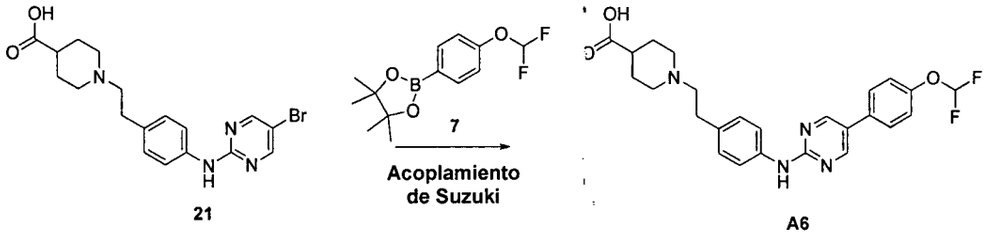
Ejemplo **A5**: Ácido 1-(4-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico



A una solución del ácido 1-(4-(5-bromo-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico **17** (0.05 milimoles) en 1,4-dioxano (1.0 mililitros), se le agregan ácido 4-(trifluoro-metoxi)-fenil-borónico (0.05 milimoles), Na_2CO_3 3M (0.15 milimoles), y $Pd(PPh_3)_4$ (0.0025 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 150°C durante 10 minutos. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona el ácido 1-(4-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico **A5**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 10.06 (s, 1H), 8.89 (s, 2H), 7.88 (M, 4H), 7.48

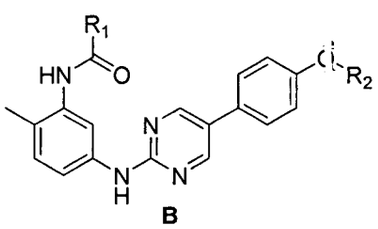
(d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 4.23 (s, 2H), 2.95 (m, 1H), 2.51 (m, 4H), 2.09 (m, 2H), 1.71 (m, 2H). MS (m/z) $(M+1)^+$: 473.2.

Ejemplo **A6**: Ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico



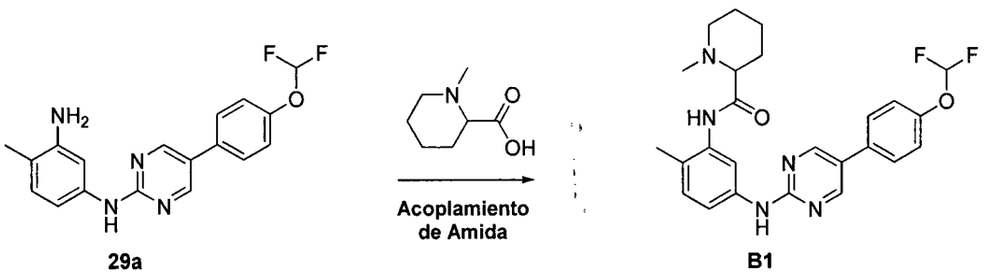
A una solución del ácido 1-(4-(5-bromo-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico **21** (0.05 milimoles) en 1,4-dioxano (1.0 mililitros), se le agregan 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7** (0.05 milimoles), Na_2CO_3 3M (0.15 milimoles), y $Pd(PPh_3)_4$ (0.0025 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta en un horno de microondas a 150°C durante 10 minutos. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona el ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico **A6**. MS (m/z) $(M+1)^+$: 469.2.

Compuestos Tipo B



B

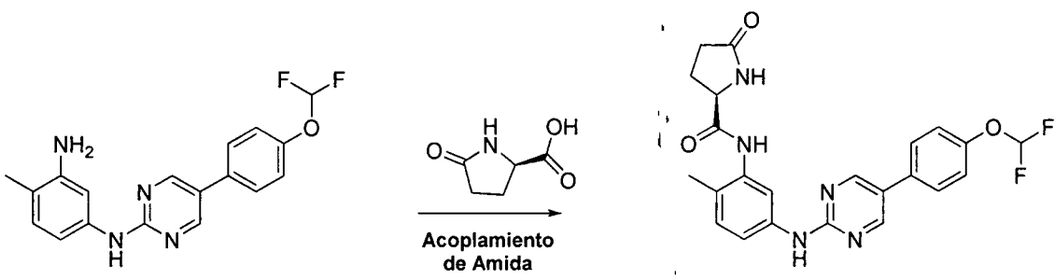
Ejemplo **B1**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1-metil-piperidin-2-carboxamida



29a **B1**

La N1-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il)-4-metil-bencen-1,3-diamina **29a** (0.1 milimoles), ácido 1-metil-piperidin-2-carboxílico (0.1 milimoles), y HATU (0.15 milimoles), se disuelven en dimetil-formamida seca (0.5 mililitros) a temperatura ambiente. Se agrega di-isopropil-etil-amina (0.50 milimoles) a la solución. La mezcla de reacción se agita durante 1 hora a temperatura ambiente. La purificación mediante HPLC proporciona el compuesto objetivo **B1** como una sal de ácido trifluoro-acético. MS (m/z) $(M+1)^+$: 468.2.

Ejemplo **B4**: (R)-N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-5-oxo-pirrolidin-2-carboxamida

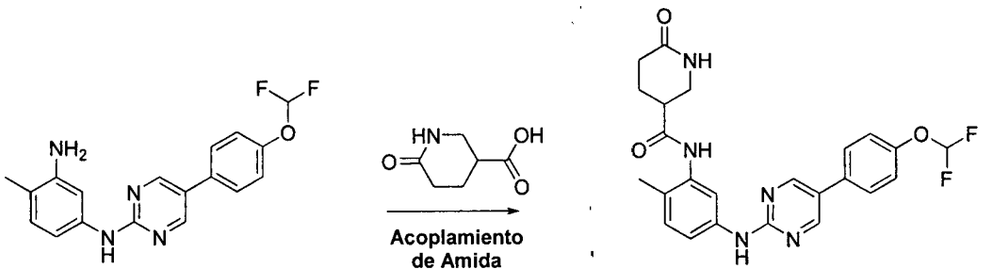


29a **B4**

Similar a la preparación del **B1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.76 (s, 1H), 9.47 (s, 1H), 8.81 (s, 2H), 7.75 (s, 1H), 7.77 (m, 3H), 7.55 (dd, J = 2.0, 8.8 Hz, 1H), 7.29 (t, J = 74.4 Hz, 1H), 7.27 (d, J =

9.2 Hz, 2H), 7.13 (d, J = 8.4 Hz, 1H), 4.26 (m, 1H), 2.40 (m, 2H), 2.14 (s, 3H), 2.04 (m, 2H). MS (m/z) $(M+1)^+$: 454.2.

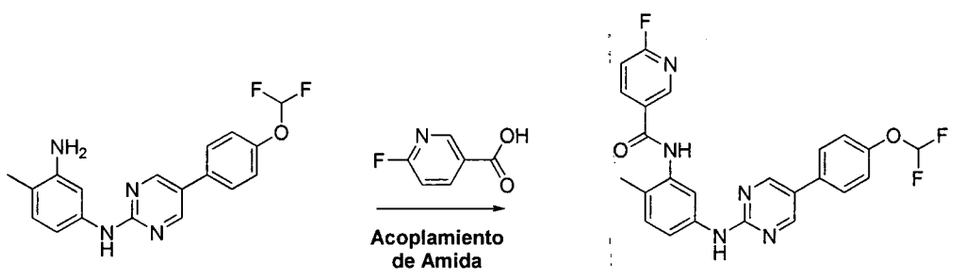
Ejemplo **B5**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-6-oxo-piperidin-3-carboxamida



29a B5

Similar a la preparación del **B1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.75 (s, 1H), 9.50 (s, 1H), 8.81 (s, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 2.0 Hz, 1H), 7.56 (m, 2H), 7.30 (t, J = 74.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 1H), 3.34 (m, 2H), 2.86 (m, 1H), 2.25 (m, 2H), 2.12 (s, 3H), 2.03 (m, 1H), 1.92 (m, 1H). MS (m/z) $(M+1)^+$: 468.2.

Ejemplo **B6**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-6-fluoro-piridin-3-carboxamida

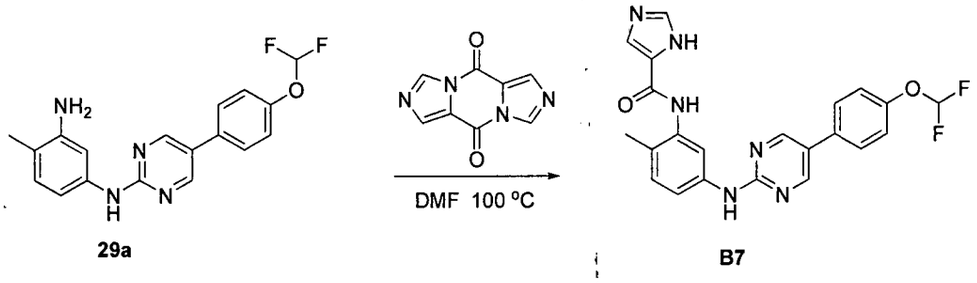


29a B6

Similar a la preparación del **B1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 10.21 (s, 1H), 9.85 (s, 1H), 8.88 (s, 1H), 8.55 (m, 1H), 7.86 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.64 (dd, J = 2.0, 8.4 Hz, 1H), 7.40 (dd, J =

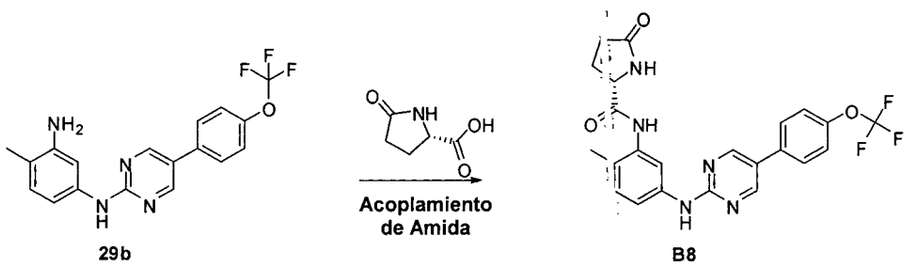
2.4, 8.4 Hz, 1H), 7.31 (t, J = 74.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.4 Hz, 1H), 2.21 (s, 3H). MS (m/z) $(M+1)^+$: 466.1.

Ejemplo **B7**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1H-imidazol-5-carboxamida



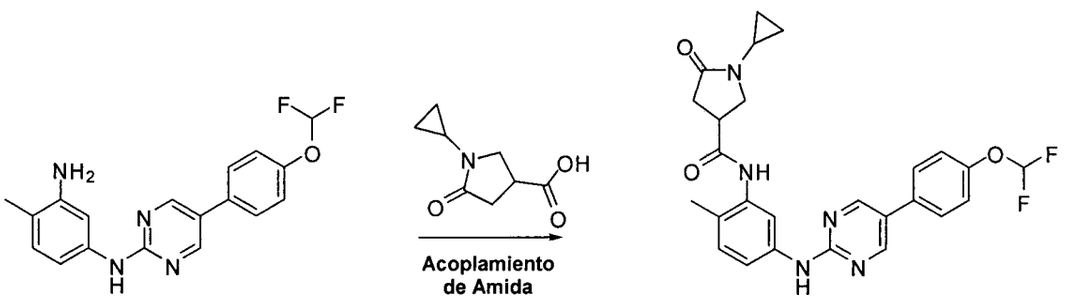
La N1-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il)-4-metil-bencen-1,3-diamina **29a** (0.1 milimoles) y 5H,10H-di-imidazo-[1,5-a:1',5'-d]-pirazin-5,10-diona (0.1 milimoles) en dimetil-formamida seca (0.5 mililitros) se calientan a 110°C durante 24 horas. La purificación mediante HPLC proporciona el compuesto objetivo **B7** como una sal de ácido trifluoro-acético. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.80 (s, 2H), 8.81 (s, 2H), 8.44 (s, 1H), 8.04 (s, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.57 (m, 1H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 1H), 2.20 (s, 3H). MS (m/z) $(M+1)^+$: 437.2.

Ejemplo **B8**: (S)-N-(2-metil-5-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-5-oxo-pirrolidin-2-carboxamida



La 4-metil-N1-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il)-bencen-1,3-diamina **29b** (0.1 milimoles), ácido (S)-5-oxo-pirrolidin-2-carboxílico (0.1 milimoles), y HATU (0.15 milimoles), se disuelven en dimetil-formamida seca (0.5 mililitros) a temperatura ambiente. Se agrega di-isopropil-etil-amina (0.50 milimoles) a la solución, y la mezcla de reacción se agita durante 1 hora a temperatura ambiente. La purificación mediante HPLC proporciona el compuesto objetivo **B8** como una sal de ácido trifluoro-acético. MS (m/z) $(M+1)^+$: 473.1.

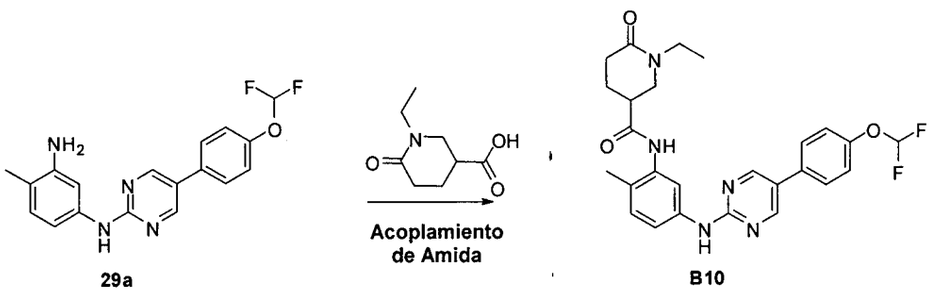
Ejemplo **B9**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1-ciclopropil-5-oxo-pirrolidin-3-carboxamida



29a **B9**

Similar a la preparación del **B1**. ^{1}H RMN (400MHz, *d4*-MeOD) δ 8.84 (s, 2H), 7.71 (m, 3H), 7.36 (s, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.91 (t, J = 74.0 Hz, 1H), 3.52-3.56 (m, 2H), 3.46 (m, 1H), 2.74 (m, 2H), 2.64 (m, 1H), 2.29 (s, 3H), 0.77 (m, 4H). MS (m/z) $(M+1)^+$: 494.2.

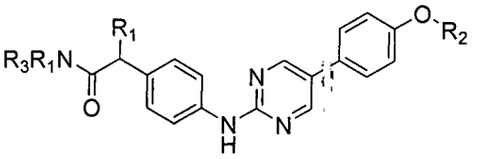
Ejemplo **B10**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1-etil-6-oxo-piperidin-3-carboxamida



29a B10

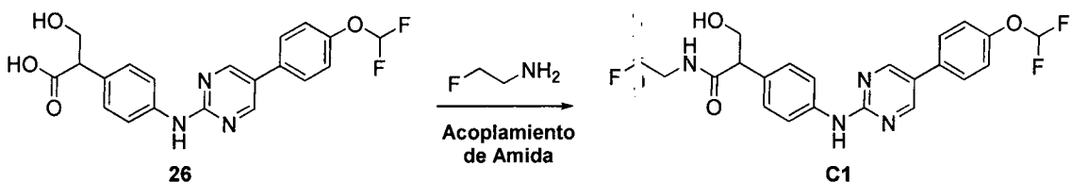
Similar a la preparación del **B1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.75 (s, 1H), 9.52 (s, 1H), 8.79 (s, 2H), 7.76 (m, 3H), 7.55 (m, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 7.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 3.2-3.5 (m, 2H), 2.9-3.0 (m, 1H), 2.5 (m, 2H), 2.3 (m, 2H), 2.13 (s, 3H), 1.80-2.08 (m, 2H), 1.05 (t, J = 6.8 Hz, 3H). MS (m/z) $(M+1)^+$: 496.2.

Compuestos Tipo C



C

Ejemplo **C1**: 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-N-(2-fluoro-etil)-3-hidroxi-propanamida

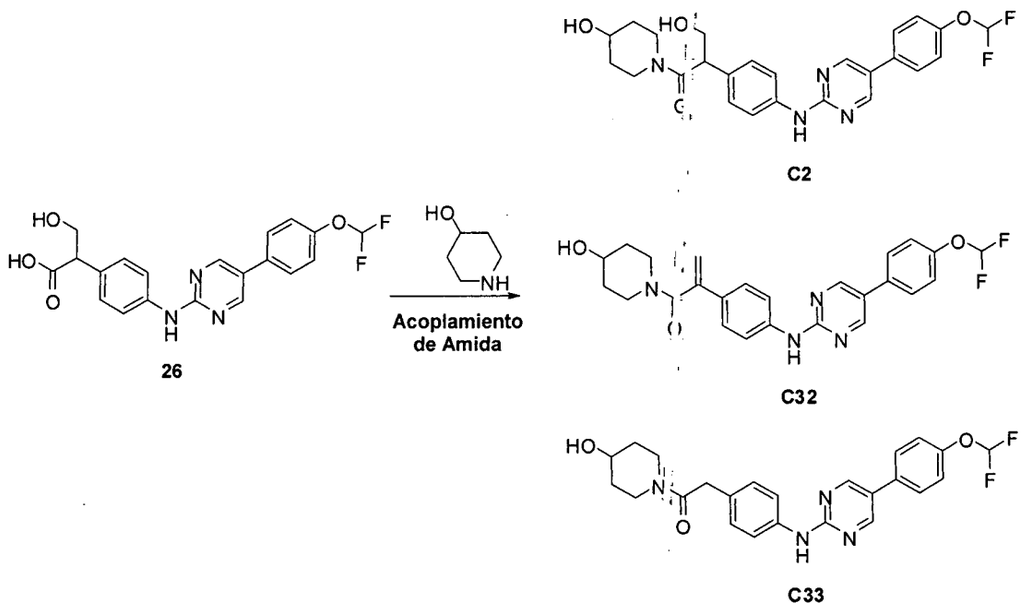


26 C1

El ácido 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoico **26** (0.1 milimoles), 2-fluoro-etanamina (0.1 milimoles), y HATU (0.15 milimoles), se disuelven en dimetil-formamida seca (0.5 mililitros) a temperatura ambiente. Se agrega

di-isopropil-etil-amina (0.50 milimoles) a la solución. La mezcla de reacción se agita durante 1 hora a temperatura ambiente. La purificación mediante HPLC (gradiente de ACN del 10 al 90 por ciento) proporciona la 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-N-(2-fluoro-etil)-3-hidroxi-propanamida **C1** como una sal de ácido trifluoro-acético. MS (m/z) $(M+1)^+$: 447.2.

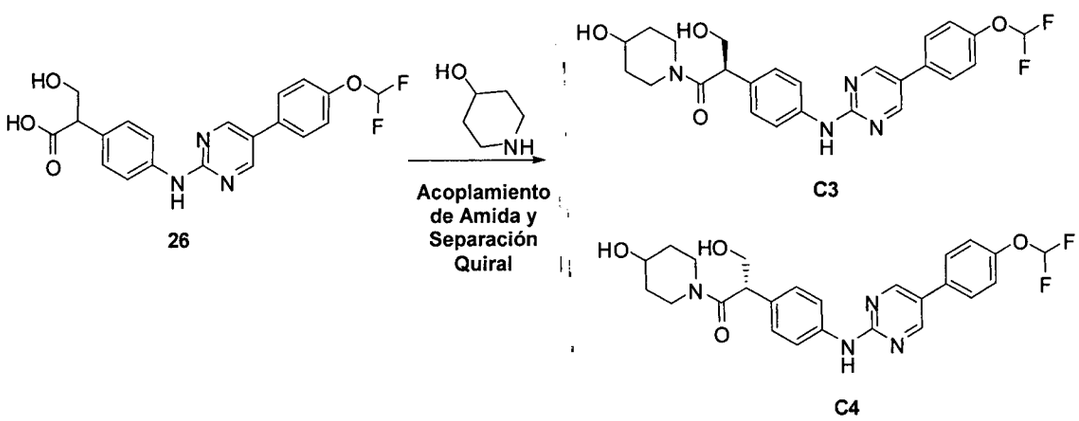
Ejemplo **C2**: 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-hidroxi-piperidin-1-il)-propan-1-ona



Similar a la preparación del **C1**. ^{1}H RMN (400MHz, *d4*-MeOH) δ 8.88 (d, J = 2.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 8.8 Hz, 2H), 7.43 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.92 (t, J = 74.0 Hz, 1H), 4.20 (m, 2H), 4.13 (m, 1H), 3.80 (m, 2H), 3.70 (m, 2H), 1.56 (m, 2H), 1.50 (m, 2H), 1.28 (m, 1H). MS (m/z) $(M+1)^+$: 485.2.

Ejemplo **C3**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-hidroxi-piperidin-1-il)-propan-1-ona

Ejemplo **C4**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-hidroxi-piperidin-1-il)-propan-1-ona

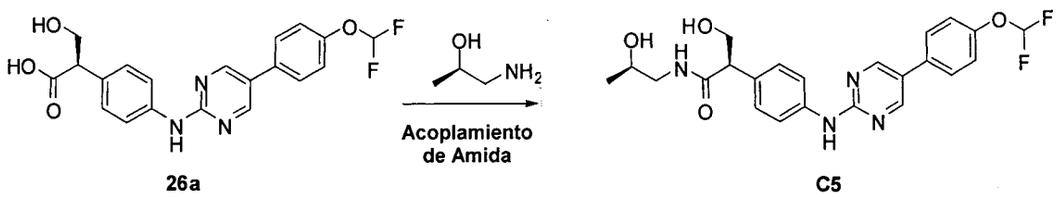


Similar a la preparación del **C1**. La separación quiral sobre una columna (R,R)-WelkO-1, y hexano : isopropanol = 70 : 30 como gradiente, proporciona los dos enantiómeros **C3** (primer pico eluido) y **C4** (segundo pico eluido). Al **C3** se le asigna arbitrariamente la configuración R. ^{1}H RMN (400MHz, *d4*-MeOH) δ 8.88 (d, J = 2.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 8.8 Hz, 2H), 7.43 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.92 (t, J = 74.0 Hz, 1H), 4.20 (m, 2H), 4.13 (m, 1H), 3.80 (m, 2H), 3.70 (m, 2H), 1.56 (m, 2H), 1.50 (m, 2H), 1.28 (m, 1H). MS (m/z) $(M+1)^+$: 485.2.

Al **C4** se le asigna arbitrariamente la configuración S. ^{1}H RMN (400MHz, *d4*-MeOH) δ 8.88 (d, J = 2.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 8.8 Hz, 2H), 7.43 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.92 (t, J = 74.0 Hz, 1H), 4.20 (m, 2H), 4.13 (m, 1H), 3.80 (m, 2H),

3.70 (m, 2H), 1.56 (m, 2H), 1.50 (m, 2H), 1.28 (m, 1H). MS (m/z) $(M+1)^+$: 485.2.

Ejemplo **C5**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((R)-2-hidroxi-propil)-propanamida

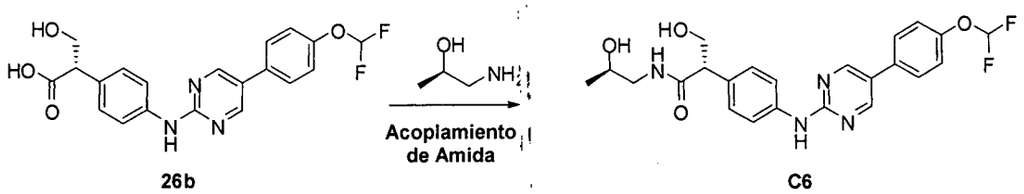


26a **C5**

El ácido 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoico **26a** (0.1 milimoles), (R)-1-amino-propan-2-ol (0.1 milimoles), y HATU (0.12 milimoles), se disuelven en dimetil-formamida seca (0.5 mililitros) a temperatura ambiente. Se agrega di-isopropil-etil-amina (0.4 milimoles), y la mezcla de reacción se agita durante 1 hora a temperatura ambiente. La purificación mediante HPLC (gradiente de ACN del 10 al 70 por ciento) proporciona la (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((R)-2-hidroxi-propil)-propanamida **C5** como una sal de ácido trifluoro-acético. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.73 (s, 1H), 8.80 (s, 2H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.77 (m, 2H), 7.30 (t, *J* = 74.0 Hz, 1H), 7.28 (m, 2H), 7.22 (m, 2H), 7.45 (t, *J* = 4.0 Hz, 1H), 3.91 (m, 1H), 3.59 (m, 2H), 3.40 (quinteto, *J* = 8.0 Hz, 1H), 0.95 (d, *J* = 8.0 Hz, 3H). MS (m/z) $(M+1)^+$: 459.2.

Ejemplo **C6**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-

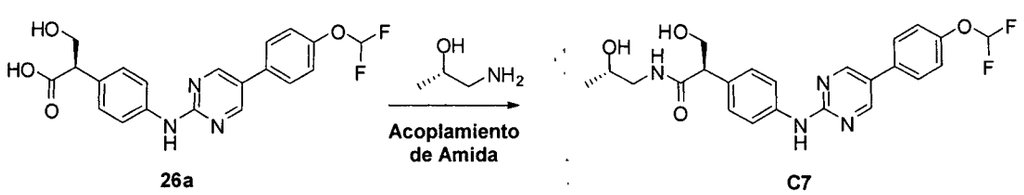
amino)-fenil)-3-hidroxi-N-((R)-2-hidroxi-propil)-propanamida



26b C6

El ácido 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-propanoico **26b** (0.1 milimoles), (R)-1-amino-propan-2-ol (0.1 milimoles), y HATU (0.12 milimoles), se disuelven en dimetil-formamida seca (0.5 mililitros) a temperatura ambiente. Se agrega di-isopropil-etil-amina (0.4 milimoles) a la solución. La mezcla de reacción se agita durante 1 hora a temperatura ambiente. La purificación mediante HPLC (gradiente de ACN del 10 al 70 por ciento) proporciona la (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((R)-2-hidroxi-propil)-propanamida **C6** como una sal de ácido trifluoro-acético. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.80 (s, 2H), 7.93 (m, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 72.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 3.93 (m, 1H), 3.61 (m, 1H), 2.99 (m, 2H), 2.51 (m, 2H), 0.95 (d, J = 6.0 Hz, 3H). MS (m/z) $(M+1)^+$: 459.1.

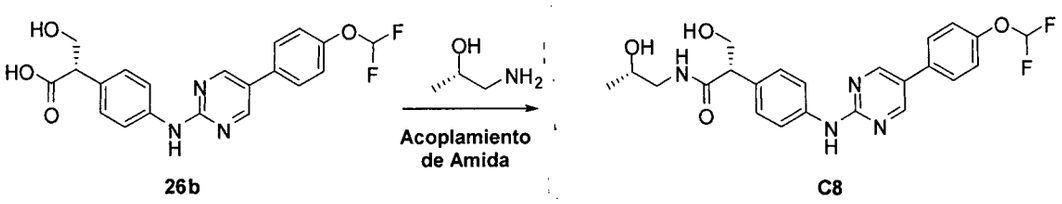
Ejemplo **C7**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((S)-2-hidroxi-propil)-propanamida



26a C7

Similar a la preparación del **C5**. ^{1}H RMN (400MHz, *d4*-MeOH) δ 8.69 (s, 2H), 7.67 (m, 4H), 7.31 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.88 (t, J = 76.0 Hz, 1H) 4.62 (s, 1H), 4.14 (m, 1H), 3.83 (m, 1H), 3.70 (m, 2H), 3.26 (dd J = 8.0, 12.0 Hz, 1H), 3.10 (dd, J = 8.0, 12.0 Hz, 1H), 1.09 (d, J = 4.0 Hz, 3H). MS (m/z) $(M+1)^+$: 459.1.

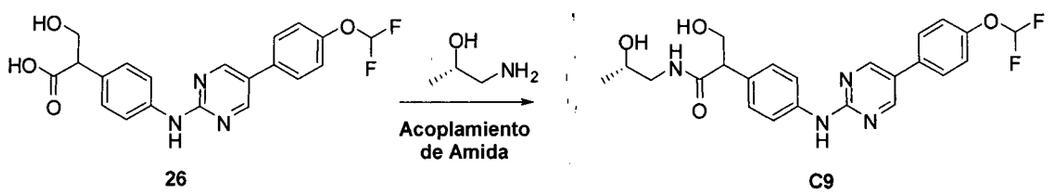
Ejemplo **C8**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((S)-2-hidroxi-propil)-propanamida



26b **C8**

Similar a la preparación del **C8**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.80 (s, 2H), 7.93 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.23 (t, J = 76 Hz, 1H), 7.21 (d, J = 8 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 3.84 (m, 1H), 3.42 (m, 3H), 3.28 (m, 1H), 1.72 (m, 3H), 1.02 (m, 6H). MS (m/z) $(M+1)^+$: 459.1.

Ejemplo **C9**: 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((S)-2-hidroxi-propil)-propanamida

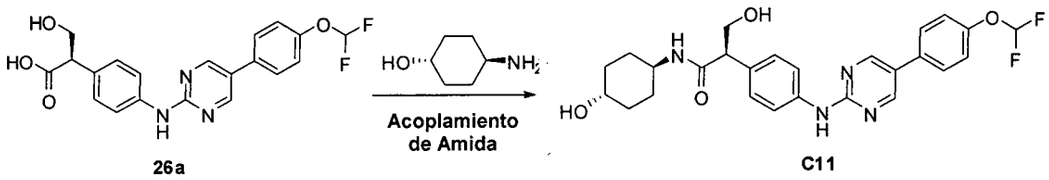


26 **C9**

Similar a la preparación del **C1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.70 (s, 1H), 8.79 (s, 2H), 8.13 (s, 1H), 7.93 (d, J = 2.1 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8 Hz, 2H),

7.26 (t, J = 75 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 3.92 (dt, J = 8.7, 2.5 Hz, 1H), 3.0 (m, 2H), 2.5 (m, 5H), 2.07 (s, 1H), 0.96 (t, *J* = 5.7 Hz, 3H). MS (m/z) $(M+1)^+$: 459.1.

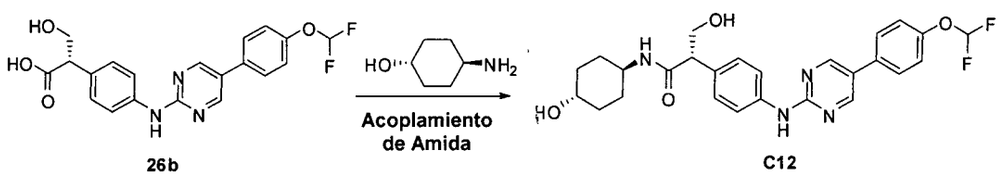
Ejemplo **C11**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,4R)-4-hidroxi-ciclohexil)-propanamida



26a C11

Similar a la preparación del **C5**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.73 (s, 1H), 8.80 (s, 2H), 7.93 (m, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 76.0 Hz, 1H), 7.27 (d, J = 8 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 3.93 (m, 1H), 3.59 (m, 1H), 3.0 (m, 2H), 2.51 (m, 2H), 0.97 (d, J = 6Hz, 3H). MS (m/z) $(M+1)^+$: 499.1.

Ejemplo **C12**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,4R)-4-hidroxi-ciclohexil)-propanamida

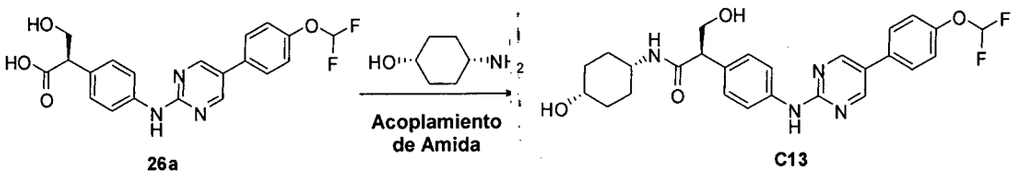


26b C12

Similar a la preparación del **C6**: ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.80 (s, 2H), 8.14 (s, 1H), 7.79 (m, 3H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.6 Hz, 2H), 7.27 (t, J = 79.6 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 3.91 (m, 1H), 2.51 (m, 4H), 1.76 (m, 2H), 1.62 (m, 1H), 1.19 (m, 5H). MS (m/z) $(M+1)^+$: 499.2.

Ejemplo **C13**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-

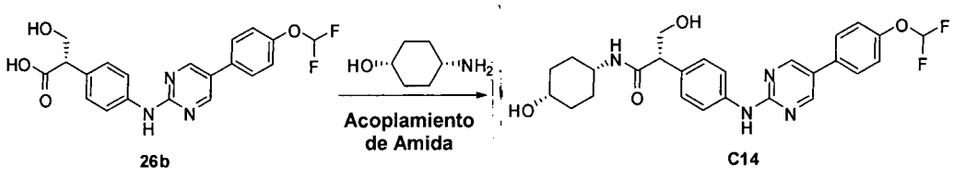
amino)-fenil)-3-hidroxi-N-((1S,4S)-4-hidroxi-ciclohexil)-propanamida



26a C13

Similar a la preparación del C5. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.74 (s, 1H), 8.81 (s, 2H), 7.84 (m, 1H), 7.78 (m, 2H), 7.68 (m, 2H), 7.30 (t, J = 76.0 Hz, 1H), 7.27 (d, J = 8 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.73 (t, J = 4.0Hz, 1H), 4.37 (d, J = 4.0Hz, 1H), 3.93 (m, 1H), 3.65 (bm, 1H), 3.58 (m, 2H), 3.48 (m, 1H), 1.62 (m, 2H), 1.38 (m, 8H). MS (m/z) $(M+1)^+$: 499.1.

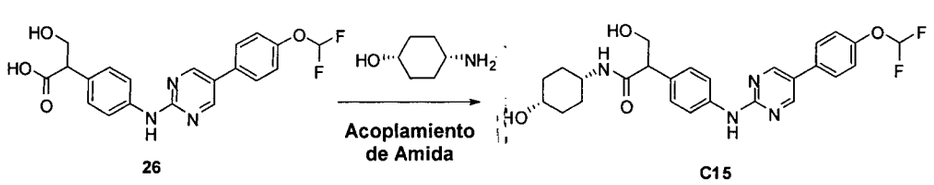
Ejemplo **C14**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,4S)-4-hidroxi-ciclohexil)-propanamida



26b C14

Similar a la preparación del C5. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.83 (d, J = 7.6Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 7.6 Hz, 2H), 7.26 (t, J = 79.6 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 3.91 (m, 1H), 3.58 (m, 1H), 2.51 (m, 4H), 1.59 (m, 2H), 1.46 (m, 5H). MS (m/z) $(M+1)^+$: 499.2.

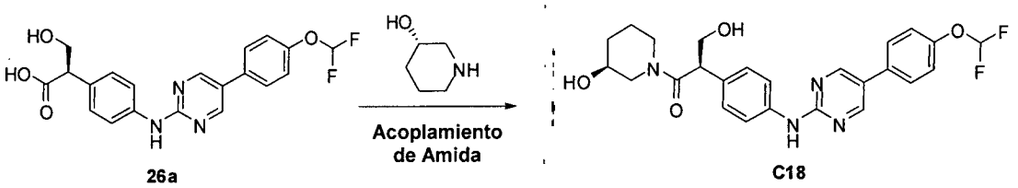
Ejemplo **C15**: 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,4S)-4-hidroxi-ciclohexil)-propanamida



26 C15

Similar a la preparación del **C1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 74 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.91 (t, J = 9 Hz, 1H), 3.6 (m, 2H), 2.51 (m, 3H), 1.46 (m, 9H). MS (m/z) $(M+1)^+$: 499.4.

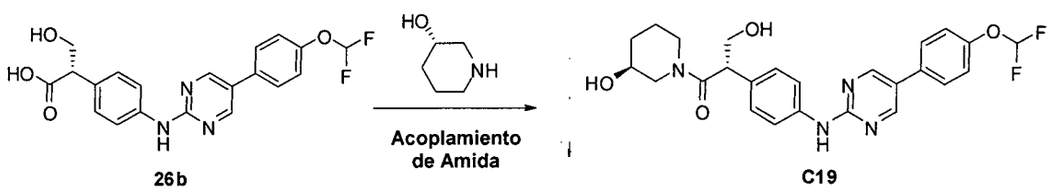
Ejemplo **C18**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((S)-3-hidroxi-piperidin-1-il)-propan-1-ona



26a C18

Similar a la preparación del **C5**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.75 (s, 1H), 8.82 (s, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.70 (m, 2H), 7.28 (t, J = 70.0 Hz, 1H), 7.27 (m, 4H), 4.32 (m, 1H), 4.20 (m, 1H), 3.95 (m, 2H), 3.74 (m, 1H), 2.91 (m, 1H), 1.90 (m, 2H), 1.68 (m, 1H), 1.41 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

Ejemplo **C19**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((S)-3-hidroxi-piperidin-1-il)-propan-1-ona

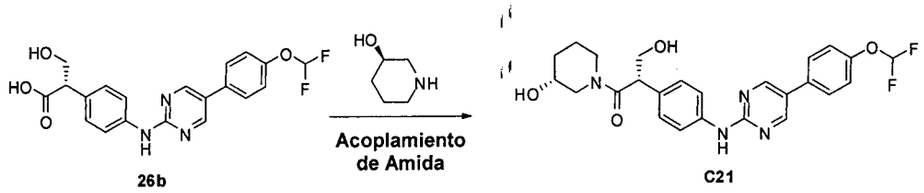


26b C19

Similar a la preparación del **C6**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.76 (d, J = 10.8 Hz, 1H), 8.82 (s, 2H), 7.77 (d, J = 7.6 Hz, 2H), 7.71 (m, 2H), 7.28 (t, J = 67.6 Hz, 1H), 7.27 (d, J = 6.8 Hz, 2H), 3.95 (m, 2H), 2.92 (m, 1H), 2.55 (m, 6H), 2.53 (m, 2H), 1.68 (m, 1H), 1.37 (m,

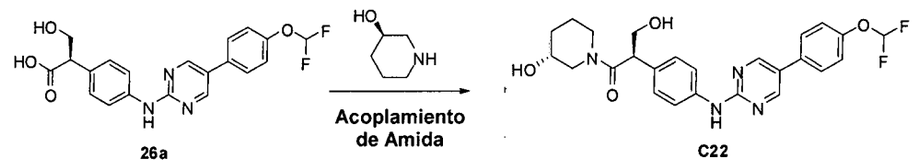
2H). MS (m/z) $(M+1)^+$: 485.1.

Ejemplo **C21**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((R)-3-hidroxi-piperidin-1-il)-propan-1-ona



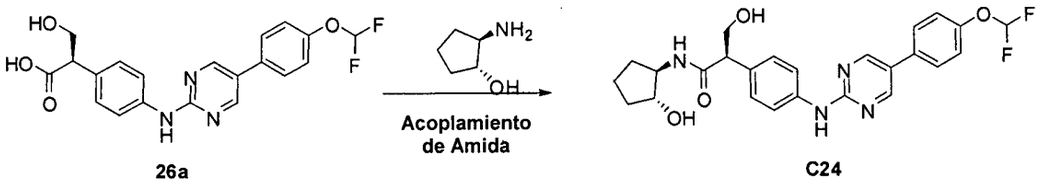
Similar a la preparación del **C6**, ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.77 (s, 1H), 8.82 (s, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.71 (m, 2H), 7.28 (t, J = 68 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 3.95 (m, 2H), 2.92 (m, 1H), 2.55 (m, 6H), 2.53 (m, 2H), 1.68 (m, 1H), 1.37 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

Ejemplo **C22**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((R)-3-hidroxi-piperidin-1-il)-propan-1-ona



Similar a la preparación del **C5**, ^{1}H RMN (400MHz, *d4*-MeOH) δ 8.68 (s, 2H), 7.58 (m, 4H), 7.22 (m, 4H), 6.79 (t, J = 72.0 Hz, 1H), 4.20 (m, 1H), 4.01 (m, 2H), 3.93 (m, 1H), 3.59 (bm, 2H), 3.38 (m, 1H), 3.33 (m, 1H), 3.06 (m, 1H), 2.72 (m, 1H), 2.64 (m, 1H). MS (m/z) $(M+1)^+$: 485.1.

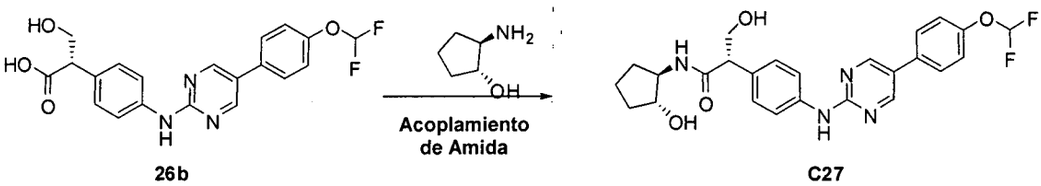
Ejemplo **C24**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,2R)-2-hidroxi-ciclopentil)-propanamida



26a C24

Similar a la preparación del **C5**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.71 (s, 1H), 8.79 (s, 2H), 7.09 (d, J = 6.8 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 71.6 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 3.92 (m, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.53 (m, 2H), 1.43 (m, 1H), 1.24 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

Ejemplo **C27**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,2R)-2-hidroxi-ciclopentil)-propanamida

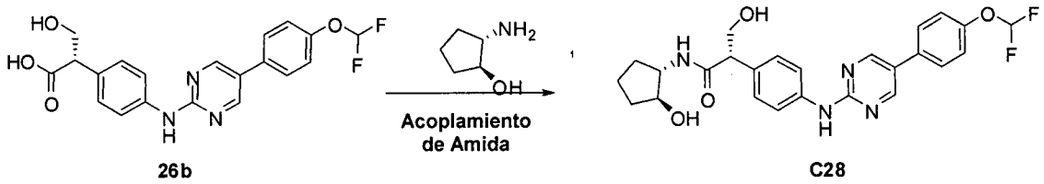


26b C27

Similar a la preparación del **C6**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.89 (d, J = 6.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 74.4 Hz, 1H) 7.27 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.91 (m, 1H), 3.73 (m, 2H),

1.99 (m, 3H), 1.65 (m, 3H), 1.38 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

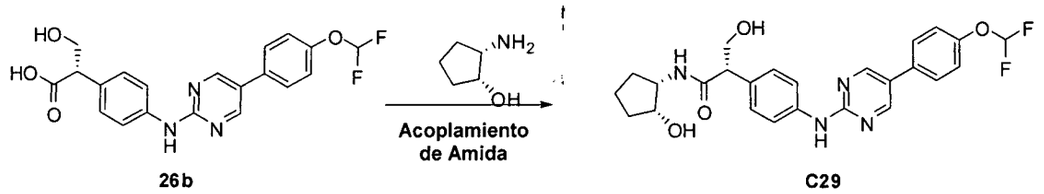
Ejemplo **C28**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2S)-2-hidroxi-ciclopentil)-propanamida



26b **C28**

Similar a la preparación del **C6**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.89 (d, J = 6.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 74.4 Hz, 1H) 7.27 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.89 (m, 2H), 3.74 (m, 1H), 1.99 (m, 2H), 1.87 (m, 1H), 1.79 (m, 1H), 1.57 (m, 2H), 1.43 (m, 1H), 1.19 (m, 1H). MS (m/z) $(M+1)^+$: 485.2.

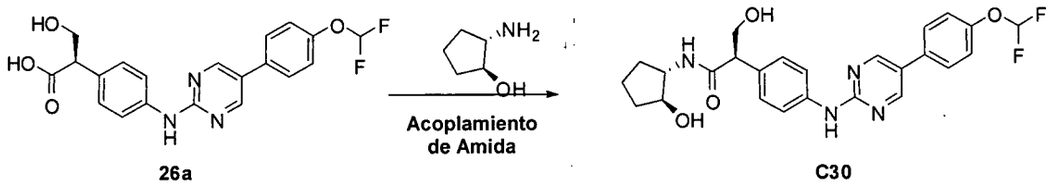
Ejemplo **C29**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2R)-2-hidroxi-ciclopentil)-propanamida



26b **C29**

Similar a la preparación del **C6**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 7.89 (d, J = 6.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 74.4 Hz, 1H) 7.27 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.97 (m, 2H), 3.80 (m, 1H), 1.99 (s, 2H), 1.71 (m, 3H), 1.54 (m, 1H), 1.41 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

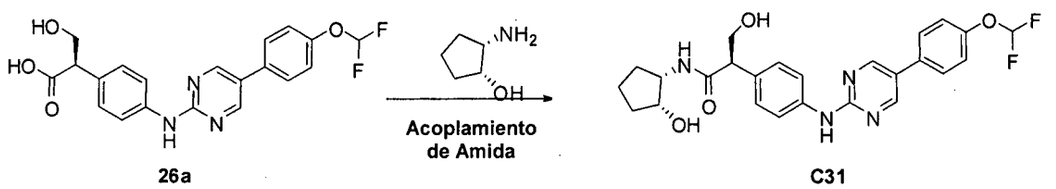
Ejemplo **C30**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2S)-2-hidroxi-ciclopentil)-propanamida



26a C30

Similar a la preparación del **C5**: ^{1}H RMN (400MHz, *d4*-MeOH) δ 8.68 (s, 2H), 7.56 (m, 4H), 7.22 (m, 4H), 6.77 (t, J = 72.0 Hz, 1H), 4.01 (m, 1H), 3.84 (m, 1H), 3.81 (m, 1H), 3.57 (m, 2H),), 2.01 (m, 1H), 1.74 (m, 1H), 1.69 (m, 2H), 1.44 (m, 2H). MS (m/z) $(M+1)^+$: 485.1.

Ejemplo **C31**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2R)-2-hidroxi-ciclopentil)-propanamida



26a C31

Similar a la preparación del **C5**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.71 (s, 1H), 8.80 (s, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.2 Hz, 1H), 7.27 (t, J = 65.6 Hz, 1H) 7.26 (m, 4H), 3.90 (m, 4H), 3.65 (m, 1H), 1.79 (m, 1H), 1.70 (m, 2H), 1.52 (m, 3H). MS (m/z) $(M+1)^+$: 485.2.

Ejemplo **C32**: 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(4-hidroxi-piperidin-1-il)-prop-2-en-1-ona

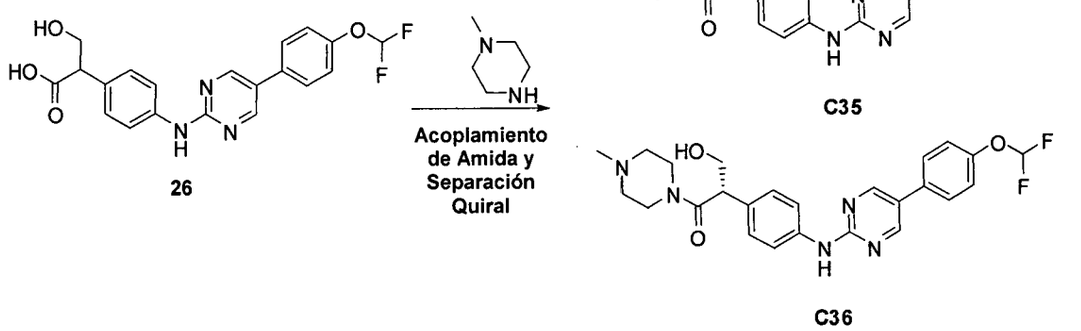
La 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(4-hidroxi-piperidin-1-il)-prop-2-en-1-ona **C32** se obtiene como un producto secundario menor durante la preparación del Ejemplo **C2**. ^{1}H RMN (400MHz, *d*6-DMSO) δ 9.97 (s, 1H), 8.85 (s, 2H), 7.2 (m, 4H), 7.35 (m, 4H), 7.29 (t, J = 74.0 Hz, 1H), 5.70 (s, 1H), 5.11 (s, 1H), 4.06 (m, 1H), 3.70 (m, 1H), 3.15 (m, 2H), 1.78 (m, 1H), 1.58 (m, 1H), 1.35 (m, 1H), 1.16 (m, 1H). MS (m/z) $(M+1)^+$: 467.2.

Ejemplo **C33**: 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(4-hidroxi-piperidin-1-il)-etanona

La 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(4-hidroxi-piperidin-1-il)-etanona **C33** se obtiene como un producto secundario menor durante la preparación del Ejemplo **C2**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.76 (s, 1H), 8.81 (s, 2H), 7.77 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.29 (t, J = 71 Hz, 1H), 7.28 (d, J = 7.4 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 3.94 (dd, J = 6.2, 4.1 Hz, 1H), 3.73 (dd, J = 8.4, 5.3 Hz, 1H), 3.64 (m, 2H), 3.15 (dd, J = 10.6, 8.6 Hz, 1H), 2.97 (m, 1H), 1.62 (m, 2H), 1.2 (m, 4H). MS (m/z) $(M+1)^+$: 455.2.

Ejemplo **C35**: (R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-metil-piperazin-1-il)-propan-1-ona

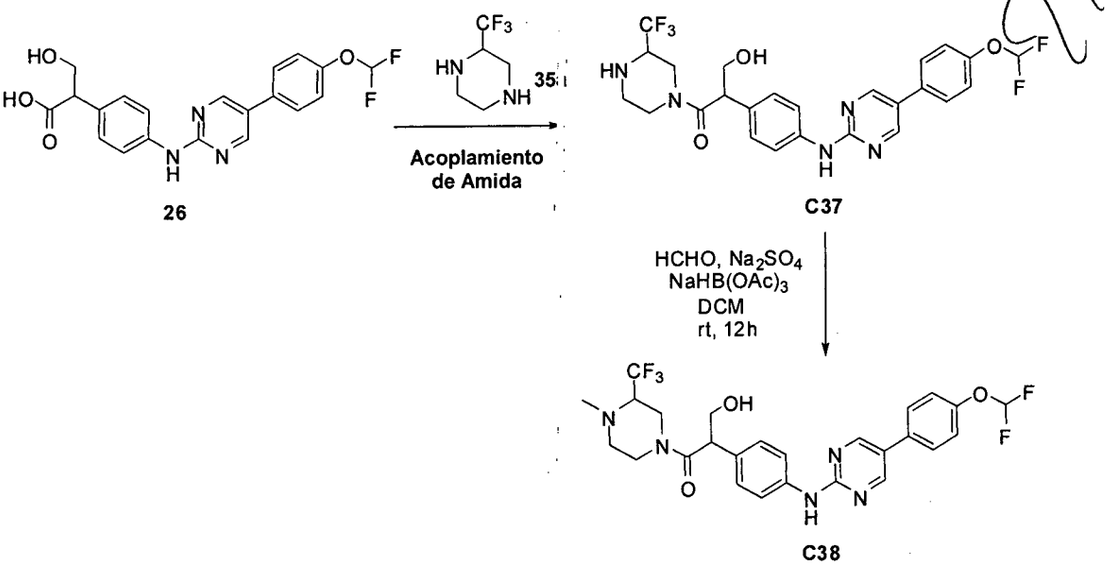
Ejemplo **C36**: (S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-metil-piperazin-1-il)-propan-1-ona



Similar a la preparación del **C**[illegible]. La separación mediante HPLC quiral sobre una columna (R,R)-WeikO-1, y hexano : isopropanol = 70 : 30 como gradiente proporciona los dos enantiómeros **C35** (primer pico eluido) y **C36** (segundo pico eluido). Al **C35** se le asigna arbitrariamente la configuración R. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.80 (s, 1H), 8.81 (s, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.1-7.5 (m, 5H), 4.09 (s, 1H), 3.96 (t, J = 8.8 Hz, 1H), 2.7-2.9 (m, 2H), 2.55 (m, 4H), 2.51 (m, 4H), 2.07 (s, 3H). MS (m/z) $(M+1)^+$: 484.2.

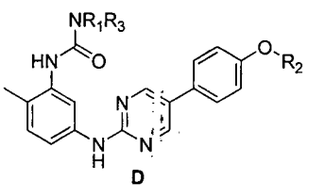
Al **C36** se le asigna arbitrariamente la configuración S. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.80 (s, 1H), 8.81 (s, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.1-7.5 (m, 5H), 4.09 (s, 1H), 3.96 (t, J = 8.8 Hz, 1H), 2.7-2.9 (m, 2H), 2.55 (m, 4H), 2.51 (m, 4H), 2.07 (s, 3H). MS (m/z) $(M+1)^+$: 484.2.

Ejemplo **C38**: 2-(4-(5-(4-(difluoro)-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(3-(trifluoro-metil)-4-metil-piperazin-1-il)-3-hidroxi-propan-1-ona

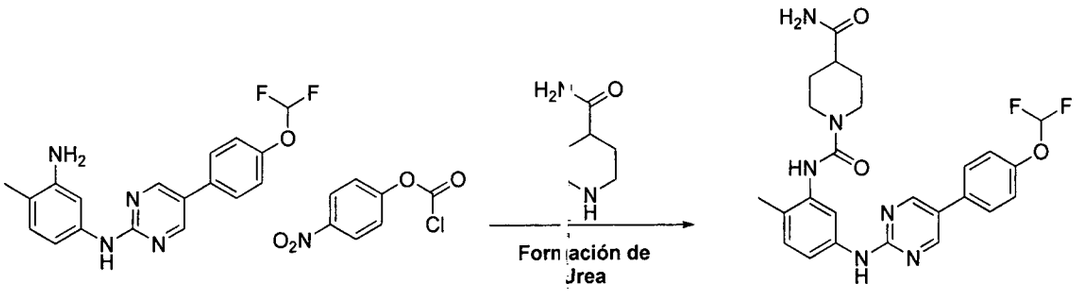


Una solución de la 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(3-(trifluoro-metil)-piperazin-1-il)-3-hidroxi-propan-1-ona **C37** (preparada como se describe para el **C1**, 0.05 milimoles), HCHO (0.15 milimoles, acuoso al 30 por ciento), y Na_2SO_4 anhidro (1.5 milimoles) en dicloro-metano (2 mililitros), se agita a temperatura ambiente durante 30 minutos. Entonces se agrega $NaHB(OAc)_3$ (0.3 milimoles), y la mezcla resultante se agita durante 12 horas. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona la 2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(3-(trifluoro-metil)-4-metil-piperazin-1-il)-3-hidroxi-propan-1-ona **C38**. MS (m/z) $(M+1)^+$: 552.2.

Compuestos Tipo D



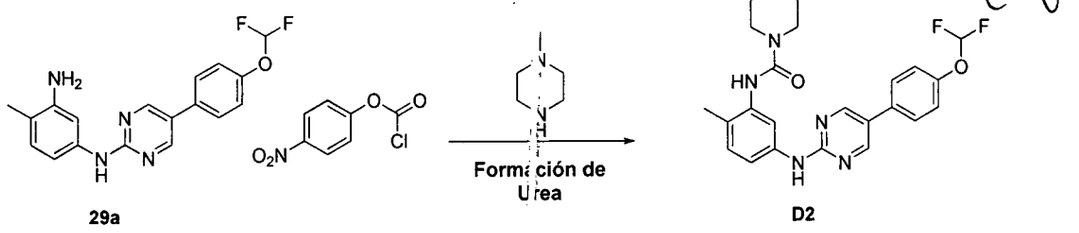
Ejemplo **D1**: N1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-piperidin-1,4-dicarboxamida



29a **D1**

La N1-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il)-4-metil-bencen-1,3-diamina **29a** (0.1 milimoles), cloroformato de 4-nitro-fenilo (0.12 milimoles), y piridina (0.24 milimoles) en dicloro-metano seco (0.5 mililitros), se agitan a temperatura ambiente durante 10 minutos. Entonces se agrega piperidin-4-carboxamida (0.12 milimoles), y la mezcla de reacción se agita durante 2 horas. La purificación mediante HPLC proporciona el compuesto objetivo **D1** como la sal de ácido trifluoro-acético. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.68 (s, 1H), 8.81 (s, 2H), 8.05 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.62 (s, 1H), 7.48 (m, 1H), 7.26 (m, 4H) 7.08 (d, J = 8.4 Hz, 1H), 6.80 (s, 1H), 4.09 (m, 2H), 2.81 (t, J = 12.4 Hz, 2H), 2.32 (m, 1H), 2.10 (s, 3H), 1.70 (m, 2H), 1.48 (m, 2H). MS (m/z) $(M+1)^+$: 497.2.

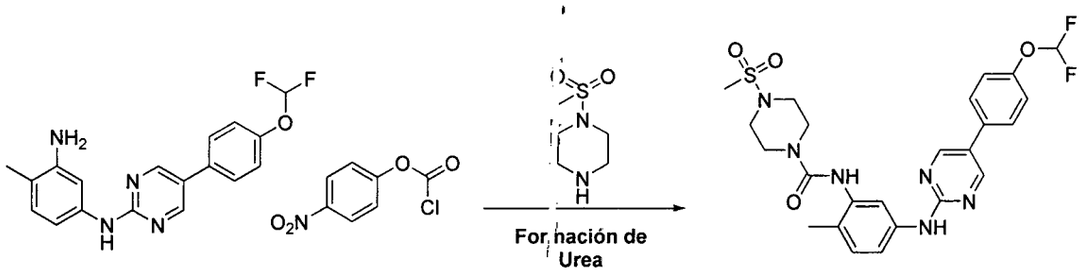
Ejemplo **D2**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-piperazin-1-carboxamida



29a D2

Similar a la preparación del **D1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.74 (s, 1H), 8.80 (s, 2H), 8.37 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.64 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.29 (s, 2H), 7.27 (t, J = 74.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 2.86 (s, 3H), 2.51 (m, 4H), 2.54 (m, 4H), 2.11 (s, 3H). MS (m/z) $(M+1)^+$: 469.2.

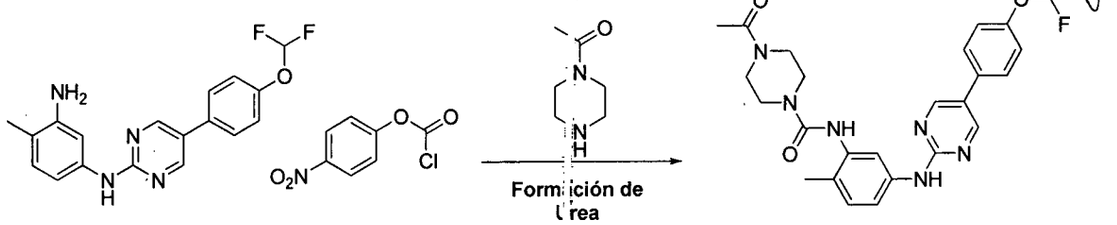
Ejemplo **D3**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metan-sulfonil-piperazin-1-carboxamida



29a D3

Similar a la preparación del **D1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.70 (s, 1H), 8.80 (s, 2H), 8.25 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.62 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 3.56 (m, 4H), 3.15 (m, 4H), 2.92 (s, 3H), 2.10 (s, 3H). MS (m/z) $(M+1)^+$: 533.2.

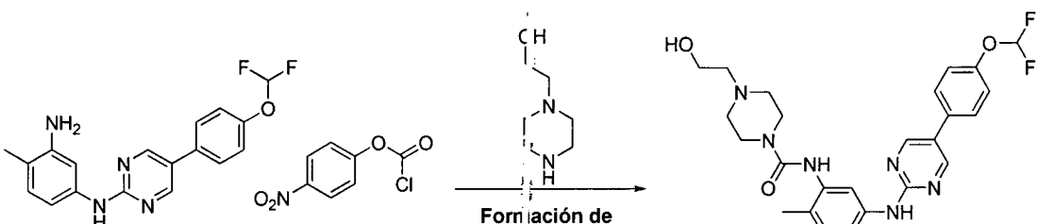
Ejemplo **D4**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-acetil-piperazin-1-carboxamida



29a D4

Similar a la preparación del **D4**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.69 (s, 1H), 8.80 (s, 2H), 8.18 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 74.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 3.56 (m, 4H), 3.35 (m, 4H), 2.10 (s, 3H), 2.04 (s, 3H). MS (m/z) $(M+1)^+$: 497.2.

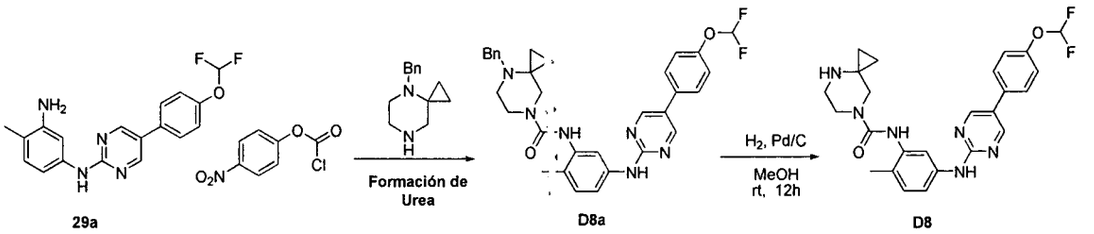
Ejemplo **D7**: N-(5-(5-(4-(difluoro(-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(2-hidroxi-etil)-piperazin-1-carboxamida



29a D7

Similar a la preparación del **D1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.72 (s, 1H), 8.8 (s, 2H), 8.4 (s, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.64 (m, 1H), 7.28 (m, 2H), 7.2 (t, J = 50 Hz, 1H), 7.1 (m, 2H), 3.8 (t, J = 4.9 Hz, 2H), 3.24 (t, J = 5 Hz, 2H), 2.51 (m, 8H), 2.11 (s, 3H). MS (m/z) $(M+1)^+$: 499.2.

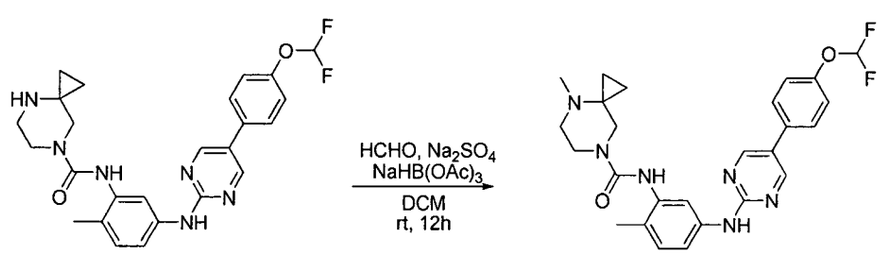
Ejemplo **D8**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida



29a D8a D8

La N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(fenil-metil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida **D8a** (preparada como se describe para el **D1**; 0.2 milimoles) se disuelve en 10 mililitros de metanol, seguido por la adición del 5 por ciento molar de Pd/C (al 10 por ciento en peso). El matraz se carga con un globo de hidrógeno durante 12 horas de agitación. La mezcla se filtra sobre un cojín de Celite y el filtrado se concentra para proporcionar la N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida **D8**, la cual se utiliza sin mayor purificación. MS (m/z) $(M+1)^+$: 523.1.

Ejemplo **D9**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-4,7-diazaespiro-[2.5]-octan-7-carboxamida

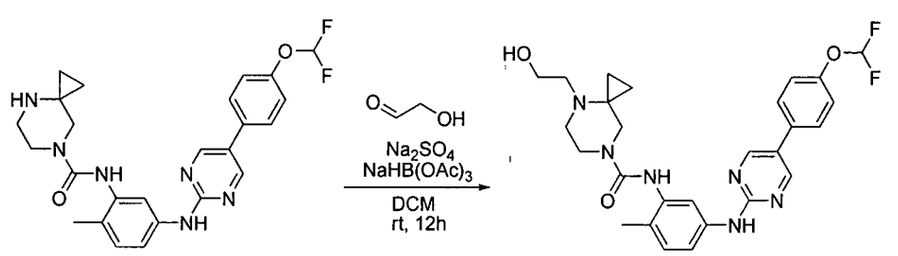


D8 D9

Una solución de la N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-

2-il-amino)-2-metil-fenil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida **D8** (0.05 milimoles), HCHO (0.15 milimoles, acuoso al 30 por ciento), y Na_2SO_4 anhidro (1.5 milimoles) en dicloro-metano (2 mililitros), se agita a temperatura ambiente durante 30 minutos. Entonces se agrega $NaHB(OAc)_3$ (0.3 milimoles), y la mezcla resultante se agita durante 12 horas. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona la N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-4,7-diazaespiro-[2.5]-octan-7-carboxamida **D9**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.67 (s, 1H), 8.79 (s, 2H), 7.98 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 76.0 Hz, 1H),7.08 (d, J = 8.4 Hz, 1H), 2.78 (m, 2H), 2.51 (m, 4H), 2.31 (s, 3H), 2.10 (s, 3H), 0.62 (m, 2H), 0.50 (m, 2H). MS (m/z) $(M+1)^+$: 537.1.

Ejemplo **D10**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(2-hidroxi-etil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida

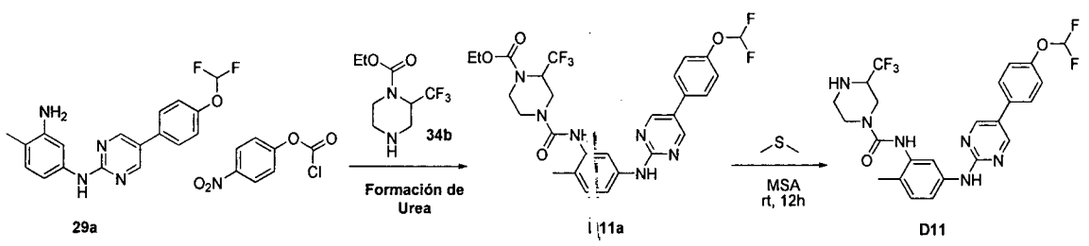


D8 **D10**

Una solución de la N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida **D8** (0.05 milimoles), 2-hidroxi-acetaldehído (0.6 milimoles), y Na_2SO_4

anhidro (1.5 milimoles) en dicloro-metano (2 mililitros), se agita a temperatura ambiente durante 30 minutos. Entonces se agrega $NaHB(OAc)_3$ (0.3 milimoles), y la mezcla resultante se agita durante 12 horas. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona la N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(2-hidroxi-etil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida **D10**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.67 (s, 1H), 8.79 (s, 2H), 7.95 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 76.0 Hz, 1H),7.08 (d, J = 8.4 Hz, 1H), 2.89 (m, 2H), 2.77 (m, 2H), 2.54 (m, 2H), 2.51 (m, 4H), 2.10 (s, 3H), 0.50-0.62 (m, 4H). MS (m/z) $(M+1)^+$: 525.2.

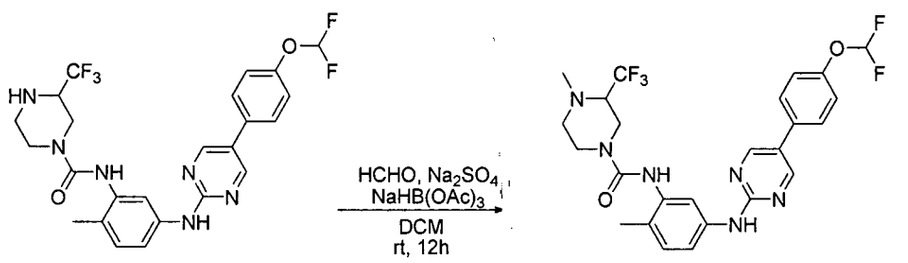
Ejemplo **D11**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-(trifluoro-metil)-piperazin-1-carboxamida



La N1-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il)-4-metil-bencen-1,3-diamina **29a** (0.4 milimoles), cloroformato de 4-nitro-fenilo (0.48 milimoles), y piridina (0.8 milimoles) en dicloro-metano seco (2 mililitros), se agitan a temperatura ambiente durante 10 minutos. Entonces se agrega 2-(trifluoro-metil)-piperazin-1-carboxilato de etilo **34b** (0.48 milimoles), y la mezcla de reacción se

agita durante 2 horas. Después de que se completa la reacción, la mezcla se diluye con 20 mililitros de dicloro-metano, y se lava con agua. La capa orgánica se separa, se seca sobre Na_2SO_4, se filtra, y se concentra al vacío, para proporcionar un residuo **D11a**. A este residuo se le agregan sulfuro de dimetilo (1.2 milimoles) y ácido metan-sulfónico (1.0 mililitros), y la mezcla resultante se agita a temperatura ambiente durante 12 horas. La purificación mediante HPLC (gradiente de ACN del 10 al 70 por ciento) proporciona el **D11** como una sal de ácido trifluoro-acético. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.73 (s, 1H), 8.80 (s, 2H), 8.43 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 74.0 Hz, 1H),7.11 (d, J = 8.4 Hz, 1H), 4.27 (m, 1H), 4.02 (m, 1H), 3.17 (m, 1H), 3.0 (s, 1H), 2.51 (m, 4H), 2.11 (s, 3H). MS (m/z) $(M+1)^+$: 523.2.

Ejemplo **D12**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-3-(trifluoro-metil)-piperazin-1-carboxamida

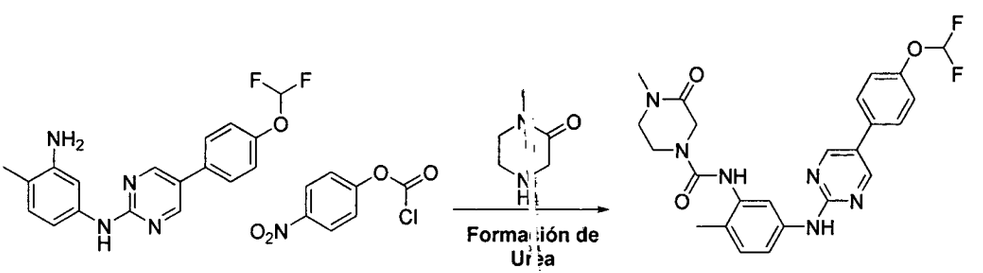


D11 **D12**

Una solución de la N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-(trifluoro-metil)-piperazin-1-carboxamida **D11** (0.05 milimoles), HCHO (0.15 milimoles, acuoso al 30 por

ciento), y Na_2SO_4 anhidro (1.5 milimoles) en dicloro-metano (2 mililitros), se agita a temperatura ambiente durante 30 minutos. Entonces se agrega $NaHB(OAc)_3$ (0.3 milimoles), y la mezcla resultante se agita durante 12 horas. La purificación mediante HPLC de preparación (gradiente de ACN del 10 al 70 por ciento) proporciona la N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-(trifluoro-metil)-4-metil-piperazin-1-carboxamida **D12** como una sal de ácido trifluoro-acético. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.69 (s, 1H), 8.80 (s, 2H), 8.15 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.61 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.4 Hz, 1H), 3.68 (m, 1H), 3.54 (m, 1H), 2.88 (m, 1H), 2.51 (m, 4H), 2.47 (s, 1H), 2.09 (s, 3H). MS (m/z) $(M+1)^+$: 537.2.

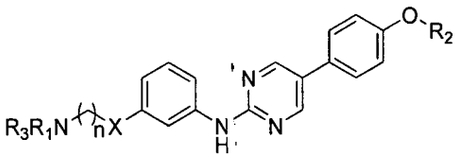
Ejemplo **D13**: N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-3-oxopiperazin-1-carboxamida



29a D13

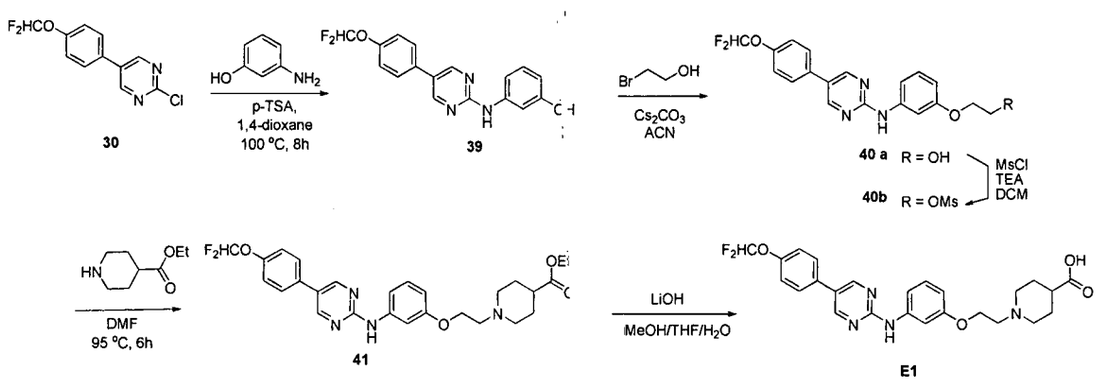
Similar a la preparación del **D1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.70 (s, 1H), 8.80 (s, 2H), 8.21 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 74.0 Hz, 1H), 7.27 (d, J = 8.4Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 4.06 (s, 2H), 2.89 (s, 3H), 2.51 (m, 4H), 2.10 (s, 3H). MS (m/z) $(M+1)^+$: 483.2.

Compuestos Tipo E



E

Ejemplo **E1**: Ácido 1-(2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxílico



A una mezcla de la 2-cloro-5-(4-(difluoro-metoxi)-fenil)-pirimidina **30** (3.2 milimoles) y 3-amino-fenol (6.42 milimoles) en 1,4-dioxano (5 mililitros), se le agrega p-TSA (5.4 milimoles). La mezcla de reacción se calienta a 100°C durante 12 horas. Después de este tiempo, la reacción se diluye con una solución 2M de Na_2CO_3 y se extrae con dicloro-metano (50 mililitros, 3 veces). La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, y se concentra. La purificación mediante cromatografía corta con SiO_2 utilizando dicloro-metano : EtOAc = 7 : 3 como eluyente, proporciona el (3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenol **39**. MS (m/z) $(M+1)^+$: 330.1.

Una solución del 3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenol **39** (1.2 milimoles), 2-bromo-etanol (1.4 milimoles), y carbonato de cesio (1.6 milimoles) en acetonitrilo (10 mililitros), se calienta a 85°C durante 12 horas, y entonces se enfría a temperatura ambiente. La reacción se evapora a sequedad, y entonces se vuelve a disolver en dicloro-metano. La mezcla orgánica se lava con agua y salmuera, y entonces se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad. La purificación mediante cromatografía en gel de sílice con hexano : EtOAc = 1 : 1 como eluyente, proporciona el 2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etanol **40a** como un sólido blanco. MS (m/z) $(M+1)^+$: 373.8.

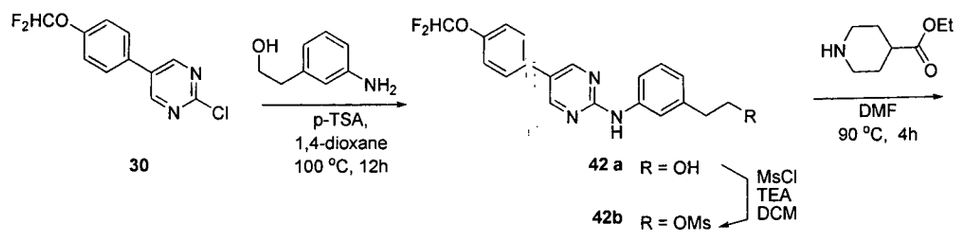
A una solución del 2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etanol **40** (0.4 milimoles) en dicloro-metano (15 mililitros) se le agregan trietil-amina (0.4 milimoles) y cloruro de metan-sulfonilo (0.4 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 12 horas, y entonces se lava con salmuera y se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad. El 2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil-metan-sulfonato **40b** crudo resultante como un sólido bronceado, se utiliza sin mayor purificación.

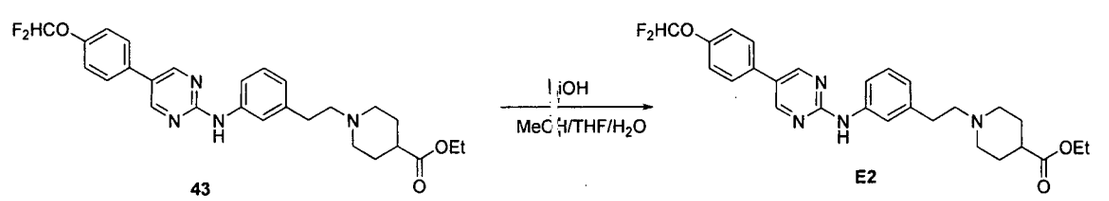
El 2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil-metan-sulfonato **40b** (0.4 milimoles), y piperidin-4-carboxilato de etilo (0.9 milimoles), se disuelven en N,N-dimetil-formamida (3 mililitros) y se calientan a 95°C durante 6 horas; entonces se enfrían a temperatura ambiente. La mezcla de reacción

se divide con EtOAC y agua. La capa orgánica se lava con agua, salmuera, se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad. El producto crudo se tritura con metanol y se filtra para proporcionar el 1-(2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxilato de etilo **41** como un sólido blanco. MS (m/z) $(M+1)^+$: 513.2.

Al 1-(2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxilato de etilo **41** (78 micromoles) se le agregan tetrahidrofurano (3 mililitros), metanol (2 mililitros), e hidróxido de litio 3M (0.5 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 6 horas hasta completarse, como se detecta mediante LCMS. Subsiguientemente, los solventes orgánicos se evaporan, y la mezcla de reacción se diluye con agua (5 mililitros) y se neutraliza con HCl 3M (0.5 milimoles). El precipitado resultante se filtra, se lava con agua, y se seca al aire, para proporcionar el ácido 1-(2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxílico **E1** como un sólido blanco. ^{1}H RMN (400MHz, *d6*-DMSO) δ 12.12 (s, 1H), 9.79 (s, 1H), 8.85 (s, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.52 (bs, 1H), 7.34 (bd, J = 8.0 Hz, 1H), 7.31 (t, J = 74.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.56 (bd, J = 8.0 Hz, 1H) 4.05 (m, 2H), 2.88 (m, 2H), 2.67 (m, 2H), 2.20 (m, 1H), 2.09 (m, 2H), 1.78 (m, 2H), 1.57 (m, 2H). MS (m/z) $(M+1)^+$: 484.2.

Ejemplo **E2**: Ácido 1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico





Una solución del 2-(3-amino-fenil)-etanol (1.8 milimoles), 2-cloro-5-(4-difluoro-metoxi-fenil)-pirimidina **30** (1.8 milimoles), y p-TSA (1.8 milimoles) en dioxano (10 mililitros), se calienta a 100°C durante 12 horas, y entonces se enfría a temperatura ambiente. La mezcla de reacción se agrega lentamente a agua (100 mililitros) con agitación. El precipitado resultante se recolecta mediante filtración, se lava con agua y se seca al aire. El precipitado crudo del 2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-etanol **42a** se utiliza sin mayor purificación. MS (m/z) $(M+1)^+$: 357.9.

A una solución del 2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-etanol **42a** (0.7 milimoles) en dicloro-metano (20 mililitros), se le agregan trietil-amina (0.8 milimoles) y cloruro de metan-sulfonilo (0.8 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 12 horas, y entonces se lava con salmuera y se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad. El 3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil-metan-sulfonato **42b** resultante como un sólido bronceado

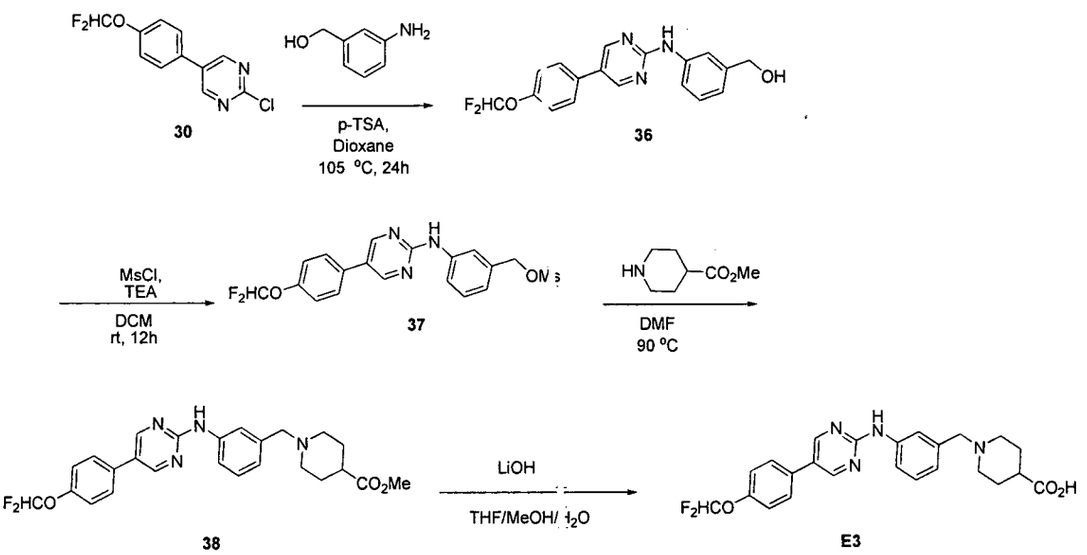
crudo, se utiliza sin mayor purificación.

El 3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil-metan-sulfonato **42b** (0.7 milimoles) y piperidin-4-carboxilato de etilo (1.7 milimoles), se disuelven en N,N-dimetil-formamida (6 mililitros), y se calientan a 95°C durante 6 horas; entonces se enfrían a temperatura ambiente. La mezcla de reacción se divide con EtOAc y agua. La capa orgánica se lava con agua, salmuera, se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad. El material crudo se purifica mediante cromatografía en columna sobre sílice con hexano : EtOAc = 1 : 1 a 100 por ciento de EtOAc como eluyente para proporcionar el 1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxilato de etilo **43** como un sólido cristalino transparente. MS (m/z) $(M+1)^+$: 497.2.

Al 1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxilato de etilo **43** (0.3 milimoles), se le agregan tetrahidrofurano (3 mililitros), metanol (2 mililitros), e hidróxido de litio 3.0 M (1.8 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 6 horas hasta completarse, como se detecta mediante LCMS. Subsiguientemente, los solventes orgánicos se evaporan, y la mezcla de reacción se diluye con agua (10 mililitros), y entonces se neutraliza con HCl 3M (1.8 milimoles). El precipitado resultante se filtra, se lava con agua, y se seca al aire para proporcionar el **E2** como un sólido blanco. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.75 (s, 1H), 8.83 (s, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.65 (m, 2H), 7.31 (t, J = 74.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.21 (t, J

= 8.0 Hz, 1H), 6.83 (d, J = 7.2 Hz, 1H), 2.71 (m, 2H), 2.21 (m, 1H), 2.03 (m, 2H), 1.81 (m, 2H), 1.58 (m, 2H). MS (m/z) $(M+1)^+$: 468.2.

Ejemplo **E3**: Ácido 1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico



A una mezcla de la 2-cloro-5-(4-(difluoro-metoxi)-fenil)-pirimidina **30** (0.40 milimoles) y (3-amino-fenil)-metanol (0.40 milimoles) en 1,4-dioxano (0.5 mililitros), se le agrega p-TSA (0.4 milimoles). La mezcla de reacción se calienta a 105°C durante 2 días. Después de este tiempo, la mezcla de reacción se diluye con una solución de Na_2CO_3 2M (30 mililitros), y se extrae con dicloro-metano (30 mililitros, 3 veces). La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4 y se concentra. La purificación mediante cromatografía en gel de sílice corta utilizando hexano : EtOAc = 1 : 2, proporciona el (3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-metanol **36**: ^{1}H RMN (400MHz, *d4*-MeOH) δ 8.56 (s, 2H), 7.65 (m, 1H), 7.48-7.52 (m, 1H), 7.42-7.46 (m, 2H),

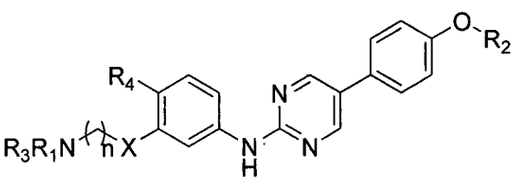
7.29 (t, J = 8 Hz, 1H), 7.15-7.18 (m, 3H), 6.99-7.03 (m, 1H), 6.49 (t, J = 73.6 Hz, 1H), 4.67 (s, 2H). MS (m/z) $(M+1)^+$ 344.1.

A una solución del (3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-metanol **36** (6.22 milimoles) en dicloro-metano (30 mililitros), se le agregan trietil-amina (9.33 milimoles) y cloruro de metan-sulfonilo (7.47 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 1.5 horas. La reacción se diluye con H_2O (10 mililitros) y se lava con una solución de Na_2CO_3 (20 mililitros, 3 veces). La capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se concentra, para proporcionar el 3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil-metan-sulfonato **37**. MS (m/z) $(M+1)^+$ 422.1.

A una solución del 3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil-metan-sulfonato **37** (0.050 milimoles) en N,N-dimetil-formamida anhidra (1 mililitro) se le agrega piperidin-4-carboxilato de metilo (0.10 milimoles), y la solución se calienta a 100°C durante 8 horas. Después de que se completa la reacción, la mezcla se diluye con tetrahidrofurano : metanol : H_2O (3 : 2 : 1, 5 mililitros). A la mezcla de reacción se le agrega LiOH 6N (0.30 milimoles). La reacción se agita a temperatura ambiente durante 1 hora. La purificación mediante LC/MS de preparación proporciona el ácido 1-(3-(5 (4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico **E3**. ^1H RMN (400MHz, *d4*-MeOH) δ 8.64 (s, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.78 (t, J = 74.0 Hz, 1H), 4.11 (s, 2H), 3.31

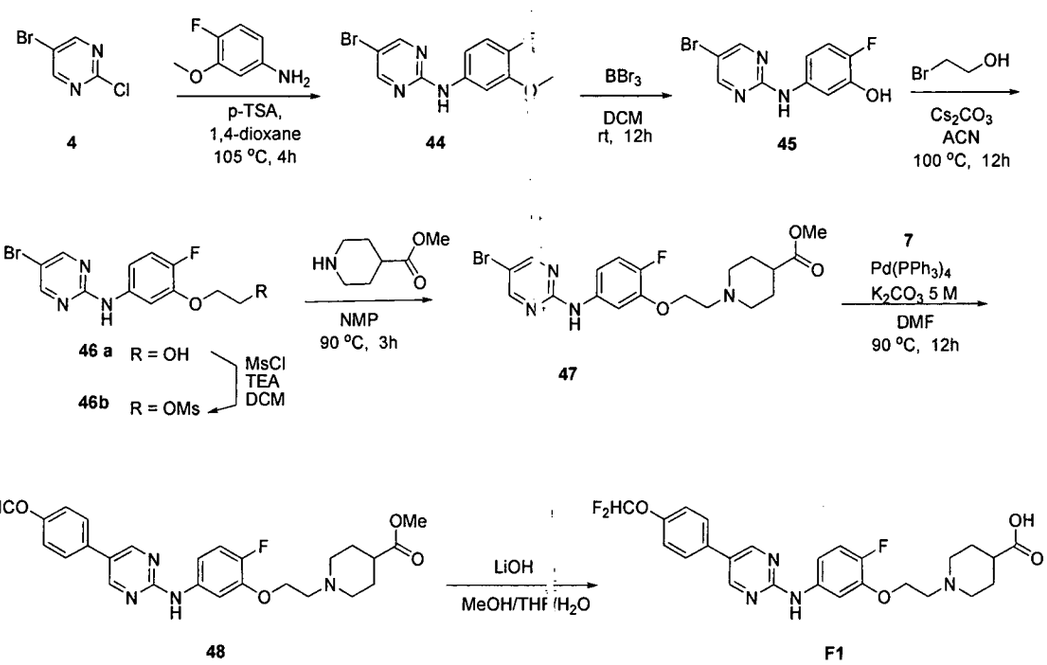
(m, 2H), 2.92 (m, 2H), 2.36 (m, 1H), 2.02 (m, 2H), 1.81 (m, 2H). MS (m/z) $(M+1)^+$: 455.2.

Compuestos Tipo F



F

Ejemplo **F1**: Ácido 1-(2-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etil)-piperidin-4-carboxílico



A una mezcla de la 5-bromo-2-cloro-pirimidina **4** (1.1 milimoles) y 4-fluoro-3-metoxi-anilina (1.1 milimoles) en 5 mililitros de 1,4-dioxano, se le agrega p-TSA (1.0 milimoles). La mezcla de reacción se calienta a 105°C durante 4 horas. Después de este tiempo, la

mezcla de reacción se diluye con una solución de Na_2CO_3 2M, y se extrae con dicloro-metano (50 mililitros, 3 veces). La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4 y se concentra. La purificación mediante HPLC de preparación (gradiente de ACN del 20 al 70 por ciento) proporciona la 5-bromo-N-(4-fluoro-3-metoxi-fenil)-pirimidin-2-amina **44** como un sólido color café. MS (m/z) $(M+1)^+$: 299.1.

A una solución de la 5-bromo-N-(4-fluoro-3-metoxi-fenil)-pirimidin-2-amina **44** (0.25 milimoles) en 3 mililitros de dicloro-metano anhidro a 0°C, se le agrega por goteo BBr_3 (1.27 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 12 horas. Después de este tiempo, la mezcla de reacción se diluye con una solución de Na_2CO_3 2M, y se extrae con dicloro-metano (20 mililitros, 2 veces). La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4 y se concentra, para proporcionar el 5-(5-bromo-pirimidin-2-il-amino)-2-fluoro-fenol **45** como un sólido castaño, el cual se utiliza sin mayor purificación. MS (m/z) $(M+1)^+$: 286.2.

Una solución del 5-(5-bromo-pirimidin-2-il-amino)-2-fluoro-fenol **45** (0.25 milimoles), 2-bromo-etanol (0.28 milimoles), y carbonato de cesio (0.36 milimoles) en acetonitrilo (3 mililitros), se calienta a 100°C durante 12 horas. La reacción se evapora a sequedad, y entonces se vuelve a disolver en dicloro-metano. La mezcla orgánica se lava con agua y salmuera, y entonces se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad, para proporcionar el 2-(5-(5-bromo-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etanol **46a** como un

sólido color café, el cual se utiliza sin mayor purificación. MS (m/z) $(M+1)^+$: 329.2.

A una solución del 2-(5-(5-bromo-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etanol **46a** (0.24 milimoles) en dicloro-metano (15 mililitros), se le agregan trietil-amina (0.24 milimoles) y cloruro de metan-sulfonilo (0.24 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 12 horas, y entonces se lava con salmuera, y se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad. El sólido bronceado resultante del 2-(5-(5-bromo-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etil-metan-sulfonato **46b** se utiliza sin mayor purificación. MS (m/z) $(M+1)^+$: 407.1.

El 2-(5-(5-bromo-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etil-metan-sulfonato **46b** (0.24 milimoles) y piperidin-4-carboxilato de metilo (0.48 milimoles) se disuelven en NMP (2 mililitros), y se calientan a 90°C durante 3 horas. La mezcla de reacción se enfría a temperatura ambiente, se diluye con agua, y se extrae con EtOAc (30 mililitros, 2 veces). La capa orgánica se lava con agua, salmuera, se seca sobre sulfato de sodio, y se concentra a sequedad. El producto crudo se purifica mediante cromatografía corta con SiO_2 utilizando dicloro-metano : hexano = 9 : 1 como eluyente, para proporcionar el 1-(2-(5-(5-bromo-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etil)-piperidin-4-carboxilato de metilo **47** como un sólido color café claro. MS (m/z) $(M+1)^+$: 454.1.

A una solución del 1-(2-(5-(5-bromo-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etil)-piperidin-4-carboxilato de metilo **47** (0.24

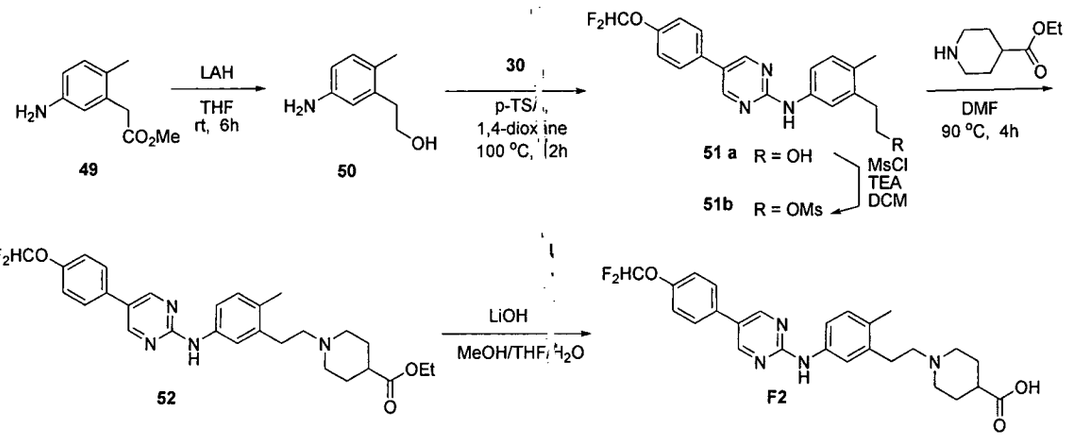
milimoles) en 1,4-dioxano (2.0 mililitros), se le agregan 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7** (0.28 milimoles), K_2CO_3 1.8M (0.5 milimoles), y $Pd(PPh_3)_4$ (0.017 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 90°C durante 12 horas. La mezcla de reacción se enfría a temperatura ambiente, se diluye con agua (10 mililitros), y se extrae con dicloro-metano (20 mililitros, 2 veces). La capa orgánica se separa, se seca sobre Na_2SO_4 y se concentra. La purificación mediante HPLC de preparación (gradiente de ACN del 20 al 70 por ciento) proporciona el 1-(2-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etil)-piperidin-4-carboxilato de metilo **48** como un sólido blanco. MS (m/z) $(M+1)^+$: 517.1.

Al 1-(2-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etil)-piperidin-4-carboxilato de metilo **48** (0.072 milimoles) se le agregan tetrahidrofurano (1 mililitro), metanol (0.8 mililitros), e hidróxido de litio 6M (0.42 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 6 horas hasta completarse mediante LCMS. Los solventes orgánicos se evaporan, y la mezcla de reacción se diluye con agua y se neutraliza con HCl 6M (0.42 milimoles). El precipitado resultante se filtra, se lava con agua y se seca al aire, para proporcionar el **F1** como un sólido blanco. ^1H RMN (400MHz, *d6*-DMSO) δ 9.88 (s, 1H), 8.85 (s, 2H), 7.79 (m, 2H), 7.71 (dd, J = 8.0, 12.0 Hz, 1H), 7.46 (m, 1H), 7.31 (m, 2H), 7.29(t, J = 69.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H),

4.41 (m, 2H), 3.58 (m, 6H), 3.14 (m, 2H), 2.12 (m, 2H),1.77 (m, 1H).

MS (m/z) $(M+1)^+$: 503.2.

Ejemplo **F2**: Ácido 1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenetil)-piperidin-4-carboxílico



A una solución del metil-éster del ácido (5-amino-2-metil-fenil)-acético **49** (1.4 milimoles) en tetrahidrofurano (7 mililitros) a 0°C, se le agrega hidruro de litio 1M y una solución de aluminio y tetrahidrofurano (1.4 milimoles). La reacción se agita a temperatura ambiente durante 6 horas, y subsiguientemente se apaga con agua helada, y se divide con acetato de etilo. La capa orgánica se lava con salmuera, se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad, para proporcionar el 2-(5-amino-2-metil-fenil)-etanol **50** como un sólido cristalino blonceado, el cual se utiliza sin mayor purificación.

Una solución de la 2-cloro-5-(4-difluoro-metoxi-fenil)-pirimidina **30** (1.3 milimoles), el 2-(5-amino-2-metil-fenil)-etanol **50** (1.3

milimoles), y p-TSA (0.24 gramos, 1.3 milimoles) en dioxano (10 mililitros), se calienta a 100°C durante 12 horas, y entonces se enfría a temperatura ambiente. La mezcla de reacción se agrega lentamente a agua (100 mililitros) con agitación. El precipitado resultante se recolecta mediante filtración, se lava con agua, y se seca al aire. El precipitado crudo se purifica mediante cromatografía en columna sobre sílice con hexanos : EtOAc = 1:1 como eluyente, para proporcionar el 2-{5-[5-(4-difluoro-metoxi-fenil)-pirimidin-2-il-amino]-2-metil-fenil}-etanol **51a** como un sólido. MS (m/z) $(M+1)^+$: 372.3.

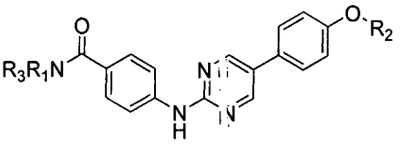
A una solución del 2-{5-[5-(4-difluoro-metoxi-fenil)-pirimidin-2-il-amino]-2-metil-fenil}-etanol **51a** (0.8 milimoles) en dicloro-metano (25 mililitros), se le agregan trietil-amina (1.0 milimoles) y cloruro de metan-sulfonilo (0.9 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 12 horas, y entonces se lava con salmuera, y se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad. El 5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenetil-metan-sulfonato **51b** resultante como un aceite color ámbar transparente, se utiliza sin mayor purificación. MS (m/z) $(M+1)^+$: 450.1.

El 5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenetil-metan-sulfonato **51b** (0.9 milimoles), y piperidin-4-carboxilato de etilo (2.2 milimoles), se disuelven en N,N-dimetil-formamida (10 mililitros), y se calientan a 90°C durante 4 horas; entonces se enfrían a temperatura ambiente. La mezcla de reacción se divide con EtOAc

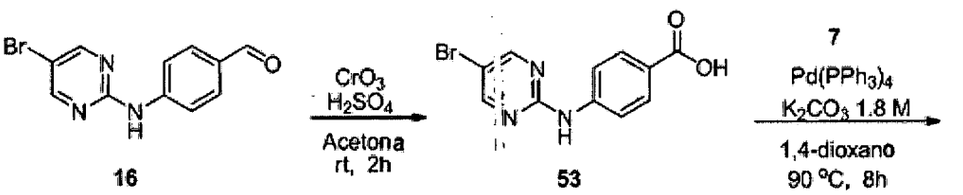
y agua. La capa orgánica se lava con agua, salmuera, se seca sobre sulfato de magnesio, se filtra, y se reduce a sequedad. El material crudo se purifica mediante cromatografía en columna sobre sílice con hexano : EtOAc = 1 : 1 a 100 por ciento de EtOAc como eluyente, para proporcionar el 1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenetil)-piperidin-4-carboxilato de etilo **52** como un aceite viscoso transparente. MS (m/z) $(M+1)^+$: 511.2.

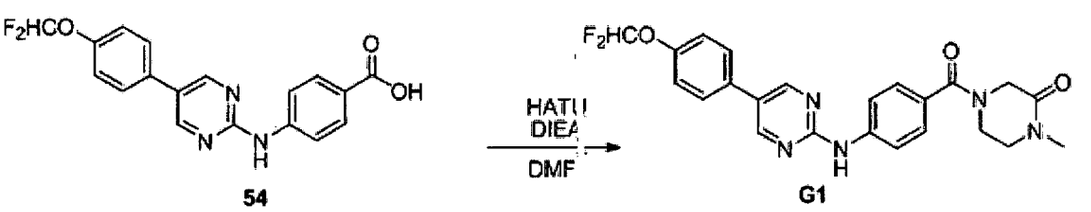
Al 1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenetil)-piperidin-4-carboxilato de etilo **52** (0.6 milimoles) se le agregan tetrahidrofurano (3 mililitros), metanol (2 mililitros), e hidróxido de litio 3M (7.3 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 6 horas hasta completarse, como se detecta mediante LCMS. Subsiguientemente, los solventes orgánicos se evaporan, y la mezcla de reacción se diluye con agua (10 mililitros), y entonces se neutraliza con HCl 3M (7.3 milimoles). El precipitado resultante se filtra, se lava con agua, y se seca al aire. El precipitado crudo se purifica mediante LCMS de preparación, para proporcionar el ácido 1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenetil)-piperidin-4-carboxílico **F2** como un sólido blanco. ^{1}H RMN (400MHz, *d6*-DMSO) δ 9.69 (s, 1H), 8.79 (s, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.60 (bd, J = 8.0 Hz, 1H), 7.56 (bs, 1H), 7.46 (s, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 1H), 3.19 (m, 1H), 2.96 (m, 2H), 2.27 (s, 3H), 2.10 (m, 2H), 1.75 (m, 2H). MS (m/z) $(M+1)^+$: 483.2.

Compuestos Tipo G



Ejemplo **G1**: 4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-1-metil-piperazin-2-ona





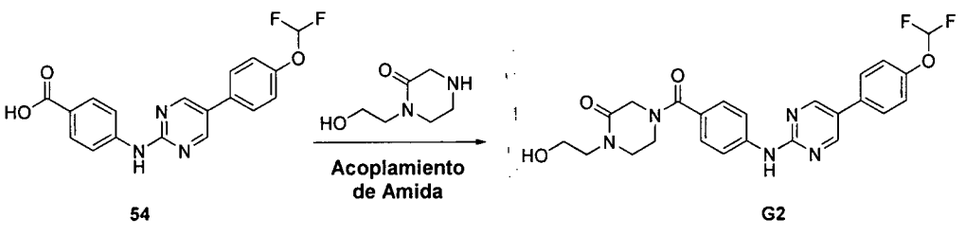
A una solución del 4-(5-bromo-pirimidin-2-il-amino)-benzaldehído **16** (1.26 milimoles) en acetona (5 mililitros), se le agrega reactivo de Jones (3.0 milimoles de una solución 4M) en porciones hasta la conversión completa, como se detecta mediante LCMS. Se agrega isopropanol (10 mililitros), y la mezcla de reacción se agita a temperatura ambiente durante 1 hora; entonces el solvente se remueve al vacío. El residuo verde se vuelve a disolver en agua, y se divide con acetato de etilo. La capa orgánica se lava con agua, salmuera, se seca sobre sulfato de sodio, se filtra, y se reduce a sequedad, para proporcionar el ácido 4-(5-bromo-pirimidin-2-il-amino)-benzoico **53** como un sólido amarillo, el cual se utiliza sin mayor purificación. MS (m/z) $(M+1)^+$: 295.1.

Al ácido 4-(5-bromo-pirimidin-2-il-amino)-benzoico **53** (0.25 milimoles) en 1,4-dioxano (2.0 mililitros) se le agrega el 2-(4-(difluoro-metoxi)-fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano **7** (0.28 milimoles), K_2CO_3 1.8M (0.5 milimoles), y $Pd(PPh_3)_4$ (0.017 milimoles). La reacción se evacua y se vuelve a llenar con nitrógeno dos veces, y entonces se calienta a 90°C durante 8 horas. La mezcla de reacción se diluye con agua (10 mililitros), se neutraliza con HCl 2M, y se extrae con dicloro-metano (20 mililitros, 3 veces). La purificación mediante HPLC de preparación (gradiente de ACN del 20 al 70 por ciento) proporciona el ácido 4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoico **54** como un sólido blanco. MS (m/z) $(M+1)^+$: 358.2.

El ácido 4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoico **54** (0.022 milimoles), HATU (0.027 milimoles), y 1-metil-piperazin-2-ona (0.022 milimoles), se disuelven en dimetil-formamida seca (0.5 mililitros) a temperatura ambiente. Se agrega di-isopropil-etil-amina (0.06 milimoles) a la solución. La mezcla de reacción se agita durante 1 hora a temperatura ambiente. La purificación mediante HPLC proporciona la 4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-1-metil-piperazin-2-ona **G1** como una sal de ácido trifluoro-acético. ^{1}H RMN (400MHz, *d6*-DMSO) δ 10.1 (s, 1H), 8.87 (s, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.4Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 51.2 Hz, 1H), 4.1 (s, 2H), 2.87 (s, 3H), 2.55 (m, 4H). MS (m/z) $(M+1)^+$: 454.2.

Ejemplo **G2**: 4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-

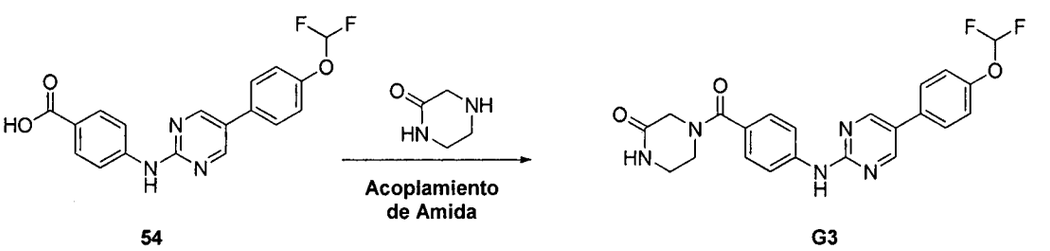
amino)-benzoil)-1-(2-hidroxi-etil)-piperazin-2-ona



54 G2

Similar a la preparación del **G1**. ^{1}H RMN (400MHz, *d6*-DMSO) δ 10.1 (s, 1H), 8.87 (s, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.2 (t, J = 50.2 Hz, 1H), 4.1 (s, 2H), 2.55 (m, 6H), 2.51 (m, 4H). MS (m/z) $(M+1)^+$: 484.1.

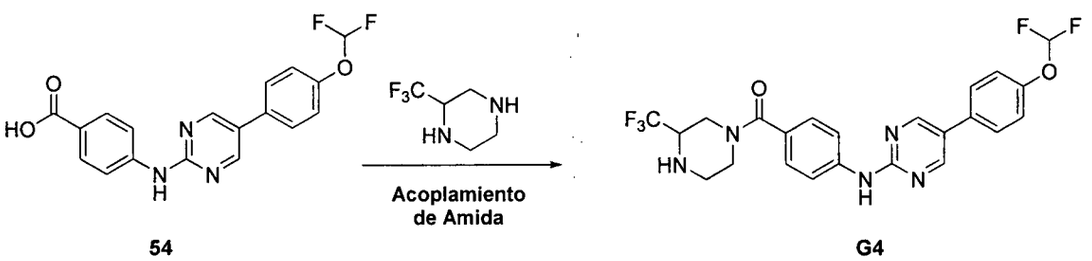
Ejemplo **G3**: 4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-piperazin-2-ona



54 G3

Similar a la preparación del **G1**. H RMN (400MHz, *d6*-DMSO) δ 10.12 (s, 1H), 8.89 (s, 2H), 8.14 (bs, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 72.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 4.01 (s, 2H), 3.65 (m, 2H), 3.28 (m, 4H). MS (m/z) $(M+1)^+$: 440.2.

Ejemplo **G4**: (4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-(3-(trifluoro-metil)-piperazin-1-il)-metanona

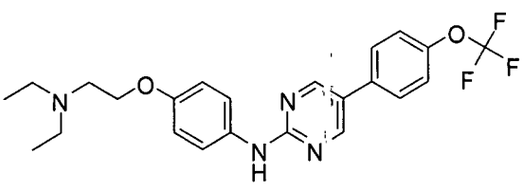
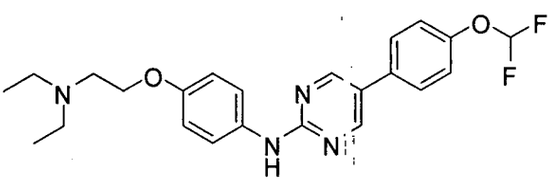
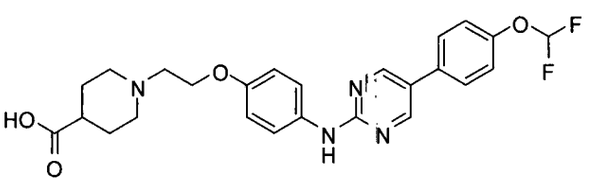
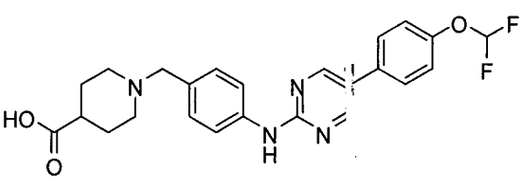
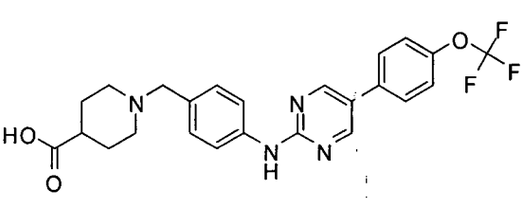


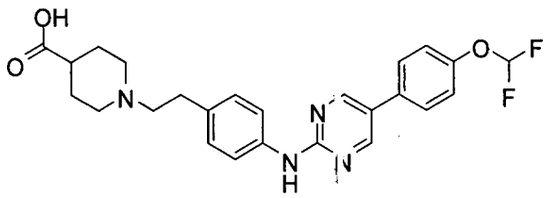
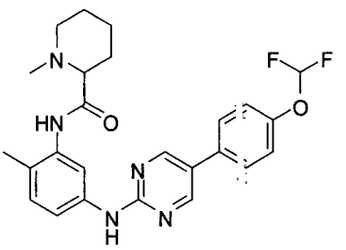
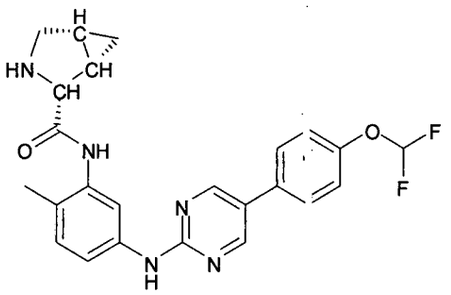
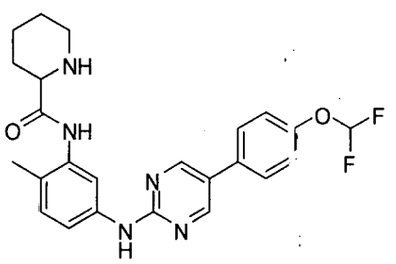
54 **G4**

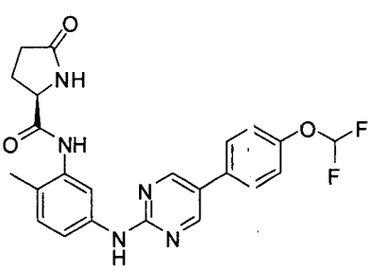
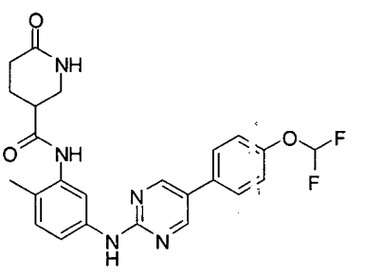
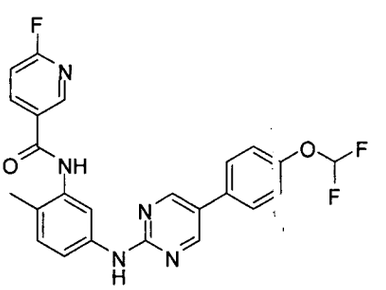
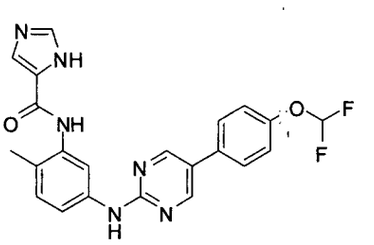
Similar a la preparación del **G1**; ^{1}H RMN (400MHz, *d6*-DMSO) δ 10.13 (s, 1H), 8.89 (s, 2H), 7.93 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 76.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 4.01 (bs, 4H), 3.30 (bs, 2H), 3.28 (bs, 2H). MS (m/z) $(M+1)^+$: 494.2.

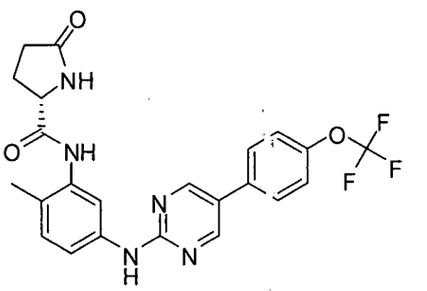
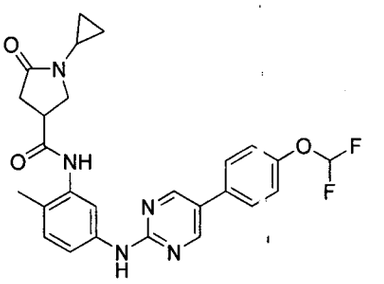
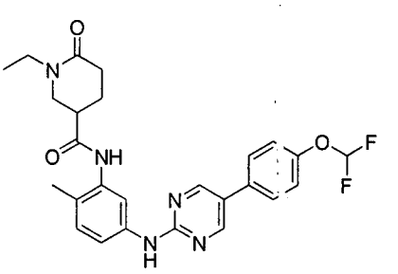
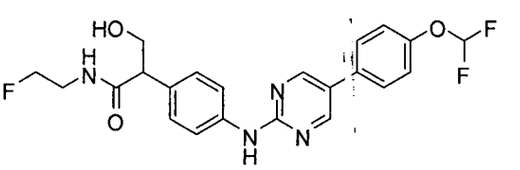
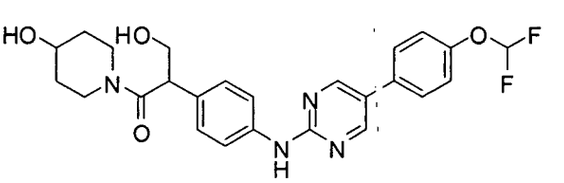
La Tabla 1 describe los compuestos representativos de la invención, preparados siguiendo los procedimientos descritos anteriormente. Los compuestos en la Tabla 1 tienen una actividad de < 1 μM en el ensayo de c-kit Mo7e y/o en el ensayo de PDGFR TG-HA-VSMC.

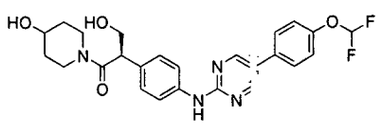
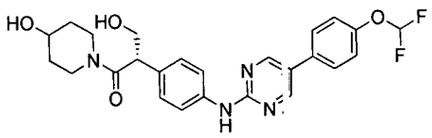
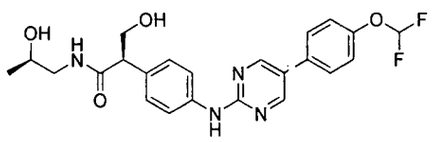
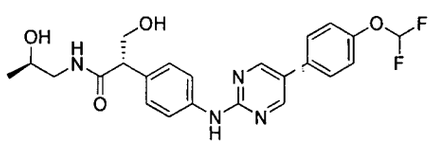
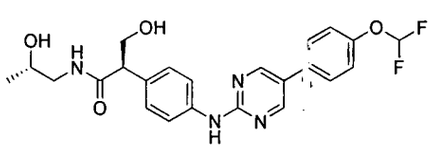
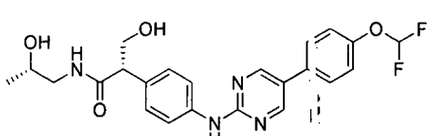
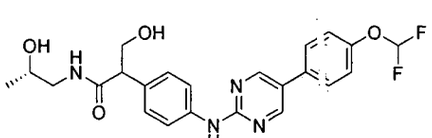
Tabla 1

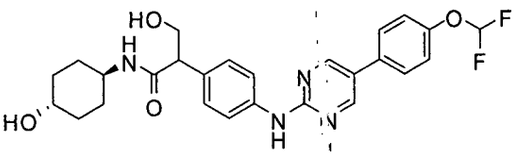
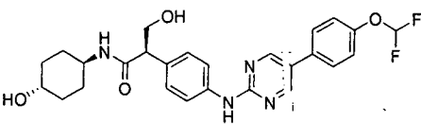
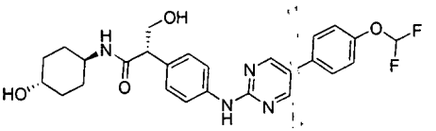
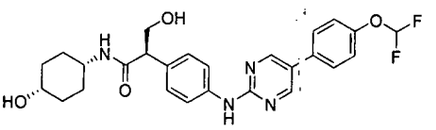
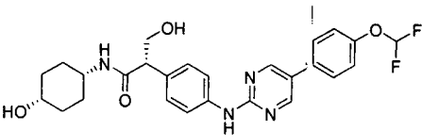
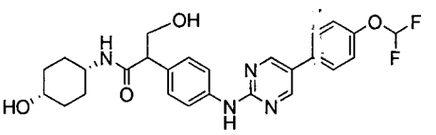
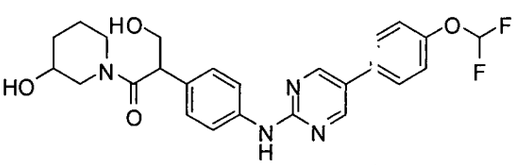
Ejemplo No.	Estructura	MS [M+1]$^+$
A1		447.2
A2		429.2
A3		485.2
A4		455.2
A5		473.2

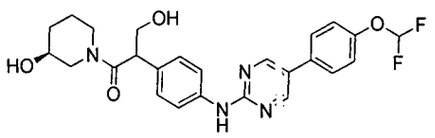
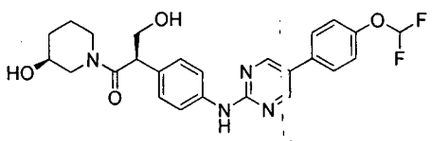
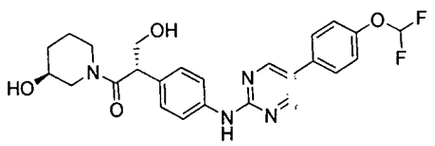
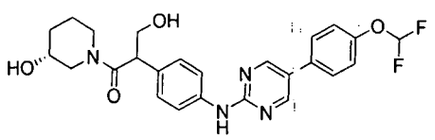
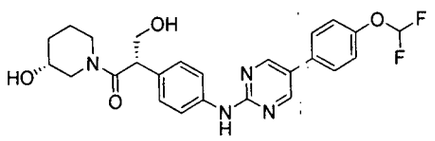
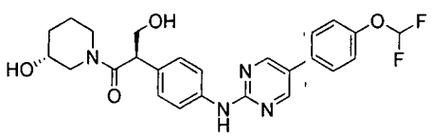
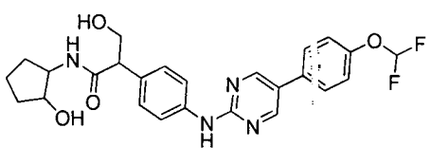
Ejemplo No.	Estructura	MS $[M+1]^+$
A6		469.2
B1		468.2
B2		452.2
B3		454.2

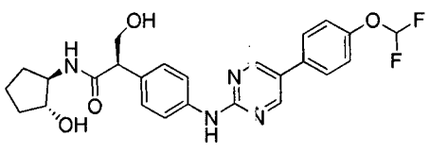
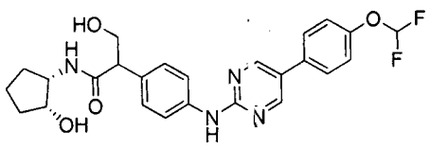
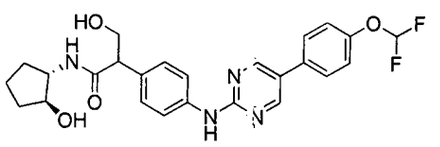
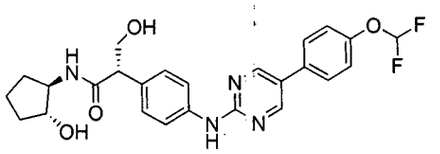
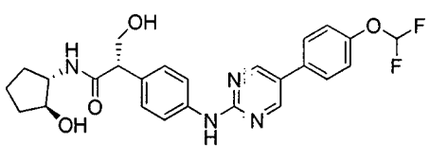
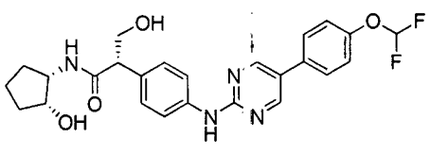
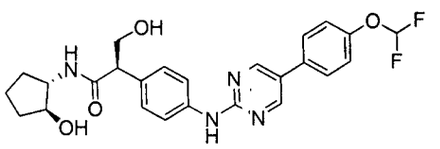
Ejemplo No.	Estructura	MS $[M+1]^+$
B4		454.2
B5		468.2
B6		466.1
B7		437.2

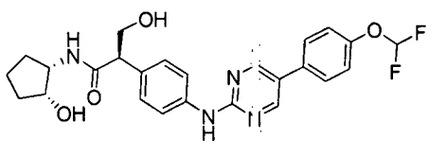
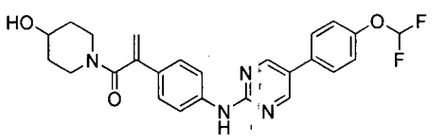
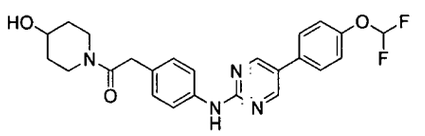
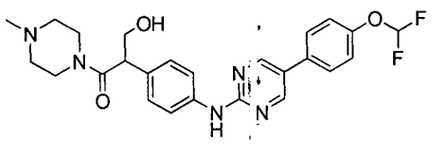
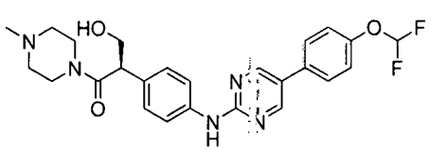
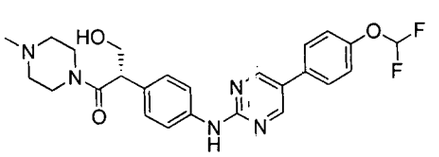
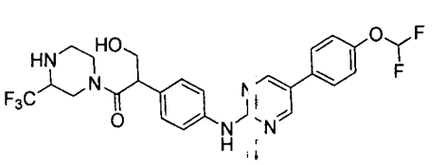
Ejemplo No.	Estructura	MS [M+1]$^+$
B8		472.2
B9		494.1
B10		496.2
C1		447.2
C2		485.2

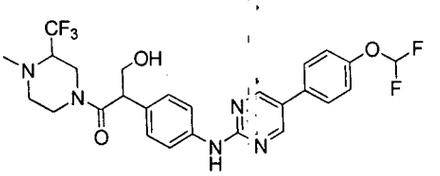
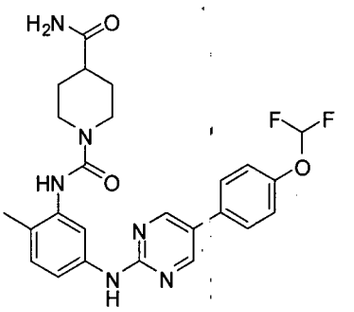
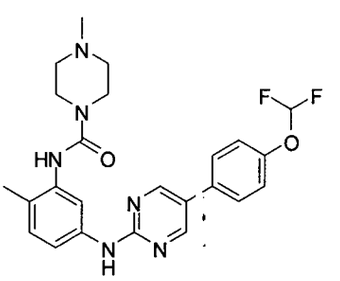
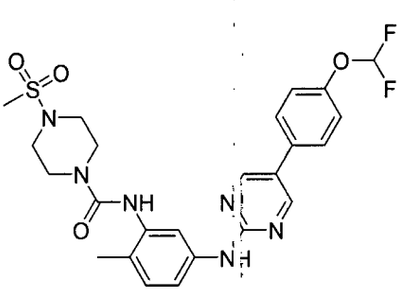
Ejemplo No.	Estructura	MS [M+1]$^+$
C3		485.1
C4		485.1
C5		459.1
C6		459.1
C7		459.1
C8		459.1
C9		459.2

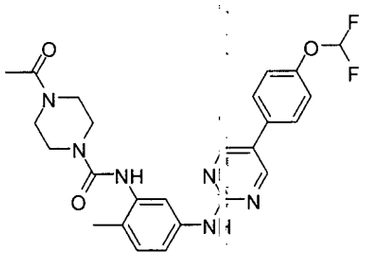
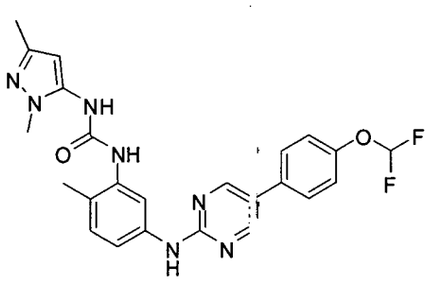
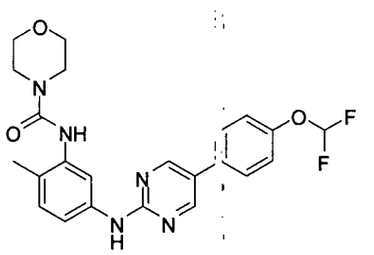
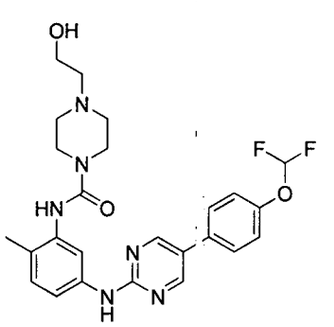
Ejemplo No.	Estructura	MS $[M+1]^+$
C10		499.2
C11		499.1
C12		499.2
C13		499.1
C14		499.2
C15		499.2
C16		485.2

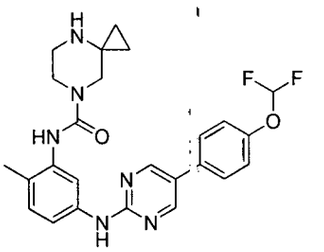
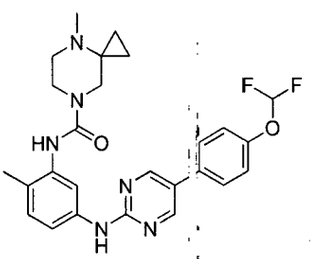
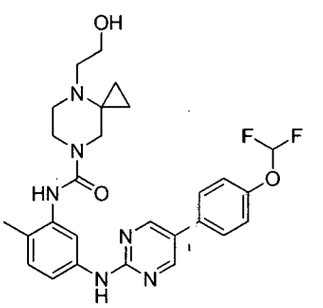
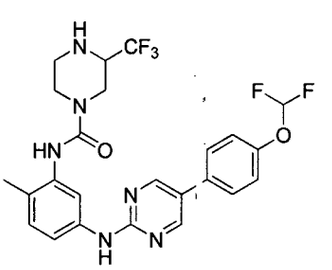
Ejemplo No.	Estructura	MS [M+1]$^+$
C17		485.2
C18		485.1
C19		485.1
C20		485.2
C21		485.1
C22		485.2
C23		485.2

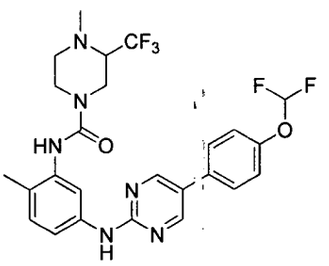
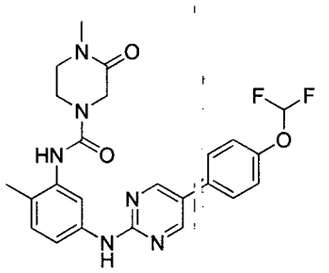
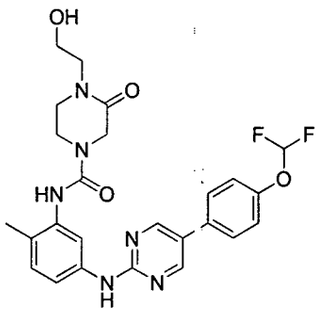
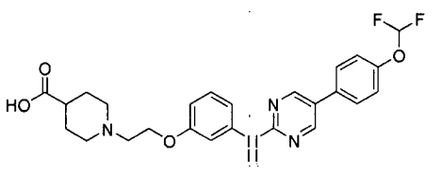
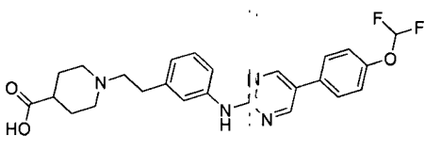
Ejemplo No.	Estructura	MS [M+1]$^+$
C24		485.1
C25		485.2
C26		485.2
C27		485.1
C28		485.1
C29		485.2
C30		485.1

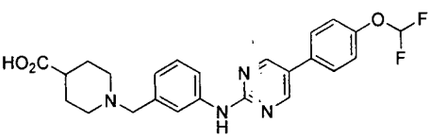
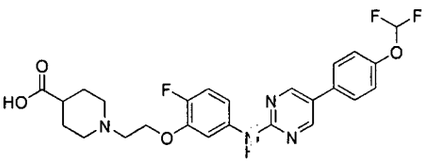
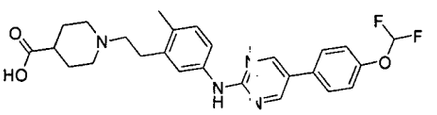
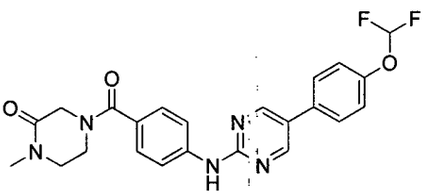
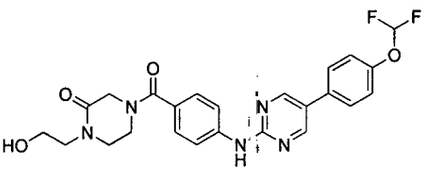
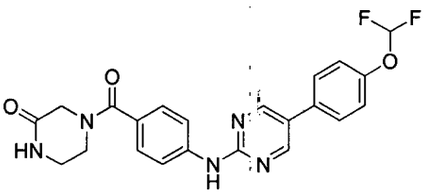
Ejemplo No.	Estructura	MS [M+1]$^+$
C31		485.2
C32		467.2
C33		455.1
C34		484.4
C35		484.1
C36		484.2
C37		538.1

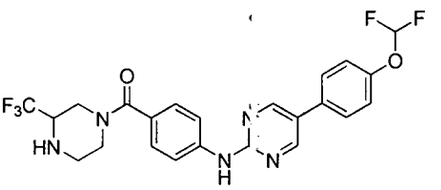
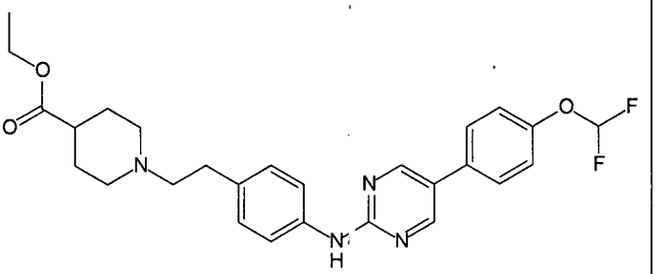
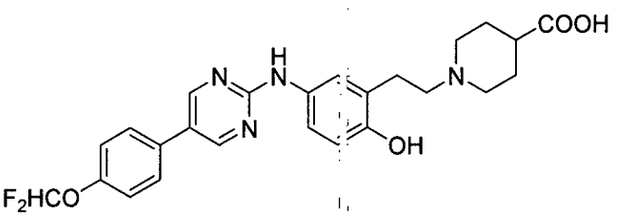
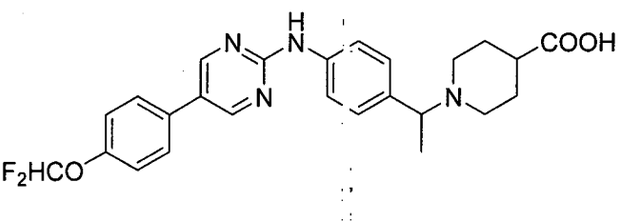
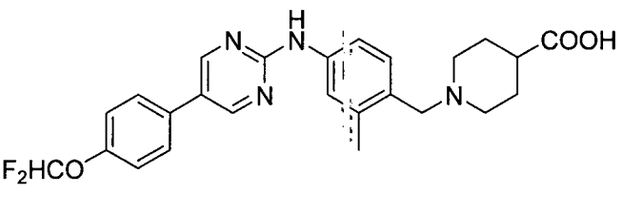
Ejemplo No.	Estructura	MS [M+1]$^+$
C38		552.1
D1		497.2
D2		469.2
D3		533.2

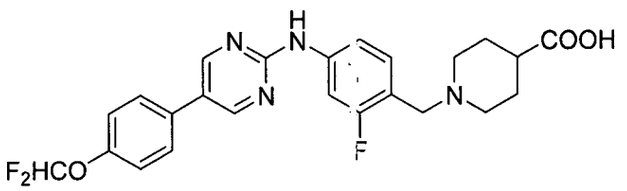
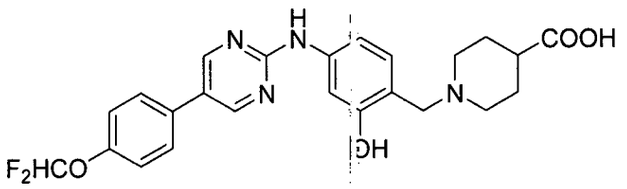
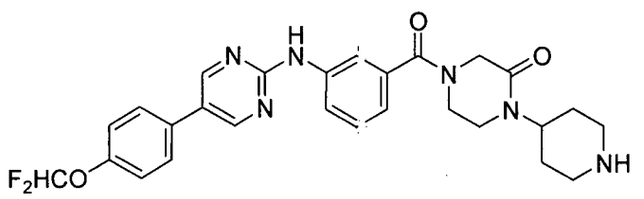
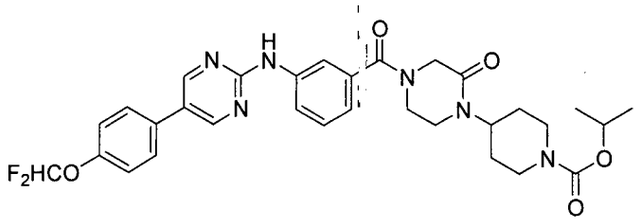
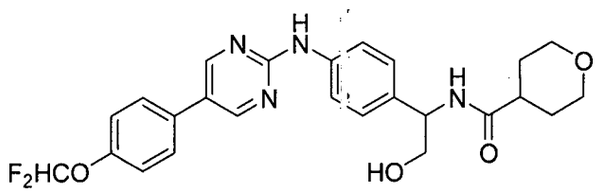
Ejemplo No.	Estructura	MS $[M+1]^+$
D4		497.2
D5		480.2
D6		456.2
D7		499.2

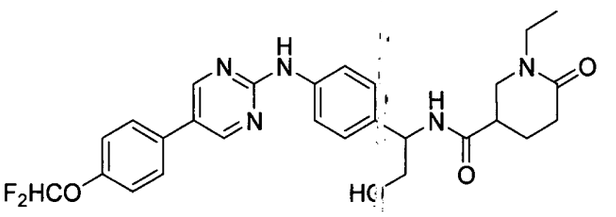
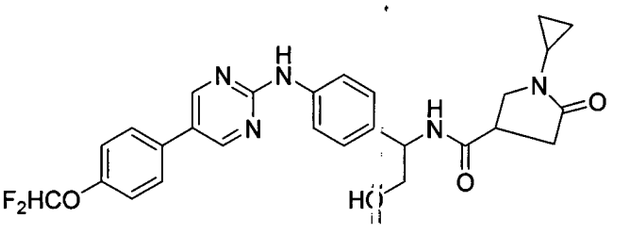
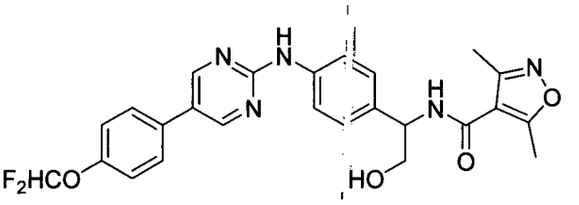
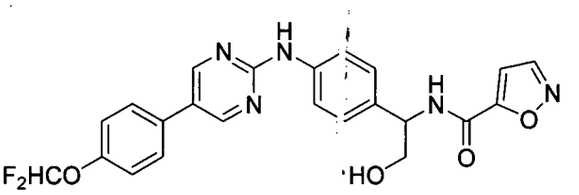
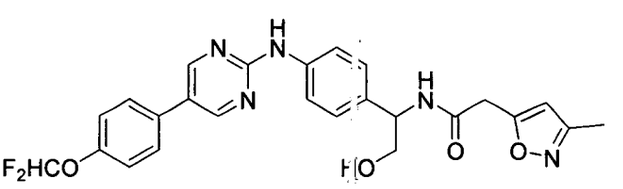
Ejemplo No.	Estructura	MS $[M+1]^+$
D8		481.2
D9		495.2
D10		524.56
D11		522.47

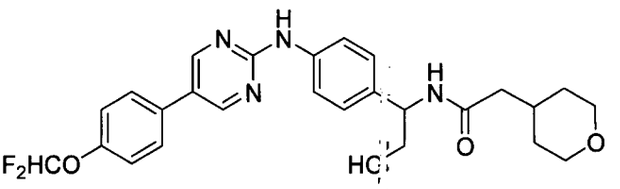
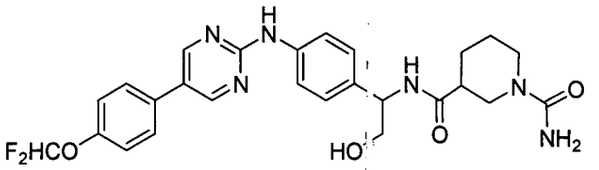
Ejemplo No.	Estructura	MS [M+1]$^+$
D12		536.50
D13		483.2
D14		513.1
E1		485.2
E2		469.2

Ejemplo No.	Estructura	MS [M+1]$^+$
E3		455.1
F1		503.2
F2		483.2
G1		454.2
G2		485.2
G3		439.4

Ejemplo No.	Estructura	MS $[M+1]^+$
G4		495.1
		
		
		
		

Ejemplo No.	Estructura	MS $[M+1]^+$
		
		
		
		
		

Ejemplo No.	Estructura	MS $[M+1]^+$
		
		
		
		
		

Ejemplo No.	Estructura	MS $[M+1]^+$
		
		

Ensayos

Los compuestos de la presente invención se ensayan para medir su capacidad para inhibir selectivamente la proliferación de las células Ba/F3 de tipo silvestre y las células Ba/F3 transformadas con la cinasa Tel c-kit y las cinasas de tirosina fusionadas con Tel PDGFR. En adición, los compuestos de la invención pueden inhibir selectivamente la proliferación dependiente de SCF en células Mo7e. Además, los compuestos se ensayan para medir su capacidad para inhibir las cinasas Abl, ARG, BCR-Abl, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 y TrkB.

Ensayo de proliferación: Biblioteca BaF3 – Protocolo de Lectura Bright glo

Los compuestos se prueban para determinar su capacidad para inhibir la proliferación de las células Ba/F3 de tipo silvestre, y las

células Ba/F3 transformadas con cinasas de tirosina fusionadas con Tel. Las células Ba/F3 no transformadas se mantienen en un medio que contiene IL3 recombinante. Las células se aplican a placas de 384 pozos a 5,000 células en 50 microlitros del medio por pozo, y se agrega el compuesto de prueba, de 0.06 nM a 10 µM. Las células se incuban entonces durante 48 horas a 37°C, con CO_2 al 5 por ciento. Después de incubar las células, se agregan 25 microlitros de BRIGHT GLO® (Promega) a cada pozo siguiendo las instrucciones del fabricante, y las placas se leen utilizando un Analyst GT – Modo de luminiscencia – 50000 tiempo de integración en RLU. Los valores IC_{50} se determinan a partir de una curva de respuesta a la dosis.

Ensayo de Mo7e

Los compuestos descritos en la presente se prueban para determinar la inhibición de la proliferación dependiente de SCF utilizando células Mo7e, las cuales expresan endógenamente c-kit en un formato de 96 pozos. Se evalúan los compuestos de prueba diluidos en serie dos veces (Cmax = 10 µM), para determinar su actividad antiproliferativa de las células Mo7e, estimulada con SCF humano recombinante. Después de 48 horas de incubación a 37°C, se mide la viabilidad celular utilizando un ensayo colorimétrico MTT de Promega.

Protocolo de c-kit HTRF

Una alícuota (5 microlitros) de una concentración 2x de la mezcla de enzima c-kit, 25 nanogramos de c-kit (5 nanogramos/ microlitro) y 2 µM del péptido de Biotina-EEEPQYEEIPIYLELLP-NH_2

en regulador de cinasa (Tris 20 mM, pH de 7.5, $MgCl_2$ 10 mM, albúmina de suero bovino al 0.01 por ciento, Brij35 al 0.1 por ciento, DTT 1 mM, glicerol al 5 por ciento, Na_3VO_4 0.05 mM), se agregan a cada pozo de una proxiplaca 384 (Packard). Cada pozo de la última fila de la proxiplaca tiene 5 microlitros de la mezcla enzimática c-kit para aseverar el nivel del fondo. Los compuestos de la invención se agregan a cada pozo, y las placas se incuban durante 30 minutos a temperatura ambiente. Se agrega a cada pozo ATP 2x (40 µM) en regulador de cinasa (5 microlitros), y la placa se incuba a temperatura ambiente durante 3 horas. La mezcla de detección (KF al 50 por ciento, regulador de cinasa al 40 por ciento, EDTA al 10 por ciento, Mab PT66-K diluido a 1:100 (cat# 61T66KLB) y Estreptavidina-XL diluida a 1:100 (cat# 611SAXLB)0 (10 microlitros)) se agrega a cada pozo, y las placas se incuban adicionalmente durante 1 a 2 horas a temperatura ambiente. Entonces se lee la señal de HTRF en un detector.

Ensayo de Proliferación de TG-HA-VSMC Humanas

Las células TG-HA-VSMC humanas (ATCC) se cultivan en DMEM complementado con FBS al 10 por ciento hasta una confluencia del 80 al 90 por ciento antes de volver a suspender en DMEM complementado con FBS al 1 por ciento y 30 nanogramos/mililitro de PDGF-BB humana recombinante, a 64 células/mililitro. Entonces las células se ponen en alícuotas en placas de 384 pozos a 50 microlitros/pozo, se incuban durante 20 horas a 37°C, y entonces se tratan con 0.5 microlitros de los compuestos 100x durante 48

horas a 37°C. Después del tratamiento, se agregan a cada pozo 25 microlitros de CellTiter-Glo durante 15 minutos, y entonces las placas se leen en el CLIPR (Molecular Devices).

Protocolo de Ensayo Lance de PDGFRα/ß

Una alícuota (2.5 microlitros) de una concentración 2x del péptido PDGFRß y mezcla de ATP (péptido de biotina-βA-βA-βA-AEEEEYVFIEAKKK 4 µM, ATP 20 µM en regulador de ensayo (Hepes 20 mM, $MgCl_2$ 54 mM, albúmina de suero bovino al 0.01 por ciento, Tween-20 al 0.05 por ciento, DTT 1 mM, glicerol al 10 por ciento, Na_3VO_4 50 µM)) se agrega a cada pozo de una proxiplaca 384 (Packard). Las placas se centrifugan y se agregan a cada pozo los compuestos de la invención (50 nanolitros) por medio de un dosificador diminuto. A cada pozo se le agregan (2.5 microlitros) de una concentración 2x de la mezcla enzimática (PDGFRα a 4.5 nanogramos/microlitro (cat# PV4117) o PDGFRß a 1.5 nanogramos/microlitro (cat# PV3591) en regulador de ensayo), o regulador de ensayo solo sin enzima PDGFRαß. Las placas se incuban durante 1.5 horas a temperatura ambiente. Se agrega a cada pozo la mezcla de detección (5 microlitros; KF 1M al 50 por ciento, regulador de cinasa al 40 por ciento, EDTA al 10 por ciento, Mab PT66-K diluido a 1:100 (cat# 61T66KLB) y Estreptavidina-XL diluida a 1:100 (cat# 611SAXLB), y la proxiplaca se incuba durante 1 hora a temperatura ambiente antes de leer la señal de HTRF en un detector.

Ensayo de Proliferación de Ba/F3 FL FLT3

La línea celular de murino utilizada es la línea celular pro-B de

murino Ba/F3 que sobre-expresa la construcción de FLT3 de longitud completa. Estas células se mantienen en RPMI 1640/suero bovino fetal al 10 por ciento (RPMI/FBS) complementado con 50 microgramos/mililitro de penicilina, 50 microgramos/mililitro de estreptomicina y L-glutamina 200 mM con la adición de IL3 recombinante de murino. Las células de FLT3 de longitud completa Ba/F3 se someten a agotamiento de IL3 durante 16 horas, y entonces se aplican a placas TC de 384 pozos a 5,000 células en 25 microlitros del medio por pozo, y se agrega el compuesto de prueba a 0.06 nM a 10 µM. Después de la adición del compuesto, se agregan el ligando de FLT3 o IL3 para el control de la citotoxicidad en 25 microlitros del medio por pozo, en las concentraciones apropiadas. Las células se incuban entonces durante 48 horas a 37°C, con CO_2 al 5 por ciento. Después de incubar las células, se agregan a cada pozo 25 microlitros de BRIGHT GLO® (Promega) siguiendo las instrucciones del fabricante, y las placas se leen utilizando el Analyst GT – modo de Luminiscencia – tiempo de integración de 50000 en RLU.

Inhibición de la proliferación celular dependiente de BCR-Abl (método de Alta Producción).

La línea celular de murino utilizada es la línea celular progenitora hematopoiética 32D transformada con ADNc de BCR-Abl (32D-p210). Estas células se mantienen en RPMI/suero fetal de becerro al 10 por ciento (RPMI/FCS) complementado con penicilina (50 microgramos/mililitro), estreptomicina (50 microgramos/mililitro) y

L-glutamina (200 mM). Las células 32D no transformadas se mantienen de una manera similar con la adición del 15 por ciento de medio acondicionado WEHI como una fuente de IL3.

Se aplican 50 microlitros de una suspensión de células 32D ó 32D-p210 en microplacas Greiner de 384 pozos (negras), a una densidad de 5,000 células por pozo. Se agregan 50 nanolitros del compuesto de prueba (1 mM en la solución de suministro de sulfóxido de dimetilo) a cada pozo (se incluye STI571 como un control positivo). Las células se incuban durante 72 horas a 37°C, con CO_2 al 5 por ciento. Se agregan a cada pozo 10 microlitros de una solución de Alamar Blue al 60 por ciento (Tek Diagnostics), y las células se incuban durante 24 horas adicionales. La intensidad de fluorescencia (Excitación a 530 nanómetros; Emisión a 580 nanómetros) se cuantifica utilizando el sistema Acquest^{MR} (Molecular Devices).

Inhibición de la proliferación celular dependiente de BCR-Abl.

Se aplican las células 32D-p210 a placas TC de 96 pozos, a una densidad de 15,000 células por pozo. Se agregan a cada pozo 50 microlitros de diluciones en serie dobles del compuesto de prueba (C_{max} es 40 µM) (se incluye STI571 como un control positivo). Después de incubar las células durante 48 horas a 37°C, con CO_2 al 5 por ciento, se agregan 15 microlitros de MTT (Promega) a cada pozo, y las células se incuban durante 5 horas adicionales. La densidad óptica a 570 nanómetros se cuantifica espectrofotométricamente, y se determinan los valores IC_{50} a partir de una curva de

respuesta a la dosis.

Efecto sobre la distribución del ciclo celular.

Se aplican células 32D y 32D-p210 a placas TC de 6 pozos, a 2.5 x 10^6 células por pozo en 5 mililitros del medio, y se agrega un compuesto de prueba a 1 ó 10 µM (se incluye STI571 como un control). Entonces se incuban las células durante 24 ó 48 horas a 37°C, con CO_2 al 5 por ciento. Se lavan 2 mililitros de suspensión celular con suero regulado con fosfato, se fijan en EtOH al 70 por ciento durante 1 hora, y se tratan con PBS/EDTA/ARNsa A durante 30 minutos. Se agrega yoduro de propidio (Cf = 10 microgramos/ mililitro), y se cuantifica la intensidad de fluorescencia mediante citometría de flujo en el sistema FACScalibur^{MR} (BD Biosciences). Los compuestos de prueba de la presente invención demuestran un efecto apoptótico sobre las células 32D-p210, pero no inducen apoptosis en las células 32D progenitoras.

Efecto sobre la Autofosforilación Celular de BCR-Abl.

Se cuantifica la autofosforilación de BCR-Abl con ELISA de captura, utilizando un anticuerpo de captura específico de c-abl, y un anticuerpo anti-fosfotirosina. Se aplican células 32D-p210 a placas TC de 96 pozos, a 2 x 10^5 células por pozo, en 50 microlitros del medio. Se agregan a cada pozo 50 microlitros de diluciones en serie dobles de los compuestos de prueba (C_{max} es 10 µM) (se incluye STI571 como un control positivo). Las células se incuban durante 90 minutos a 37°C, con CO_2 al 5 por ciento. Entonces las células se tratan durante 1 hora sobre hielo con 150 microlitros de regulador de

lisis (Tris-HCl 50 mM, pH de 7.4, NaCl 150 mM, EDTA 5 mM, EGTA 1 mM, y NP-40 al 1 por ciento) conteniendo inhibidores de proteasa y fosfatasa. Se agregan 50 microlitros del lisado celular a optiplacas de 96 pozos previamente recubiertas con anticuerpo específico anti-abl y se bloquean. Las placas se incuban durante 4 horas a 4°C. Después de lavar con regulador TBS-Tween 20, se agregan 50 microlitros de anticuerpo anti-fosfotirosina conjugado con fosfatasa alcalina, y la placa se incuba adicionalmente durante la noche a 4°C. Después de lavar con el regulador TBS-Tween 20, se agregan 90 microlitros de un sustrato luminiscente, y se cuantifica la luminiscencia utilizando el sistema Aqcuest^{MR} (Molecular Devices). Los compuestos de prueba de la invención que inhiben la proliferación de las células que expresan BCR-Abl, inhiben la auto-fosforilación celular de BCR-Abl de una manera dependiente de la dosis.

<u>Efecto sobre la proliferación de las células que expresan formas mutantes de Bcr-abl.</u>

Se prueban los compuestos de la invención para determinar su efecto anti-proliferativo sobre células Ba/F3 que expresan las formas de tipo silvestre o mutantes de BCR-Abl (G250E, E255V, T315I, F317L, M351T) que confieren resistencia o una sensibilidad disminuida al STI571. El efecto anti-proliferativo de estos compuestos sobre las células que expresan BCR-Abl mutantes y sobre las células no transformadas, se prueba a 10, 3.3, 1.1, y 0.37 µM, como se describe en lo anterior (en un medio que carece de

IL3). Los valores IC_{50} de los compuestos que carecen de toxicidad sobre las células no transformadas se determinan a partir de las curvas de respuesta a la dosis obtenidas como se describe anteriormente.

FGFR3 (Ensayo Enzimático).

Se lleva a cabo un ensayo de la actividad de cinasa con FGFR3 purificado (Upstate) en un volumen final de 10 microlitros, conteniendo 0.25 microgramos/mililitro de enzima en regulador de cinasa (Tris-HCl 30 mM, pH de 7.5, $MgCl_2$ 15 mM, $MnCl_2$ 4.5 mM, Na_3VO_4 15 µM, y 50 microgramos/mililitro de albúmina de suero bovino), y sustratos (5 microgramos/mililitro de biotina-poli-EY(Glu, Tyr) (CIS-US, Inc.) y ATP 3 µM). Se hacen dos soluciones: la primera solución de 5 microlitros que contiene la enzima FGFR3 en regulador de cinasa se dosifica primeramente en una ProxiPlate® de formato-384 (Perkin-Elmer), seguido por la adición de 50 nanolitros de los compuestos disueltos en sulfóxido de dimetilo. Luego se agregan 5 microlitros de una segunda solución que contiene el sustrato (poli-EY) y ATP en regulador de cinasa a cada pozo. Las reacciones se incuban a temperatura ambiente durante una hora, se detienen mediante la adición de 10 microlitros de mezcla de detección HTRF, que contiene Tris-HCl 30 mM, pH de 7.5, KF 0.5 M, EDTA 50 mM, 0.2 miligramos/mililitro de albúmina de suero bovino, 15 microgramos/mililitro de estreptavidina-XL665 (CIS-US, Inc.), y 150 nanogramos/mililitro de anticuerpo anti-fosfotirosina conjugado con criptato (CIS-US, Inc.). Después de una hora de incubación a

temperatura ambiente para permitir la interacción de la estreptavidina-biotina, se leen las señales fluorescentes resueltas en el tiempo en el Analyst GT (Molecular Devices, Corp.). Los valores IC_{50} se calculan mediante análisis de regresión lineal del porcentaje de inhibición de cada compuesto en 12 concentraciones (dilución a 1:3 desde 50 µM hasta 0.28 nM). En este ensayo, los compuestos de la invención tienen una IC_{50} en el intervalo de 10 nM a 2 µM.

FGFR3 (Ensayo Celular).

Los compuestos de la invención se prueban para determinar su capacidad para inhibir la proliferación de células Ba/F3-TEL-FGFR3 transformadas, la cual depende de la actividad de cinasa celular de FGFR3. Se cultivan las células Ba/F3-TEL-FGFR3 hasta 800,000 células/mililitro en suspensión, con RPMI 1640 complementado con suero bovino fetal al 10 por ciento como el medio de cultivo. Las células se dosifican en una placa de formato de 384 pozos a 5,000 células/pozo en 50 microlitros del medio de cultivo. Los compuestos de la invención se disuelven y se diluyen en sulfóxido de dimetilo (DMSO). Se hacen diluciones en serie de doce puntos a 1:3, en sulfóxido de dimetilo, para crear un gradiente de concentraciones típicamente en el intervalo desde 10 mM hasta 0.05 µM. Se agregan las células con 50 nanolitros de los compuestos diluidos, y se incuban durante 48 horas en una incubadora de cultivo celular. Se agrega a las células Alamar Blue® (TREK Diagnostics Systems), que se puede utilizar para monitorear el medio ambiente reductor creado por las células en proliferación, a una concentración final del 10 por

ciento. Después de cuatro horas adicionales de incubación en una incubadora de cultivo celular a 37°C, se cuantifican las señales de fluorescencia a partir del Alamar Blue® reducido (Excitación a 530 nanómetros, Emisión a 580 nanómetros) en el Analyst GT (Molecular Devices Corp.). Los valores IC_{50} se calculan mediante análisis de regresión lineal del porcentaje de inhibición de cada compuesto en 12 concentraciones.

b-RAF - Ensayo Enzimático

Se prueban los compuestos de la invención para determinar su capacidad para inhibir la actividad de b-Raf. El ensayo se lleva a cabo en placas MaxiSorp de 384 pozos (NUNC) con paredes negras y fondo transparente. El sustrato, IκEα, se diluye en DPBS (1:750), y se agregan 15 microlitros a cada pozo. Las placas se incuban a 44°C durante la noche, y se lavan 3 veces con TBST (Tris 25 mM, pH de 8.0, NaCl 150 mM, y Tween 20 al 0.05 por ciento), utilizando el lavador de placas EMBLA. Las placas se bloquean mediante Superblock (15 microlitros/pozo) durante 3 horas a temperatura ambiente, se lavan tres veces con TBST, y se secan. Se agrega el regulador de ensayo conteniendo ATP 20 µM (10 microlitros) a cada pozo, seguido por 100 nanolitros ó 500 nanolitros del compuesto. Se diluye b-Raf en el regulador de ensayo (1 microlitro en 25 microlitros), y se agregan 10 microlitros de b-Raf diluida a cada pozo (0.4 microgramos/pozo). Las placas se incuban a temperatura ambiente durante 2.5 horas. La reacción de cinasa se detiene lavando las placas seis veces con TBST. Se diluye el anticuerpo

Phosph-IκBα (Ser32/36) en Superblock (1:10,000), y se agregan 15 microlitros a cada pozo. Las placas se incuban a 44°C durante la noche, y se lavan 6 veces con TBST. Se diluye la IgG de cabra anti-ratón conjugada con AP en Superblock (1:1,500), y se agregan 15 microlitros a cada pozo. Las placas se incuban a temperatura ambiente durante 1 hora, y se lavan 6 veces con TBST. Se agregan a cada pozo 15 microlitros de sustrato fluorescente Attophos AP (Promega), y las placas se incuban a temperatura ambiente durante 15 minutos. Las placas se leen en el Acquest o Analyst GT utilizando un Programa de Intensidad de Fluorescencia (Excitación a 455 nanómetros, Emisión a 580 nanómetros).

b-Raf - Ensayo Celular

Los compuestos de la invención se prueban en células A375, para determinar su capacidad para inhibir la fosforilación de MEK. La línea celular A375 (ATCC) se deriva a partir de un paciente de melanoma humano, y tiene una mutación V599E, sobre el gen B-Raf. Los niveles de MEK fosforilada se elevan debido a la mutación de B-Raf. Se incuban células A375 desde subconfluentes hasta confluentes se incuban con los compuestos durante 2 horas a 37°C, en un medio sin suero. Luego las células se lavan una vez con suero regulado con fosfato frío, y se lisan con el regulador de lisis conteniendo Triton X100 al 1 por ciento. Después de la centrifugación, los sobrenadantes se someten a SDS-PAGE, y entonces se transfieren a membranas de nitrocelulosa. Luego las membranas se someten a Western blot con el anticuerpo anti-fosfo-

MEK (ser217/221) (Cell Signaling). La cantidad de MEK fosforilada se monitorea mediante la densidad de las bandas de fosfo-MEK sobre las membranas de nitrocelulosa.

Upstate KinaseProfiler^{MR} – Ensayo de enlace de filtro radio-enzimático

Los compuestos de la invención se evalúan para determinar su capacidad para inhibir a los miembros individuales del panel de cinasa. Los compuestos se prueban por duplicado a una concentración final de 10 µM siguiendo este protocolo genérico. Se mezclan regulador de cinasa (2.5 microlitros, 10x - conteniendo $MnCl_2$ cuando se requiera), cinasa activa (0.001-0.01 Unidades; 2.5 microlitros), péptido específico o Poli(Glu4-Tyr) (5-500 µM ó 0.01 miligramos/mililitro) en regulador de cinasa, y regulador de cinasa (50 µM; 5 microlitros), en un Eppendorf sobre hielo. Se agrega una mezcla de Mg/ATP (10 microlitros; $MgCl_2$ 67.5 ó 33.75 mM, ATP 450 ó 225 µM, y 1 µCi/µl [γ-^{32}P]-ATP (3000 Ci/milimol)), y la reacción se incuba a aproximadamente 30°C durante aproximadamente 10 minutos. La mezcla de reacción se mancha (20 microlitros) sobre un P81 de 2 centímetros x 2 centímetros (fosfocelulosa, para los sustratos de péptidos positivamente cargados), o un cuadro de papel Whatman No. 1 (para el sustrato de péptido de poli(Glu4-Tyr)). Los cuadros del ensayo se lavan cuatro veces, durante 5 minutos cada una, con ácido fosfórico al 0.75 por ciento, y se lavan una vez con acetona durante 5 minutos. Los cuadros del ensayo se transfieren a un frasco de cintilación, se agregan 5 mililitros de cóctel de

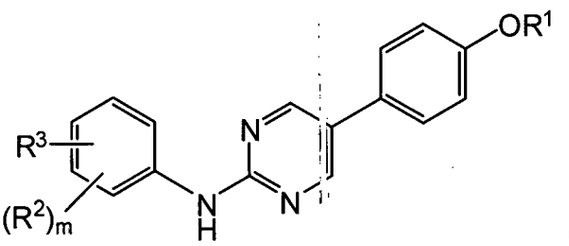
cintilación, y se cuantifica la incorporación de ^{32}P (cpm) al sustrato peptídico con un contador de cintilación Beckman. Se calcula el porcentaje de inhibición para cada reacción.

* * * * *

Se entiende que los ejemplos y las modalidades descritas en la presente son para propósitos ilustrativos solamente, y que las personas expertas en la técnica pensarán en diferentes modificaciones o cambios a la luz de las mismas, y se deben incluir dentro del espíritu y alcance de esta solicitud, y del alcance de las reivindicaciones adjuntas. Todas las publicaciones, patentes, y solicitudes de patente citadas en la presente se incorporan a la presente como referencia para todos los propósitos.

REIVINDICACIONES

1. Un compuesto de la fórmula (1):



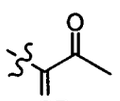
(1)

o una sal farmacéuticamente aceptable del mismo;

R^1 es un halo-alquilo que tiene de 1 a 6 átomos de flúor;

R^2 es 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; halógeno, ciano, nitro, $(CR_2)_kOR^7$, $(CR_2)_kO(CR_2)_{1-4}R^7$, $(CR_2)_kSR^7$, $(CR_2)_kNR^9R^{10}$, $(CR_2)_kC(O)O_{0-1}R^7$, $OC(O)R^7$, $(CR_2)_kC(S)R^7$, $(CR_2)_kC(O)NR^9R^{10}$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^9R^{10}$, $(CR_2)_kS(O)_{1-2}R^8$, $(CR_2)_kNRS(O)_{1-2}R^8$ o $(CR_2)_kR^6$; o cualesquiera dos grupos R^2 adyacentes pueden formar juntos un anillo de arilo o heteroarilo carbocíclico, heterocíclico, de 5 a 8 miembros, opcionalmente sustituido;

R^3 es $-L-NR^4R^5$, $-X-NR-C(O)R^8$ o $-X-NR-C(O)NR^4R^5$ en donde L es $-X-C(O)$, $-X-OC(O)$, $-(CR_2)_j$, $-SO_{0-2}(CR_2)_j$, $-O(CR_2)_{1-4}$,



; y X es $(CR_2)_j$ o $[C(R)-(CR_2OR)]$;

R^4, R^5, R^9 y R^{10} son independientemente 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, alcoxilo, ciano, carboxilo o R^6; $(CR_2)_kCN$, $(CR_2)_{1-6}NR^7R^7$, $(CR_2)_{1-6}OR^7$, $(CR_2)_kC(O)O_{0-1}R^7$, $(CR_2)_kC(O)NR^7R^7$ o $(CR_2)_k$-R^6;

R^6 es un cicloalquilo de 3 a 7 átomos de carbono opcionalmente sustituido, arilo de 6 a 10 átomos de carbono, o un anillo de heteroarilo de 5 a 10 miembros o heterocíclico de 5 a 7 miembros;

R^7 y R^8 son independientemente $(CR_2)_k$-R^6 o 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, amido, hidroxilo, alcoxilo, ciano, carboxilo o R^6; o R^7 es H;

de una manera alternativa, R^4 y R^5 junto con N en cada NR^4R^5, R^7 y R^7 junto con N en NR^7R^7, o R^9 y R^{10} junto con N en NR^9R^{10} pueden formar un anillo heterocíclico de 4 a 7 miembros opcionalmente sustituido con 1 a 3 grupos R^{11};

R^{11} es R^8, $(CR_2)_k$–OR^7, CO_2R^7, $(CR_2)_k$–C(O)-$(CR_2)_k$-R^8, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ o $(CR_2)_kNRS(O)_{1-2}R^8$;

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

cada k es de 0 a 6; y

j y **m** son independientemente de 0 a 4;

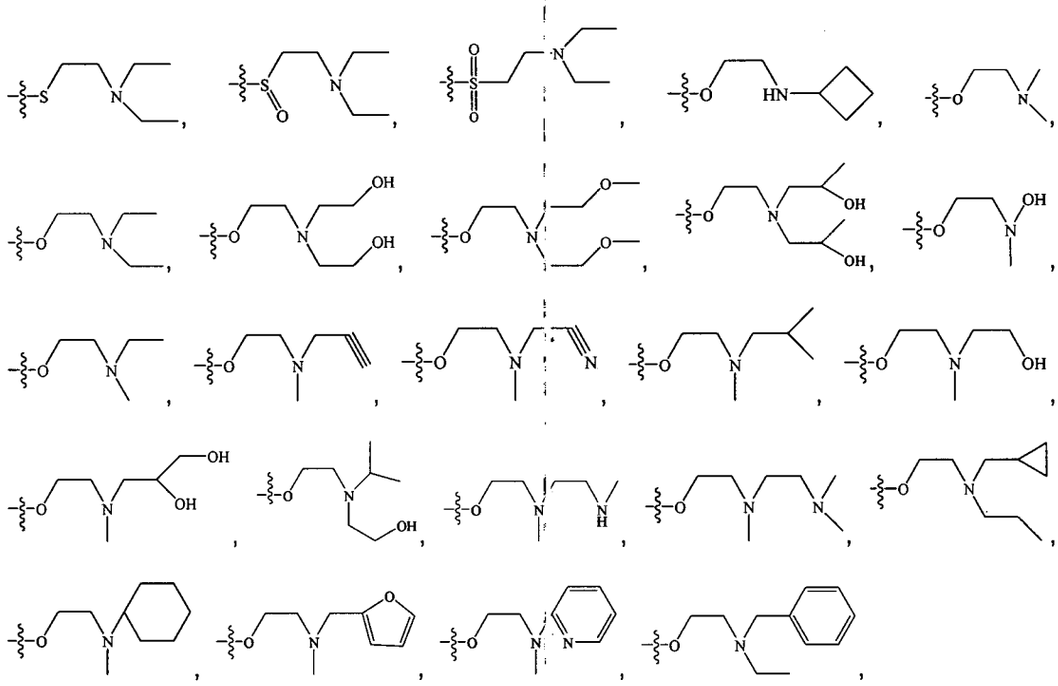
en el entendido de que R^1 no es trifluoro-metoxilo cuando R^3 es $C(O)NH_2$, $C(O)NR^{12}R^{13}$ o $SO_2NH(CH_2)_{2-3}NR^{14}R^{15}$; en donde R^{12} y R^{13} forman juntos piperazinilo, y R^{14} y R^{15} forman juntos morfolinilo.

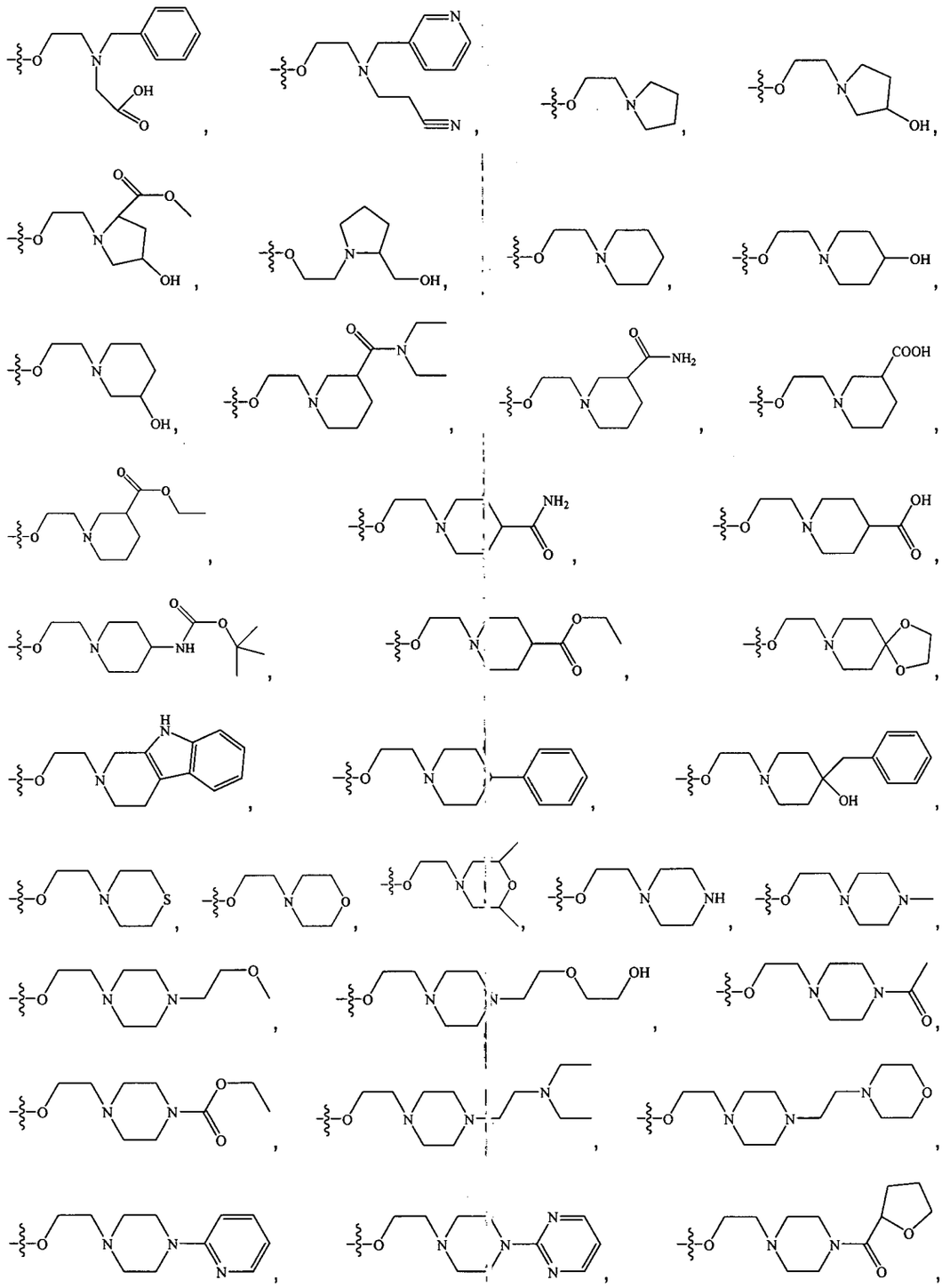
2. El compuesto de la reivindicación 1, en donde R^1 es $OCHF_2$, OCF_3, OCH_2CF_3, OCF_2CH_3, u OCH_2CF_3.

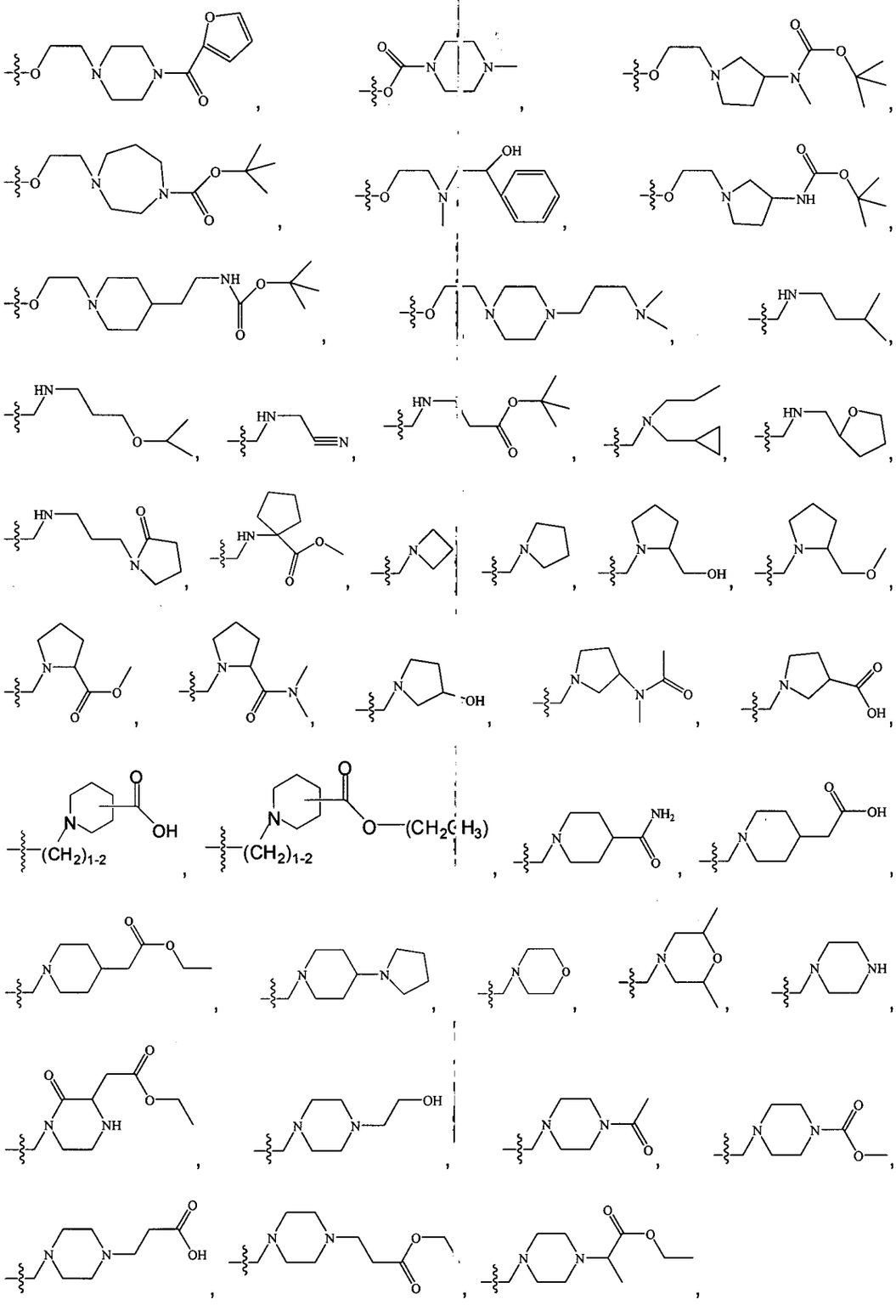
3. El compuesto de la reivindicación 2, en donde R^1 es $OCHF_2$.

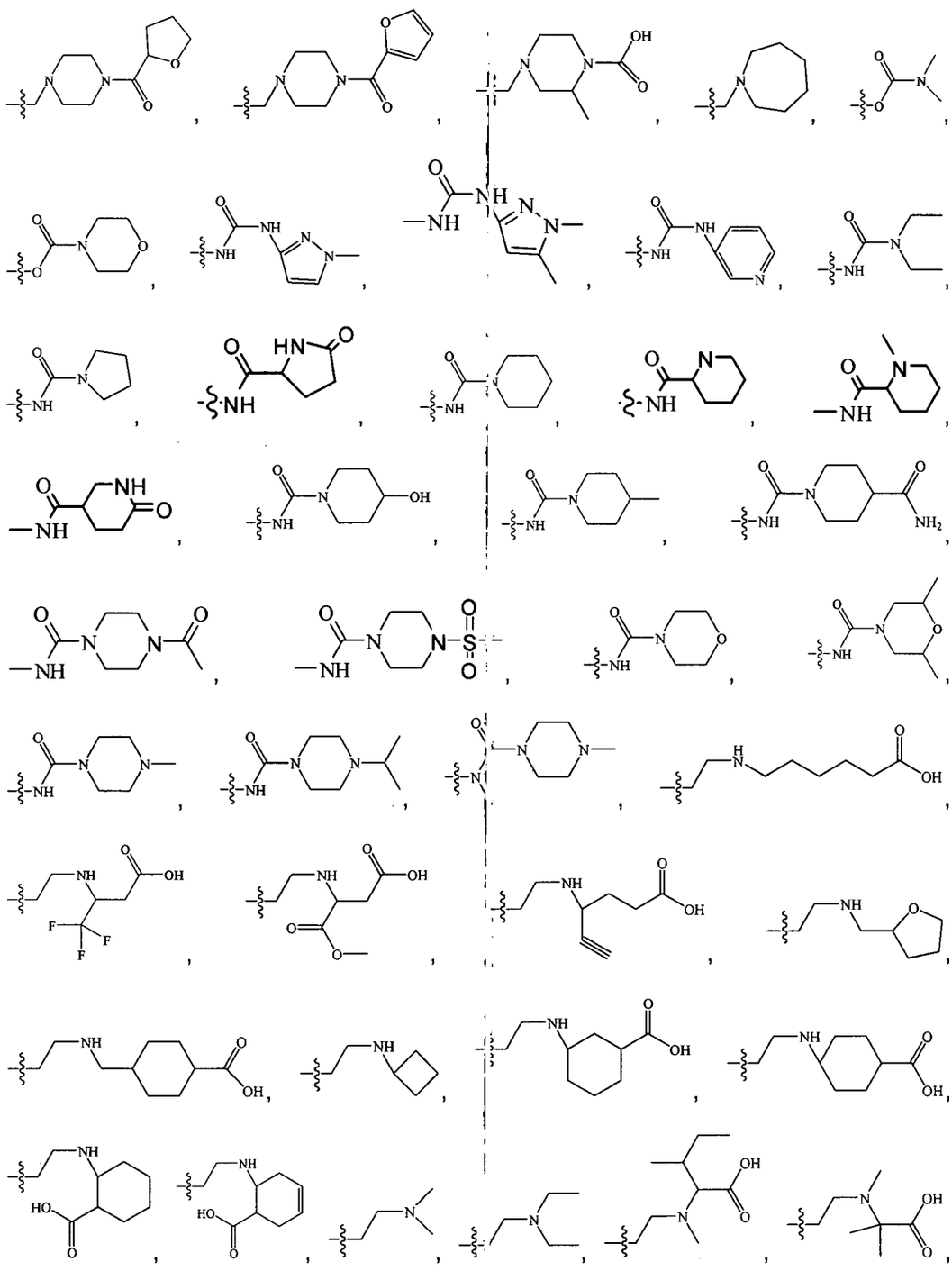
4. El compuesto de cualquiera de las reivindicaciones 1 a 3, en donde R^2, si está presente, es halógeno, alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, hidroxilo o CO_2R^7, y R^7 es H o alquilo de 1 a 6 átomos de carbono.

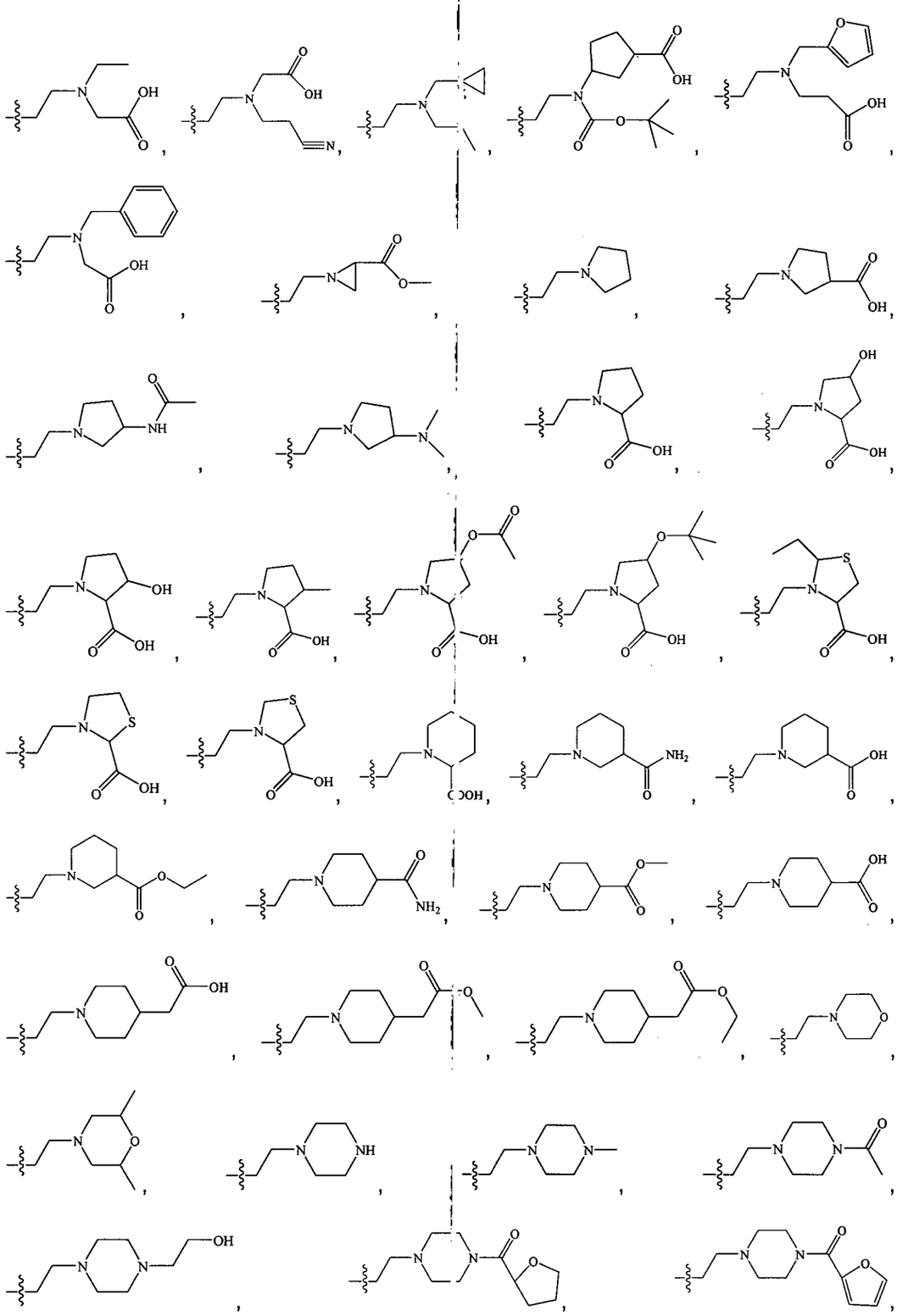
5. El compuesto de cualquiera de las reivindicaciones 1 a 4, en donde R^3 se selecciona a partir del grupo que consiste en

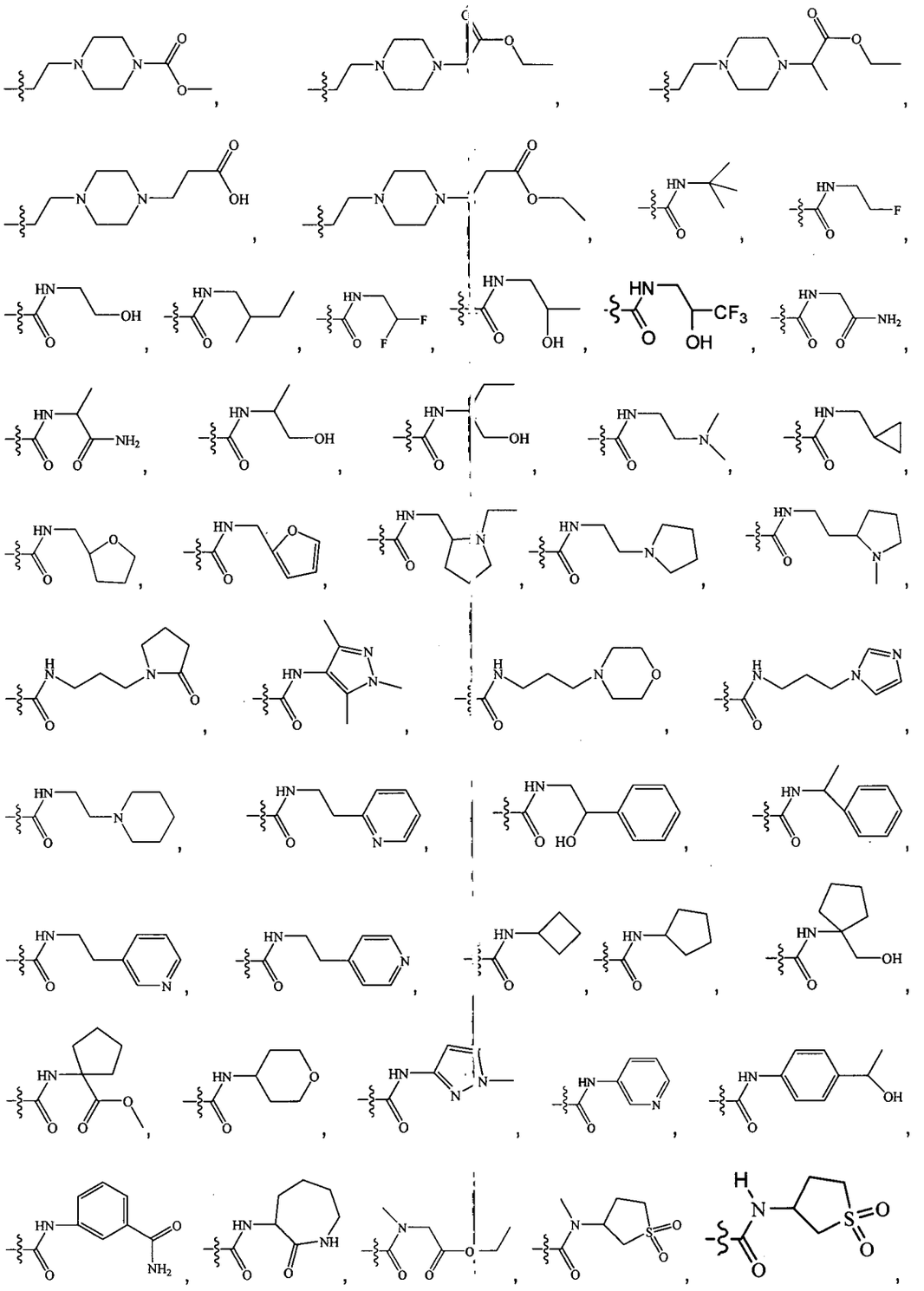


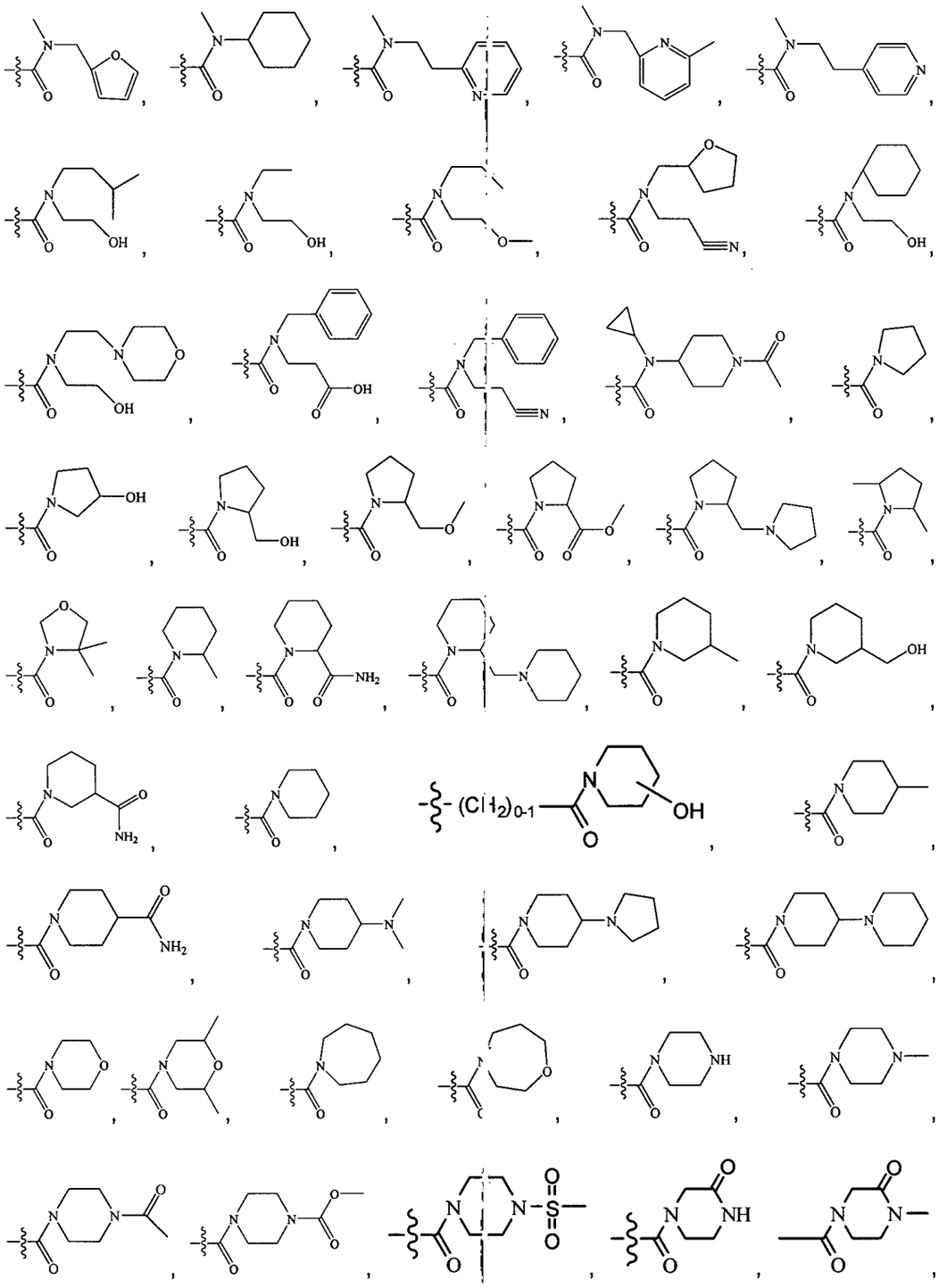


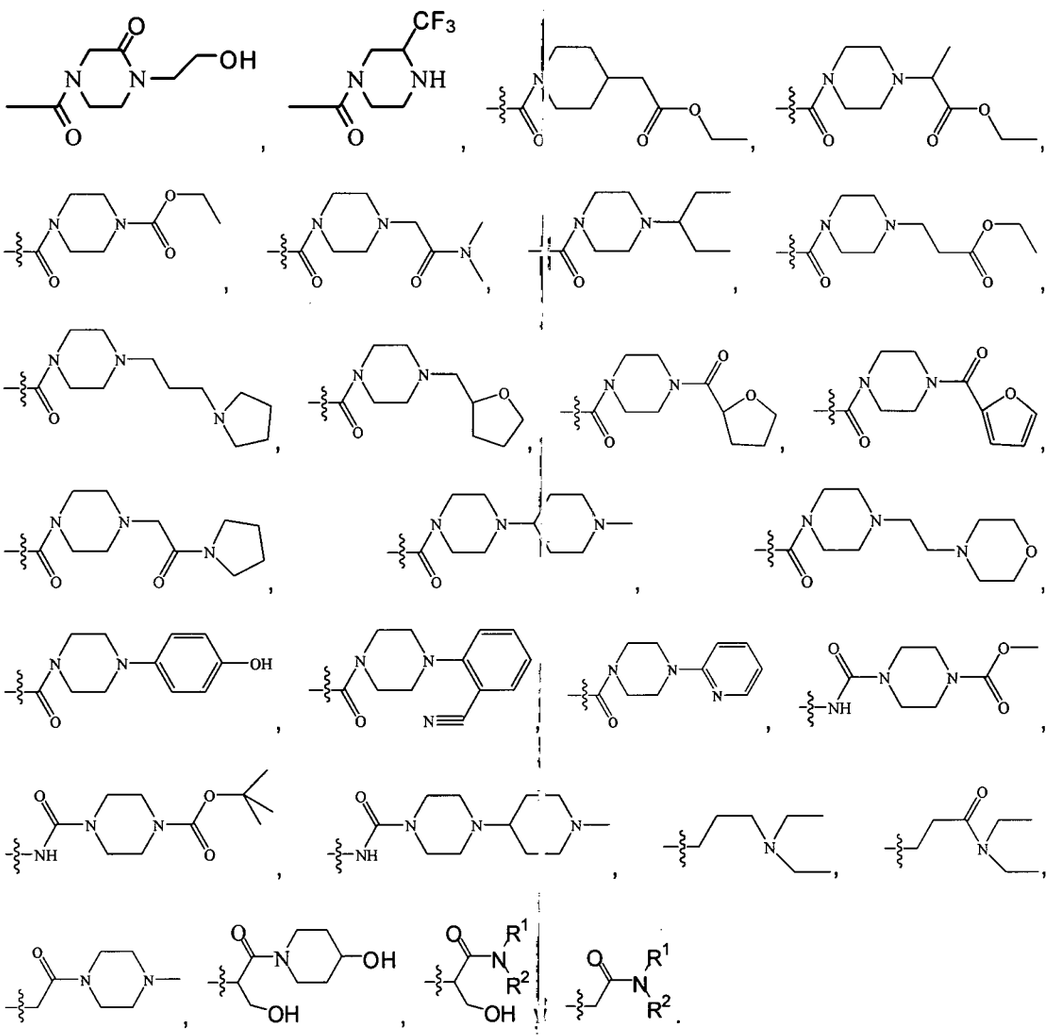




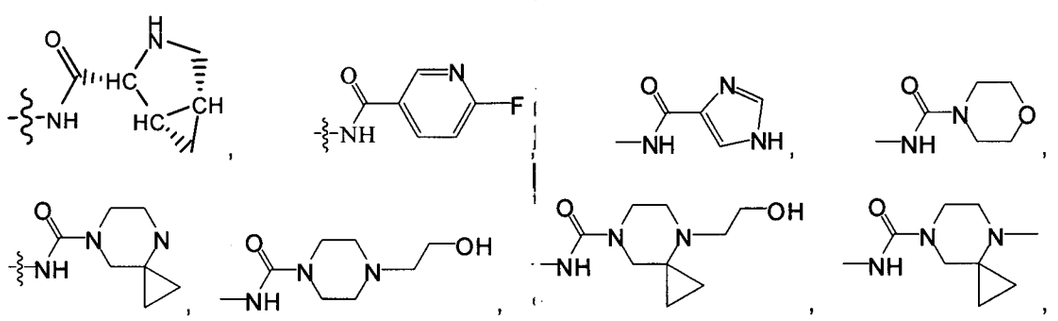


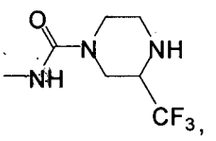
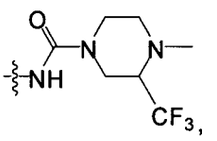
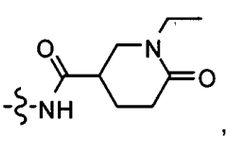
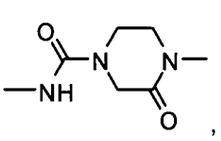
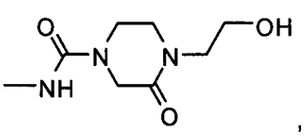
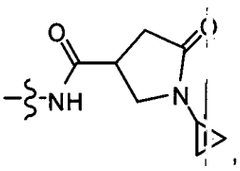
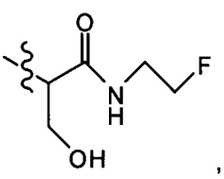
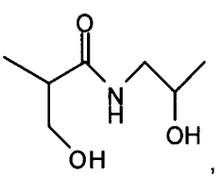
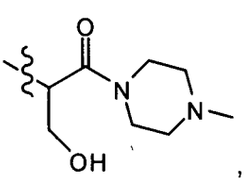
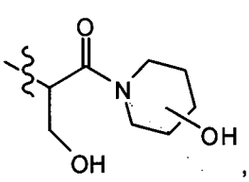
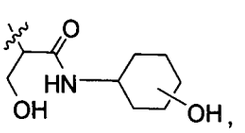
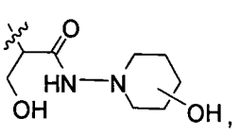
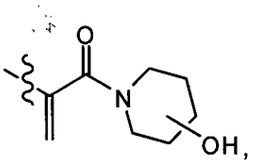
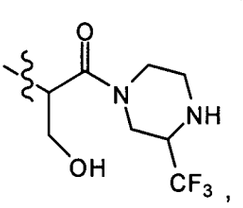
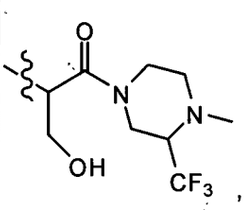
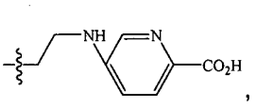
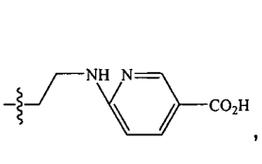
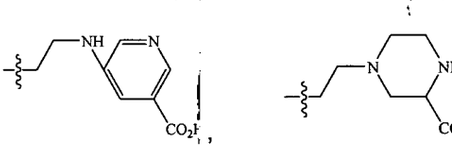
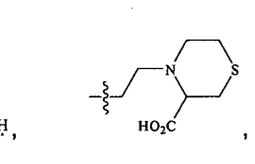
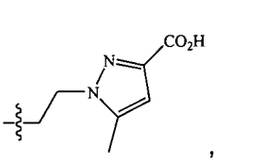
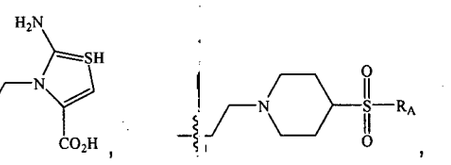
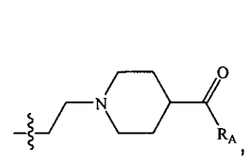
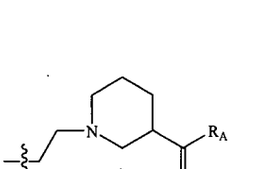


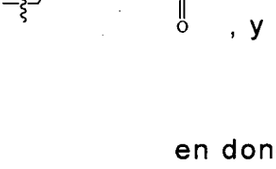
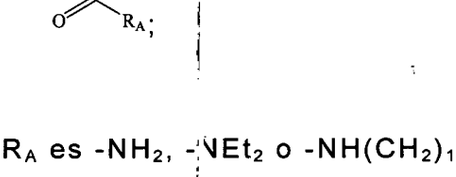
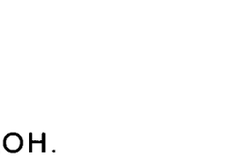
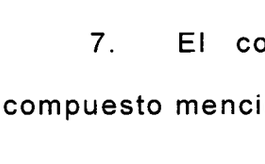
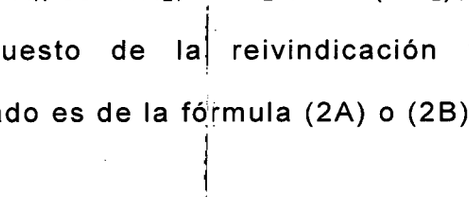
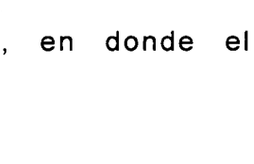




6. El compuesto de cualquiera de las reivindicaciones 1 a 4, en donde R^3 se selecciona a partir del grupo que consiste en

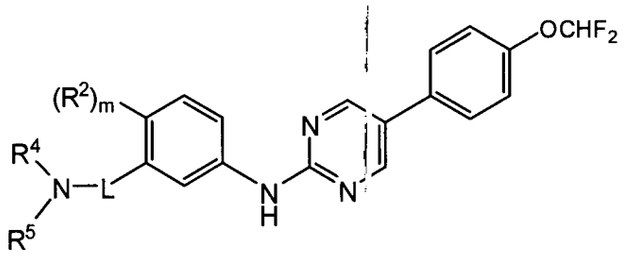


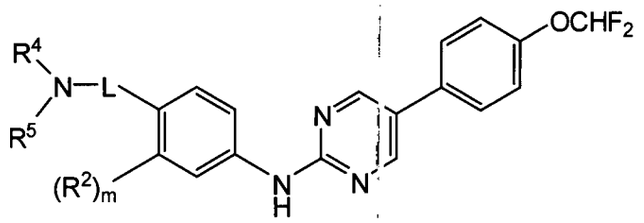








en donde R_A es $-NH_2$, $-NEt_2$ o $-NH(CH_2)_{1-6}OH$.

7. El compuesto de la reivindicación 1, en donde el compuesto mencionado es de la fórmula (2A) o (2B):



(2A)



(2B);

en donde R^4 y R^5 junto con N forman un anillo heterocíclico de 5 a 6 miembros que opcionalmente contiene NR^{16}, O, S, =O o un doble enlace; en donde este anillo heterocíclico está opcionalmente sustituido con 1 a 2 grupos R^{11};

R^{11} es R^8, $(CR_2)_kOR^7$, CO_2R^7, $(CR_2)_k-C(O)-(CR_2)_k-R^8$, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_kNRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ o $(CR_2)_kNRS(O)_{1-2}R^8$;

R^{16} es H, R^8, $-(CR_2)_{1-4}CO_2R^7$, $(CR_2)_k-C(O)-(CR_2)_k-R^8$, $(CR_2)_kC(O)NR^7R^7$, $(CR_2)_kC(O)NR(CR_2)_{0-6}C(O)O_{0-1}R^7$, $(CR_2)_{1-4}NRC(O)O_{0-1}R^7$, $(CR_2)_kS(O)_{1-2}NR^7R^7$, $(CR_2)_kS(O)_{1-2}R^8$ o $(CR_2)_kNRS(O)_{1-2}R^8$;

R^7 y R^8 son independientemente $(CR_2)_k-R^6$ o 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, amido,

hidroxilo, alcoxilo, ciano, carboxilo o R^6; o R^7 es H;

R^6 es un cicloalquilo de 3 a 7 átomos de carbono opcionalmente sustituido, arilo de 6 átomos de carbono, o un anillo de heteroarilo de 5 a 6 miembros o heterocíclico de 5 a 7 miembros;

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

k es de 0 a 4.

8. El compuesto de la reivindicación 7, en donde R^4 y R^5 junto con N forma un piperidinilo, piperazinilo o morfilinilo opcionalmente sustituido.

9. El compuesto de la reivindicación 7, en donde L es –X-C(O), $-(CR_2)_{1-4}$ u $-O(CR_2)_{1-4}$;

X es $(CR_2)_{0-1}$ o $[C(R)-(CR_2OR)]$; y

R es H o alquilo de 1 a 6 átomos de carbono.

10. El compuesto de la reivindicación 9, en donde L es $(CR_2)_{1-2}$.

11. El compuesto de la reivindicación 1, en donde este compuesto se selecciona a partir del grupo que consiste en :

N-(4-(2-(dietil-amino)-etoxi)-fenil)-5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-amina;

N-(4-(2-(dietil-amino)-etoxi)-fenil)-5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-amina;

ácido 1-(2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1-metil-piperidin-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-azabiciclo-[3.1.0]-hexan-2-carboxamida;

(1S,2R,5R)-N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-azabiciclo-[3.1.0]-hexan-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-piperidin-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-5-oxo-pirrolidin-2-carboxamida;

(R)-N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-5-oxo-pirrolidin-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-6-oxo-piperidin-3-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-6-fluoro-piridin-3-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1H-imidazol-5-carboxamida;

N-(2-metil-5-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-5-oxo-pirrolidin-2-carboxamida;

(S)-N-(2-metil-5-(5-(4-(trifluoro-metoxi)-fenil)-pirimidin-2-

il-amino)-fenil)-5-oxo-pirrolidin-2-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1-ciclopropil-5-oxo-pirrolidin-3-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-1-etil-6-oxo-piperidin-3-carboxamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-N-(2-fluoro-etil)-3-hidroxi-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-hidroxi-piperidin-1-il)-propan-1-ona;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-hidroxi-piperidin-1-il)-propan-1-ona;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-hidroxi-piperidin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-(2-hidroxi-propil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((R)-2-hidroxi-propil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((R)-2-hidroxi-propil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((S)-2-hidroxi-propil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((S)-2-hidroxi-propil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((S)-2-hidroxi-propil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-(4-hidroxi-ciclohexil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,4R)-4-hidroxi-ciclohexil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,4R)-4-hidroxi-ciclohexil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,4R)-4-hidroxi-ciclohexil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,4S)-4-hidroxi-ciclohexil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,4S)-4-hidroxi-ciclohexil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,4S)-4-hidroxi-ciclohexil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(3-hidroxi-piperidin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((S)-3-hidroxi-piperidin-1-il)-propan-1-ona;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((S)-3-hidroxi-piperidin-1-il)-propan-1-ona;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((S)-3-hidroxi-piperidin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((R)-3-hidroxi-piperidin-1-il)-propan-1-ona;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-

amino)-fenil)-3-hidroxi-1-((R)-3-hidroxi-piperidin-1-il)-propan-1-ona;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-((R)-3-hidroxi-piperidin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-(2-hidroxi-ciclopentil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,2R)-2-hidroxi-ciclopentil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2R)-2-hidroxi-ciclopentil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2S)-2-hidroxi-ciclopentil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1R,2R)-2-hidroxi-ciclopentil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2S)-2-hidroxi-ciclopentil)-propanamida;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2R)-2-hidroxi-ciclopentil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2S)-2-hidroxi-ciclopentil)-propanamida;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-N-((1S,2R)-2-hidroxi-ciclopentil)-propanamida;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(4-hidroxi-piperidin-1-il)-prop-2-en-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(4-hidroxi-piperidin-1-il)-etanona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-metil-piperazin-1-il)-propan-1-ona;

(R)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-metil-piperazin-1-il)-propan-1-ona;

(S)-2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(4-metil-piperazin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-3-hidroxi-1-(3-(trifluoro-metil)-piperazin-1-il)-propan-1-ona;

2-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-1-(3-(trifluoro-metil)-4-metil-piperazin-1-il)-3-hidroxi-propan-1-ona;

N1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-piperidin-1,4-dicarboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metan-sulfonil-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-acetil-piperazin-1-carboxamida;

1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-(1,3-dimetil-1H-pirazol-5-il)-urea;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)morfolin-4-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(2-hidroxi-etil)-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-4,7-diazaespiro-[2.5]-octan-7-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(2-hidroxi-etil)-4,7-diazaespiro-[2.5]-octan-7-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-3-(trifluoro-metil)-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-3-(trifluoro-metil)-piperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-metil-3-oxopiperazin-1-carboxamida;

N-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenil)-4-(2-hidroxi-etil)-3-oxopiperazin-1-carboxamida;

ácido 1-(2-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenoxi)-etil)-piperidin-4-carboxílico;

ácido 1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxílico;

ácido 1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-bencil)-piperidin-4-carboxílico;

ácido 1-(2-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-fluoro-fenoxi)-etil)-piperidin-4-carboxílico;

ácido 1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-fenetil)-piperidin-4-carboxílico;

4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-1-metil-piperazin-2-ona;

4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-1-(2-hidroxi-etil)-piperazin-2-ona;

4-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-piperazin-2-ona;

(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-(3-(trifluoro-metil)-piperazin-1-il)-metanona;

1-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenetil)-piperidin-4-carboxilato de metilo;

ácido 1-(5-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-hidroxi-fenetil)-piperidin-4-carboxílico;

ácido 1-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-etil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-metil-bencil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-fluoro-bencil)-piperidin-4-carboxílico;

ácido 1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-2-hidroxi-bencil)-piperidin-4-carboxílico;

4-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-1-(piperidin-4-il)-piperazin-2-ona;

4-(4-(3-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-benzoil)-2-oxopiperazin-1-il)-piperidin-1-carboxilato de isopropilo;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-

fenil)-2-hidroxi-etil)-tetrahidro-2H-piran-4-carboxamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-1-etil-6-oxo-piperidin-3-carboxamida;

1-ciclopropil-N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-5-oxo-pirrolidin-3-carboxamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-3,5-dimetil-isoxazol-4-carboxamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-isoxazol-5-carboxamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-2-(3-metil-isoxazol-5-il)-acetamida;

N-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-2-(tetrahidro-2H-piran-4-il)-acetamida; y

N3-(1-(4-(5-(4-(difluoro-metoxi)-fenil)-pirimidin-2-il-amino)-fenil)-2-hidroxi-etil)-piperidin-1,3-dicarboxamida.

12. Una composición farmacéutica, la cual comprende una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 11, y un vehículo farmacéuticamente aceptable.

13. El uso de un compuesto de cualquiera de las reivindicaciones 1 a 11, o una composición farmacéutica del mismo, y opcionalmente en combinación con un segundo agente terapéutico, para la fabricación de un medicamento para el tratamiento de una condición mediada por PDGFRα, PDGFRß y/o c-kit, en donde esta

condición es asma, dermatitis atópica, urticaria, síndrome de intestino irritable (IBS), o una enfermedad fibrótica.

14. El uso de la reivindicación 13, en donde la enfermedad fibrótica mencionada es esclerodermia, fibrosis pulmonar, fibrosis pulmonar idiopática (IPF), hipertensión pulmonar primaria (PPH), hipertensión arterial pulmonar primaria (PPAH), hipertensión arterial idiopática (IPAH), fibrosis hepática, fibrosis renal y fibrosis cardíaca.

15. El uso de la reivindicación 13, en donde el segundo agente terapéutico es un agente anti-fibrótico, pirfenidona, tacrolimus, 5-cloro-2-{(1E)-3-[2-(4-metoxi-benzoil)-4-metil-1H-pirrol-1-il]prop-1-en-1-il}-*N*-(metil-sulfonil)-benzamida, un agente anti-inflamatorio, un corticosteroide, una cromolina, un antagonista de leucotrieno, un bloqueador de IgE, un broncodilatador, un agonista-$ß_2$, xantinas, un anticolinérgico, o un agente quimioterapéutico.

16. El uso de la reivindicación 13, en donde el compuesto de cualquiera de las reivindicaciones 1 a 11 se administra antes de, simultáneamente con, o después del segundo agente terapéutico.

17. Un método para modular la actividad de la cinasa, el cual comprende administrar a un sistema de células o tejidos, o a un sujeto mamífero, una cantidad terapéuticamente efectiva del compuesto de cualquiera de las reivindicaciones 1 a 11, o una sal farmacéuticamente aceptable del mismo, en donde esta cinasa es cinasa c-kit, PDGFRα, PDGFRß, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFß, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2ß, BRK, Fms, KDR, c-raf o b-raf;

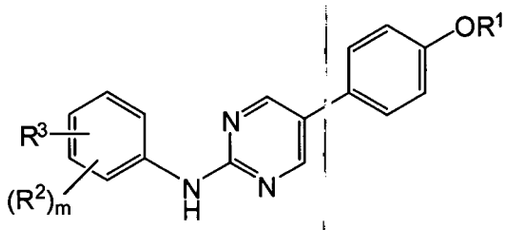
modulando de esta manera la actividad de la cinasa.

18. El método de la reivindicación 17, en donde esta cinasa es c-kit, PDGFRα o PDGFRß.

19. El método de la reivindicación 17, en donde el compuesto de cualquiera de las reivindicaciones 1 a 11 hace contacto directamente con c-kit, PDGFRα o PDGFRß *in vitro* o *in vivo*.

RESUMEN

La invención proporciona compuestos de la fórmula (I):



(1)

y composiciones farmacéuticas de los mismos, los cuales son útiles como inhibidores de cinasa de proteína, así como métodos para utilizar tales compuestos con el fin de tratar, disminuir, o prevenir una condición asociada con una actividad de cinasa anormal o mal regulada. En algunas modalidades, la invención proporciona métodos para utilizar tales compuestos con el fin de tratar, disminuir, o prevenir enfermedades o trastornos que involucren una activación anormal de las cinasas c-kit, PDGFRα, PDGFRß, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFß, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2ß, BRK, Fms, KDR, c-raf o b-raf.

* * * * *

PATENT COOPERATION TREATY PCT/US2008/073573

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

TONGCO WU, Emily
Genomics Institute of the Novartis Research Foundation
10675 John Jay Hopkins Drive
San Diego, CA 92121
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
20 January 2010 (20.01.2010)

Applicant's or agent's file reference
P1310PC10

IMPORTANT NOTIFICATION

International application No.
PCT/US2008/073573

International filing date *(day/month/year)*
19 August 2008 (19.08.2008)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
IRM LLC
Hurst Holme, 12 Trott Road, Bermuda
Hamilton, HM 11
Bermuda

State of Nationality: US
State of Residence: US
Telephone No.: 858-812-1539
Facsimile No.: 858-812-1909
E-mail address: etongcowu@gnf.org

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
IRM LLC
131 Front Street
P.O. Box HM 2899
Hamilton HM LX
Bermuda

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 71 30

Authorized officer
Gallay Laurence
e-mail pt09.pct@wipo.int
Telephone No. +41 22 338 74 09

PATENT COOPERATION TREATY PCT/US2008/073573

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

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IMPORTANT NOTIFICATION

International application No.
PCT/US2008/073573

International filing date *(day/month/year)*
19 August 2008 (19.08.2008)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
MOLTENI, Valentina
2475 E Street
San Diego, California 92102
United States of America

State of Nationality	State of Residence
IT	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
MOLTENI, Valentina
2475 E Street
San Diego, California 92102
United States of America

State of Nationality	State of Residence
US	US

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 71 30

Authorized officer
Gallay Laurence
e-mail pt09.pct@wipo.int
Telephone No. +41 22 338 74 09

Form PCT/IB/306 (January 2009) 1/EB18NLMI0

PATENT COOPERATION TREATY PCT/US2008/073573

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

TONGCO WU, Emily
Genomics Institute of the Novartis Research Foundation
10675 John Jay Hopkins Drive
San Diego, CA 92121
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
20 January 2010 (20.01.2010)

Applicant's or agent's file reference
P1310PC10

IMPORTANT NOTIFICATION

International application No.
PCT/US2008/073573

International filing date *(day/month/year)*
19 August 2008 (19.08.2008)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
LIU, Xiaodong
8468 Capricorn Way
San Diego, California 92126
United States of America

State of Nationality	State of Residence
CN	US

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
LIU, Xiaodong
9135 Judicial Drive, # 3307
San Diego, California 92122
United States of America

State of Nationality	State of Residence
CN	US

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 71 30

Authorized officer
Gallay Laurence
e-mail pt09.pct@wipo.int
Telephone No. +41 22 338 74 09

Form PCT/IB/306 (January 2009) 1/EB18PKMI0

PATENT COOPERATION TREATY

PCT/US2008/073573

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To:

TONGCO WU, Emily
Genomics Institute of the Novartis Research Foundation
10675 John Jay Hopkins Drive
San Diego, CA 92121
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
20 January 2010 (20.01.2010)

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International application No.
PCT/US2008/073573

International filing date *(day/month/year)*
19 August 2008 (19.08.2008)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
NABAKKA, Juliet
10107 Carefree Drive
Santee, California 92071
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
NABAKKA, Juliet
9855 Fieldthorn Street
San Diego, CA 92127
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 71 30

Authorized officer
Gallay Laurence
e-mail pt09.pct@wipo.int
Telephone No. +41 22 338 74 09

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

To:

GENOMICS INSTITUTE OF THE NOVARTIS RESEARCH FOUNDATION
Attn. Tongco Wu, Emily
10675 John Jay Hopkins Drive
San Diego, CA 92121
ETATS-UNIS D'AMERIQUE

GNF Legal Department
RECEIVED
JAN 26 2009
BY:

(PCT Rule 44.1)

Applicant's or agent's file reference P1310PC10	Date of mailing (day/month/year) 16/01/2009 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2008/073573	International filing date (day/month/year) 19/08/2008
Applicant IRM LLC	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Birgit Hohmann

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P1310PC10	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2008/073573	International filing date *(day/month/year)* 19/08/2008	(Earliest) Priority Date *(day/month/year)* 22/08/2007
Applicant IRM LLC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant

[X] the text has been established by this Authority to read as follows:

5-(4-(HALOALKOXY)PHENYL)PYRIMIDINE-2-AMINE COMPOUNDS AND COMPOSITIONS AS KINASE INHIBITORS

5. With regard to the **abstract,**

[ ] the text is approved as submitted by the applicant

[X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant

[ ] as selected by this Authority, because the applicant failed to suggest a figure

[ ] as selected by this Authority, because this figure better characterizes the invention

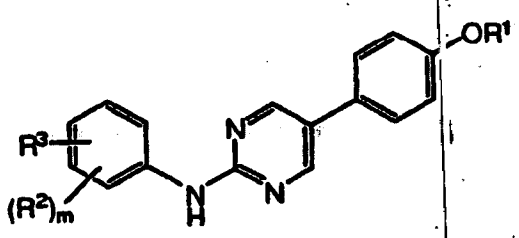
b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/073573

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The invention provides compounds of formula (1) and pharmaceutical compositions thereof, which are useful as protein kinase inhibitors, as well as methods for using such compounds to treat, ameliorate or prevent a condition associated with abnormal or deregulated kinase activity. In some embodiments, the invention provides methods for using such compounds to treat, ameliorate or prevent diseases or disorders that involve abnormal activation of c-kit, PDGFRα, PDGFRβ, CSF1R, Abl, BCR-Abl, CSK, JNK1, JNK2, p38, p70S6K, TGFβ, SRC, EGFR, trkB, FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6, SAPK2β, BRK, Fms, KDR, c-raf or b-raf kinases.



(1)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/073573

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D239/42 C07D401/12 C07D403/12 C07D413/12 A61K31/505
A61K31/506 A61P1/00 A61P7/04 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/038669 A (IRM LLC; NOVARTIS AG [CH]; MOLTENI VALENTINA [US]; LI XIAOLIN [US]; CH) 5 April 2007 (2007-04-05) claims 1-3,5,8,9,22,23,42-44,57,68,72,84,85; table 1; compounds 221-227,228-236, ...	1-19
A	ROSSIGNOL ET AL: "Synthesis of aminopyrimidylindoles structurally related to meridianins" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 63, no. 41, 1 August 2007 (2007-08-01), pages 10169-10176, XP022226165 ISSN: 0040-4020 Scheme 1: compound 13	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2008	16/01/2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Stroeter, Thomas

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/073573

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007038669 A	05-04-2007	AU 2006297089 A1	05-04-2007
		CA 2622494 A1	05-04-2007
		EP 1928236 A2	11-06-2008
		KR 20080048041 A	30-05-2008

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/073573	19.08.2008	22.08.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D239/42 C07D401/12 C07D403/12 C07D413/12 A61K31/505 A61K31/506 A61P1/00 A61P7/04 A61P11/06

Applicant
IRM LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Stroeter, Thomas Telephone No. +49 89 2399-8088

Form PCT/ISA/237 (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2008/073573

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2008/073573

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	17-19

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 The present application is directed to N-phenyl-5-(4'-(haloalkoxy)phenyl)-pyrimidine-2-amine compounds which are said to be protein kinase inhibitors and which are said to be useful in the treatment of conditions like irritable bowel syndrome, fibrotic diseases or asthma.

2 Claims 17-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

3 Reference is made to the following documents:

D1: WO 2007/038669 A (IRM LLC; NOVARTIS AG) 5 April 2007
D2: ROSSIGNOL ET AL: "Synthesis of aminopyrimidylindoles structurally related to meridianins" TETRAHEDRON, vol. 63, no. 41, 1 August 2007, pages 10169-10176

4 Claims 1-3 of D1 encompass the presently claimed compounds: The group Ar in formulae (1) and (46) can be an haloalkoxy-substituted phenyl (see dependent claim 3 of D1). Several example compounds of D1 like compounds 221-227 and many others are also N-phenyl-5-(4'-(alkoxy)phenyl)-pyrimidine-2-amine compounds but lack halogen-substitution on the alkoxy group. Since no compounds having the present haloalkoxy group OR^1 are specifically disclosed in D1, it appears that the presently claimed compounds are a novel selection of the content of D1 (Art. 33(2) PCT).

5 As stated under item 4, the present subject-matter is a selection of certain

haloalkoxy-substituted compounds falling under the scope of D1 which represents the closest prior art.

The problem to be solved by the present invention may therefore be considered as the provision of further protein kinase inhibitors for the treatment of various diseases. The solution proposed by the Applicant being the specific substitution R^1 is already disclosed in D1 although no compounds are explicitly described. The mere choice of specific compounds within a group of compounds known for the same pharmacological activity cannot be considered inventive per se since if it is an arbitrary choice. If the Applicant considers the present selection to be a purposive one, he is requested to submit further information and argumentation in order to demonstrate an unexpected effect, e.g. a better inhibition activity over the closest prior art. No comparative tests (let alone any exact inhibition data for specific example compounds - only general statements on the activity in the different assays are given in the example section) which would support the involvement of an inventive step have yet been provided. Thus, the present claims are not inventive (Art. 33(3) PCT).

Any comparative tests filed by the Applicant in order to re-establish inventive step to the presently claimed subject-matter must be made with the structurally closest prior art compound(s).

At this stage it is merely remarked that D2 reveals the 5-(4'-(haloalkoxy)phenyl)-pyrimidine-2-amine compound 13 which is expected to show kinase inhibiting activity and features a haloalkoxy group.

6 The subject-matter of the present claims 1-16 is industrially applicable and thus fulfils the requirements of Article 33(4) PCT.

Claims 17-19 cannot be considered as industrially applicable as the modulation of a kinase can not be considered in itself as a therapeutic application. The discovery, that a substance modulates the activity of a kinase, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of any pathological condition in order to make a technical contribution to the art (see item VIII (1)).

Re Item VII
Certain defects in the international application

The requirements of Rule 5.1(a)(ii) PCT are not met since the most relevant background art D1 has not been identified in the description.

Re Item VIII
Certain observations on the international application

1 The subject-matter of the present claims 17-19 is not considered to be clear (Article 6 PCT), since no instructions, in the form of any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise, which conditions fall within the functional definition, e.g. any condition susceptible of being improved or prevented by the modulation of the activity of one or more kinases, and accordingly within the scope of the claim. The reason for the necessity of this clarification is, that a claim referring to a condition to be treated, which is functionally defined, would not be limited to the treatment of said specified condition (here cancer etc), but by contrast embraces an undefined number of conditions all allegedly capable of being improved or prevented by the modulation of the kinase. Under these circumstances the independent claim can only be regarded as clear if means are available to the skilled person for assessing whether or not an additional condition not expressly filed in the application but nevertheless affected by the administration of the said compounds is comprised in the scope of the claim.

2 The vague and imprecise statement in the description on page 117, last paragraph, implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-033947- -00000-0000

Fecha: 2010-03-23 17:01:15 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 370

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que p· solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ MODELO DE UTILIDAD PCT ☐ **Art.33 Decisión 486/00, Circular Única**

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA		
	Radicación No.	10 33947
	Solicitud internacional	PCT/US2008/073573
	Fecha inicio fase nacional	22/03/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	4315

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA ESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 26 MAR. 2010
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA	Radicación No.	10 33947
	Solicitud internacional	PCT/US2008/073573
	Fecha inicio fase nacional	22/03/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	4316

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 26 MAR. 2010
adpa11

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