CSA296214

1/2

OF

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-340440

SOLICITUD DE PATENTE DE INVENCIÓN

1/2

TITULO: COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE PROTEINQUINASAS

SOLICITANTE: IRM LLC y NOVARTIS AG

DIRECCIÓN: Hurst Holme, 12 Trott Road, Hamilton, HM 11, Bermudas y Lichstrasse 35, CH-4056 Basel

APODERADO: CARLOS R. OLARTE

991 BOGOTÁ 2 de Abril de 2009

P2009/000044

OLARTERAISBECK

OLARTE RAISBECK MOURE

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-034040- -00000-0000
Fecha: 2009-04-02 11:31:42 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 424

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000044**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: IRM LLC y NOVARTIS AG
Dirección: Hurts Holme, 12 Trot Road, Hamilton, HM 11 Bermudas y Lichtstrasse 35, CH-4056 Basel
Nacionalidad o Domicilio: Bermudas, Suiza
Lugar de Constitución: Bermudas , Suiza

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

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

REPRESENTANTE O APODERADO

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

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

INVENTOR (ES) (72)

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

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2007/079340 Fecha Septiembre 24, 2007

Publicación Internacional No. WO 2008/042639 Fecha Abril 10, 2008

(6) **Título (54)** **COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE PROTEINQUINASAS**

Clasificación Internacional (51) C07D 401/14, C07D 403/04, C07D 403/14, C07D 405/14, C07D 417/14, A61K 31/506, A61P 35/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Octubre 2, 2006	60/827,873

(9) **Comprobante de pago No.** 09-25,652 **Fecha** Abril 1 de 2009

(10) **ANEXOS**

X	Comprobante de pago de la tasa de presentación de la solicitud.
X	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
X	Poderes, si fuere el caso. Adjunto copia simple Ver Expediente No. 08-122.179 y 08-062830
	Documento de cesión del inventor al solicitante o a su causante.
	Declaraciones.
X	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
X	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
	Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
	Traducción del examen preliminar internacional efectuado por la IPEA.
	De ser el caso, copia del contrato de acceso.
	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
	De ser el caso, certificado de depósito del material biológico.
	Arte final 12 x 12.
	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
	De ser el caso, modificaciones efectuadas a la solicitud internacional.
X	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/US2007/079340

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   Nacionalidad: Canadiense

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    Nacionalidad: Estadounidense

16. **Martin SENDZIK,**
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    Estados Unidos
    Nacionalidad: Alemana

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 25,652
FECHA : ABRIL 1 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-034040- -00000-0000

Fecha: 2009-04-02 11:31:42 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 424

[redacted]

***** 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	91394656	01/04/2009	7,928,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

[redacted]

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

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

CERTIFICACIÓN

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

La autenticidad de las firmas se estableció por comparación.

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

(Firmado)

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

Protocolo de Legalización No. 1571/2006

Apostilla:

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

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

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

Certificación:

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

Título: "IRM LLC – Cert."

Fecha: 29 de Noviembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

E-mail: treseser1@yahoo.com. 8845

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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

33842-CO-PCT

Power of Attorney

Poder

The undersigned,

El suscrito,

IRM LLC, a Delaware Limited Liability Company

domiciled in

domiciliado en

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

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

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

IRM LLC, a Delaware Limited Liability Company

Signature/Firma:

Dirk Hillebrand
Group Head Patents, MCD

Peter Roth
Snr. Patent Attorney

Date/Fecha: 08 November 2006

City,Country/Ciudad,País: Basel, CH

Attestation

I, the undersigned notary public in Basel, Switzerland, certify herewith that the above signatures are the genuine signatures of **Dr. Dirk Hillebrand**, German citizen, residing in Bad Säckingen, Germany, and **Dr. Peter Roth**, German citizen, residing in Freiburg, Germany, both acting for **IRM LLC**, in Hamilton, Bermuda, both as proxy holders, both with joint signature.

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

BASEL, this 20th (twentieth) day of November 2006 (twothousandandsix).

DR. MATTHIAS STAEHELIN NOTAR BASEL

M. Staehelin, Note

Leg.Prot.Nr. 1591 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz/Suisse)
This official document
2. is signed by .....
M. Staehelin
3. in his/her function of ..... off. Not.
4. and certified by .....
Canton Basle
Certified 20. NOV. 2006
5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. No. 10 '493 117 894
9. Seal/Stamp: 10. Signature:
Heidi Fischer

STATE CHANCERY * BASLE-CITY

Nota del traductor:

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

CERTIFICACIÓN NOTARIAL

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

Traductor Oficial
JORGE E. SIERRA
Licencia 376 - 1993 M

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

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

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

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

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

Mi licencia vence el 11 de Marzo de 2009.

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

Traductor Oficial
JORGE E. SIERRA R
Licencia 376

12

Certificación:

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

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

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

Traductor Oficial
JORGE E. SIERRA
Licencia 376 - 1993 M

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chabin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chabin
Graciela Melo

Power of Attorney

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

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

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

Signature/Firma:

Arthur Canonica

Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

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

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

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

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

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

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

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

M. Staehelin

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

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

Leg.Prot.Nr. 975 /2006

15

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by .....
3. in his/her function as .....
4. and certified by the seal of the .....

Certified 24. Aug. 2009

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. 2009/1855
9. Seal / stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASLE-CITY *

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 April 2008 (10.04.2008)

PCT

(10) International Publication Number
WO 2008/042639 A1

(51) International Patent Classification:
C07D 401/14 (2006.01) *C07D 417/14* (2006.01)
C07D 403/04 (2006.01) *A61K 31/506* (2006.01)
C07D 403/14 (2006.01) *A61P 35/00* (2006.01)
C07D 405/14 (2006.01)

(21) International Application Number:
PCT/US2007/079340

(22) International Filing Date:
24 September 2007 (24.09.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/827,873 2 October 2006 (02.10.2006) US

(71) Applicants *(for all designated States except US)*: **IRM LLC** [US/—]; Hurst Holme, 12 Trott Road, Hamilton, HM 11 (BM). **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

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

(57) Abstract: The invention provides a novel class of compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with abnormal or deregulated kinase activity, particularly diseases or disorders that involve abnormal activation of the Abl, ARG, BCR-Abl, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 and TrkB kinases.

WO 2008/042639 A1

COMPOUNDS AND COMPOSITIONS AS PROTEIN KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Number 60/827,873, filed 02 October 2006. The full disclosure of this application is incorporated herein by reference in its entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The invention provides a novel class of compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with abnormal or deregulated kinase activity, particularly diseases or disorders that involve abnormal activation of the Abl, ARG, BCR-Abl, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 and TrkB kinases.

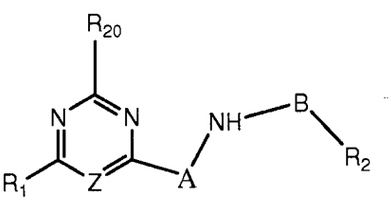
Background

[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 (PDGF-R), 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, Lck, Bmx and c-src; and serine/threonine kinases such as b-RAF, c-RAF, sgk, MAP kinases (e.g., MKK4, MKK6, etc.) and SAPK2α 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.

[0004] The novel compounds of this invention inhibit the activity of one or more protein kinases and are, therefore, expected to be useful in the treatment of kinase-associated diseases.

SUMMARY OF THE INVENTION

[0005] In one aspect, the present invention provides compounds of Formula I:



I

[0006] in which:

[0007] A is a 5 member, unsaturated or partially unsaturated, ring containing 1 to 3 heteroatoms selected from –N=, –NR_3–, –O– and –S–; wherein R_3 is selected from hydrogen, halo, substituted or unsubstituted-C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6} alkynyl, -XOR_{4a}, -XCN, -$XC(O)OR_{4a}$, -$XC(O)R_{4b}$, -$XNR_{4a}R_{4a}$, -$XNR_{4a}XNR_{4a}R_{4a}$, -$XC(O)NR_{4a}XNR_{4a}R_{4a}$, -$XC(O)NR_{4a}XR_{4b}$, -$XC(O)NR_{4a}XNR_{4a}R_{4b}$, -$XC(O)NR_{4a}XOR_{4a}$, -$XNR_{4a}XNR_{4a}R_{4b}$, -$XNR_{4a}XOR_{4a}$, -$XNR_{4a}XCF_3$, -$XC(O)NR_{4a}R_{4a}$, and -$XR_{4b}$; wherein each X is independently selected from a bond and C_{1-4}alkylene; R_{4a} is selected from hydrogen and substituted or unsubstituted C_{1-6}alkyl, and two R_{4a} on the same or adjacent atoms can optionally be joined to form a 5-6 membered ring containing up to two heteroatoms selected from N, O and S as ring members; and R_{4b} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein any cycloalkyl, heterocycloalkyl, aryl or heteroaryl of R_{4b} is optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl and -$NR_{4c}R_{4d}$; wherein each R_{4c} and R_{4d} is independently selected from hydrogen and substituted or unsubstituted C_{1-6}alkyl, and R_{4c} and R_{4d} can optionally be joined together to form a 5-6 membered ring containing N and optionally containing an additional heteroatom selected from N, O and S; with the proviso that ring A is not imidazole;

[0008] wherein any ring A can be optionally substituted with one or two R_3 radicals, with the proviso that R_3 is not halo when attached directly to a nitrogen atom;

[0009] B is 5 or 6 member, unsaturated or partially unsaturated, ring containing 0 to 3 heteroatoms selected from –N=, –NR_{21}–, –O– and –S–; wherein R_{21} is selected from hydrogen, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo; wherein B can be optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo;

[0010] Z is selected from CH and N;

[0011] R_1 is selected from –XNR_5R_6, –$XNR_5XNR_5R_6$, –XNR_5XR_5, –XNR_5XOR_6, –$XNR_6XC(O)OR_5$, –$XNR_6XC(O)NR_6R_6$, –XOR_5, –$XC(O)R_5$, –XR_5 and –$XS(O)_{0-2}R_5$; wherein X is selected from a bond and C_{1-4}alkylene optionally substituted by 1 to 2 C_{1-6}alkyl radicals; R_5 is selected from hydrogen, substituted or unsubstituted C_{1-6}alkyl, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; and each R_6 is independently selected from hydrogen and substituted or unsubstituted C_{1-6}alkyl; or R_5 and R_6 together with the nitrogen to which R_5 and R_6 are both attached form heteroaryl or heterocycloalkyl that can contain an additional heteroatom selected from N, O and S as a ring member; or R_1 together with the N1 of the pyrimidine ring to which R_1 is attached forms 2,3-dihydroimidazo[1,2-f]pyrimidine;

[0012] wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_5 or the combination of R_5 and R_6 can be optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-alkyl, halo-substituted-alkoxy, –XNR_7R_8, –XOR_7, –$XNR_7S(O)_2R_8$, –$XNR_7S(O)R_8$, –XNR_7SR_8, –$XC(O)NR_7R_8$, –$XC(O)NR_7XNR_7R_8$, –$XNR_7C(O)NR_7R_8$, –$XNR_7XNR_7R_8$, –XNR_7XOR_7, –$XNR_7C(=NR_7)NR_7R_8$, –$XS(O)_2R_9$, –$XNR_7C(O)R_8$, –$XNR_7C(O)R_9$, –XR_9, –$XC(O)OR_8$, –$XS(O)_2NR_7R_8$, –$XS(O)NR_7R_8$ and –$XSNR_7R_8$; wherein X is a bond or C_{1-4}alkylene; R_7 and R_8 are independently selected from the group consisting of hydrogen and substituted or unsubstituted C_{1-4}alkyl, and wherein R_7 and R_8 on one nitrogen can optionally cyclize to form a 5-6 membered ring that can contain an additional heteroatom selected from N, O and S as a ring member; and R_9 is selected from C_{3-10}heterocycloalkyl and C_{1-10}heteroaryl; wherein said heterocycloalkyl or heteroaryl of R_9 is optionally substituted with a radical selected from the group consisting of C_{1-4}alkyl, –$XNR_7XNR_7R_7$, XNR_7XOR_7 and –XOR_7;

[0013] R_2 is selected from $-R_{11}$, $-CONR_{10}R_{11}$, $SO_2NR_{10}R_{11}$, $-NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}S(O)_{0-2}R_{11}$ and $-NR_{10}C(O)NR_{10}R_{11}$; wherein R_{10} is selected from hydrogen and substituted or unsubstituted C_{1-6}alkyl; R_{11} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein R_{10} and R_{11} on the same nitrogen can optionally cyclize to form a 5-6 membered ring that can contain an additional heteroatom selected from N, O and S as a ring member, and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{11} is optionally substituted by 1 to 3 radicals selected from halo, nitro, cyano, hydroxy, substituted or unsubstituted C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-X_2R_{13}$, $-X_2NR_{12}C(O)R_{13}$, $-X_2NR_{12}C(O)NR_{12}R_{13}$, $-X_2NR_{12}R_{12}$, $-X_2NR_{12}R_{13}$, $-X_2NR_{12}X_2R_{13}$, $-X_2NR_{12}NR_{12}R_{12}$, $-X_2NR_{12}X_2OR_{12}$, $-X_2C(O)NR_{12}R_{13}$, $-X_2NR_{12}S(O)_{0-2}R_{13}$ and $-X_2S(O)_{0-2}NR_{12}R_{13}$; wherein X_2 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{12} is selected from hydrogen, C_{1-6}alkyl and hydroxy-substituted-C_{1-6}alkyl; R_{13} is selected from substituted or unsubstituted C_{1-6} alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein two R_{12} groups or R_{12} and R_{13} on the same nitrogen can optionally cyclize to form a 5-6 membered ring that can contain an additional heteroatom selected from N, O and S as a ring member, any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{13} is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, hydroxy, nitro, amino, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-X_3NR_7R_8$, $-X_3NR_7X_3OR_7$, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl, C_{3-10}heterocycloalkyl-C_{0-4}alkoxy and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; wherein X_3 is selected from a bond and C_{1-4}alkylene; R_7 and R_8 are as described above and wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituents of R_{13} is further optionally substituted by 1 to 3 radicals independently selected from halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-10}heterocycloalkyl and halo-substituted-C_{1-6}alkoxy;

[0014] R_{20} is selected from hydrogen, substituted or unsubstituted C_{1-6}alkyl, and $N(R_{21})_2$, wherein each R_{21} is independently H or substituted or unsubstituted C_{1-6} alkyl, and wherein two R_{21} on the same nitrogen can cyclize to form a 5-6 membered ring that can contain an additional heteroatom selected from N, O and S;

[0015] and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

[0016] In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

[0017] In a third aspect, the present invention provides a method of treating a disease in an animal in which inhibition of kinase activity, particularly Abl, ARG, BCR-Abl, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 and/or TrkB activity, can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0018] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which kinase activity, particularly Abl, ARG, BCR-Abl, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 and/or TrkB activity, contributes to the pathology and/or symptomology of the disease.

[0019] In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0020] As used herein, the terms "alkyl," "alkenyl" and "alkynyl" have their ordinary meanings and include straight-chain, branched-chain and cyclic monovalent hydrocarbon radicals, and combinations of these, which contain only C and H when they are unsubstituted. "Alkyl" groups are saturated so they contain no carbon-carbon multiple bonds; "alkenyl" groups

contain at least one carbon-carbon double bond; a nd "alkynyl" groups contain at least one carbon-carbon triple bond. Examples include methyl, ethyl, isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butynyl, and the like. The total number of carbon atoms in each such group is sometimes described herein, *e.g.*, when the group can contain up to ten carbon atoms it can be represented as 1-10C or as C1-C10 or C1-10.

[0021] Typically, the alkyl, alkenyl and alkynyl substituents of the invention contain 1-10C (alkyl) or 2-10C (alkenyl or alkynyl). Preferably they contain 1-6C (alkyl) or 2-6C (alkenyl or alkynyl). Sometimes they contain 1-4C (alkyl) or 2-4C (alkenyl or alkynyl). A single alkenyl or alkynyl group can include more than one type of multiple bond, or more than one multiple bond; such groups are included within the definition of the term "alkenyl" when they contain at least one carbon-carbon double bond, and are included within the term "alkynyl" when they contain at least one carbon-carbon triple bond.

[0022] While "alkyl" as used herein includes cycloalkyl and cycloalkylalkyl groups, the term "cycloalkyl" may be used herein to describe a carbocyclic non-aromatic group that is connected via a ring carbon atom, and "cycloalkylalkyl" may be used to describe a carbocyclic non-aromatic group that is connected to the molecule through an alkyl linker. Similarly, "heterocyclyl" may be used to describe a non-aromatic cyclic group that contains at least one heteroatom as a ring member and that is connected to the molecule via a ring atom, which may be C or N; and "heterocyclylalkyl" may be used to describe such a group that is connected to another molecule through a linker. The sizes and substituents that are suitable for the cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl groups are the same as those described above for alkyl groups As used herein, these terms also include rings that contain a double bond or two, as long as the ring is not aromatic.

[0023] "Heteroalkyl", "heteroalkenyl", and "heteroalkynyl" and the like are defined similarly to the corresponding hydrocarbyl (alkyl, alkenyl and alkynyl) groups, but the 'hetero' terms refer to groups that contain 1-3 O, S or N heteroatoms or combinations thereof within the backbone residue; thus at least one carbon atom of a corresponding alkyl, alkenyl, or alkynyl group is replaced by one of the specified heteroatoms to form a heteroalkyl, heteroalkenyl, or heteroalkynyl group. The typical and preferred sizes for heteroforms of alkyl, alkenyl and alkynyl groups are generally the same as for the corresponding hydrocarbyl groups, and the substituents that may be present on the heteroforms are the same as those described above for the

hydrocarbyl groups. For reasons of chemical stability, it is also understood that, unless otherwise specified, such groups do not include more than two contiguous heteroatoms except where an oxo group is present on N or S as in a nitro or sulfonyl group.

[0024] Alkyl, alkenyl and alkynyl groups and the corresponding cyclic groups, heteroforms of these groups, and rings formed by joining together two of these groups are often substituted to the extent that such substitution makes sense chemically. Typical substituents include, but are not limited to, halo, =O, =N-CN, =N-OR, =NR, OR, NR_2, SR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, and NO_2, wherein each R is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C1-C8 acyl, C2-C8 heteroacyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C6-C10 aryl, or C5-C10 heteroaryl, and each R is optionally substituted with halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl or C5-C10 heteroaryl. Alkyl, alkenyl and alkynyl groups can also be substituted by C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl or C5-C10 heteroaryl, each of which can be substituted by the substituents that are appropriate for the particular group.

[0025] "Alkoxy" as used herein refers to an alkyl group connected through oxygen. For example, C_{1-4}-alkoxy includes, methoxy, ethoxy, and the like. Other substituted alkyl groups are described similarly.

Halosubstituted-C_{1-6}alkyl, as used in this application, includes trifluoromethyl, pentafluoroethyl, difluoromethyl, difluoromethyl, and the like, as well as the isomer combinations thereof. Alkylene, as used in this application, is a divalent alkyl radical that can be single chain, branched or cyclized. For example C_{1-4}alkylene includes cyclobutyl, and the like.

[0026] As used herein, "acyl" encompasses groups comprising an alkyl, alkenyl, alkynyl, aryl or arylalkyl radical attached at one of the two available valence positions of a carbonyl carbon atom, and heteroacyl refers to the corresponding groups wherein at least one carbon other than the carbonyl carbon has been replaced by a heteroatom chosen from N, O and S. Thus heteroacyl includes, for example, -C(=O)OR and –C(=O)NR_2 as well as –C(=O)-heteroaryl.

[0027] Acyl and heteroacyl groups are bonded to any group or molecule to which they are attached through the open valence of the carbonyl carbon atom. Typically, they are C1-C8 acyl groups, which include formyl, acetyl, pivaloyl, and benzoyl, and C2-C8 heteroacyl groups, which include methoxyacetyl, ethoxycarbonyl, and 4-pyridinoyl. The hydrocarbyl groups, aryl groups, and heteroforms of such groups that comprise an acyl or heteroacyl group can be substituted with the substituents described herein as generally suitable substituents for each of the corresponding component of the acyl or heteroacyl group.

[0028] "Aromatic" moiety or "aryl" moiety refers to a monocyclic or fused bicyclic moiety having the well-known characteristics of aromaticity; examples include phenyl and naphthyl. Similarly, "heteroaromatic" and "heteroaryl" refer to such monocyclic or fused bicyclic ring systems which contain as ring members one or more heteroatoms selected from O, S and N. The inclusion of a heteroatom permits aromaticity in 5-membered rings as well as 6-membered rings. Typical heteroaromatic systems include monocyclic C5-C6 aromatic groups such as pyridyl, pyrimidyl, pyrazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, and imidazolyl and the fused bicyclic moieties formed by fusing one of these monocyclic groups with a phenyl ring or with any of the heteroaromatic monocyclic groups to form a C8-C10 bicyclic group such as indolyl, benzimidazolyl, indazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, pyrazolopyridyl, quinazolinyl, quinoxalinyl, cinnolinyl, and the like. Any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system is included in this definition. It also includes bicyclic groups where at least the ring which is directly attached to the remainder of the molecule has the characteristics of aromaticity. Typically, the ring systems contain 5-12 ring member atoms. Preferably the monocyclic heteroaryls contain 5-6 ring members, and the bicyclic heteroaryls contain 8-10 ring members.

[0029] Aryl and heteroaryl moieties may be substituted with a variety of substituents including C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C5-C12 aryl, C1-C8 acyl, and heteroforms of these, each of which can itself be further substituted; other substituents for aryl and heteroaryl moieties include halo,OR, NR_2, SR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, and NO_2, wherein each R is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12

heteroarylalkyl, and each R is optionally substituted as described above for alkyl groups. The substituent groups on an aryl or heteroaryl group may of course be further substituted with the groups described herein as suitable for each type of such substituents or for each component of the substituent. Thus, for example, an arylalkyl substituent may be substituted on the aryl portion with substituents described herein as typical for aryl groups, and it may be further substituted on the alkyl portion with substituents described herein as typical or suitable for alkyl groups.

[0030] Similarly, "arylalkyl" and "heteroarylalkyl" refer to aromatic and heteroaromatic ring systems which are bonded to their attachment point through a linking group such as an alkylene, including substituted or unsubstituted, saturated or unsaturated, cyclic or acyclic linkers. Typically the linker is C1-C8 alkyl or a hetero form thereof. These linkers may also include a carbonyl group, thus making them able to provide substituents as an acyl or heteroacyl moiety. An aryl or heteroaryl ring in an arylalkyl or heteroarylalkyl group may be substituted with the same substituents described above for aryl groups. Preferably, an arylalkyl group includes a phenyl ring optionally substituted with the groups defined above for aryl groups and a C1-C4 alkylene that is unsubstituted or is substituted with one or two C1-C4 alkyl groups or heteroalkyl groups, where the alkyl or heteroalkyl groups can optionally cyclize to form a ring such as cyclopropane, dioxolane, or oxacyclopentane. Similarly, a heteroarylalkyl group preferably includes a C5-C6 monocyclic heteroaryl group that is optionally substituted with the groups described above as substituents typical on aryl groups and a C1-C4 alkylene that is unsubstituted or is substituted with one or two C1-C4 alkyl groups or heteroalkyl groups, or it includes an optionally substituted phenyl ring or C5-C6 monocyclic heteroaryl and a C1-C4 heteroalkylene that is unsubstituted or is substituted with one or two C1-C4 alkyl or heteroalkyl groups, where the alkyl or heteroalkyl groups can optionally cyclize to form a ring such as cyclopropane, dioxolane, or oxacyclopentane.

[0031] Where an arylalkyl or heteroarylalkyl group is described as optionally substituted, the substituents may be on either the alkyl or heteroalkyl portion or on the aryl or heteroaryl portion of the group. The substituents optionally present on the alkyl or heteroalkyl portion are the same as those described above for alkyl groups generally; the substituents optionally present on the aryl or heteroaryl portion are the same as those described above for aryl groups generally.

[0032] "Arylalkyl" groups as used herein are hydrocarbyl groups if they are unsubstituted, and are described by the total number of carbon atoms in the ring and alkylene or similar linker. Thus a benzyl group is a C7-arylalkyl group, and phenylethyl is a C8-arylalkyl.

[0033] "Heteroarylalkyl" as described above refers to a moiety comprising an aryl group that is attached through a linking group, and differs from "arylalkyl" in that at least one ring atom of the aryl moiety or one atom in the linking group is a heteroatom selected from N, O and S. The heteroarylalkyl groups are described herein according to the total number of atoms in the ring and linker combined, and they include aryl groups linked through a heteroalkyl linker; heteroaryl groups linked through a hydrocarbyl linker such as an alkylene; and heteroaryl groups linked through a heteroalkyl linker. Thus, for example, C7-heteroarylalkyl would include pyridylmethyl, phenoxy, and N-pyrrolylmethoxy.

[0034] "Arylene" means a divalent radical derived from an aryl group. A ring described as "unsaturated" contains at least one carbon-carbon multiple bond, and can be aromatic; a ring described as "partially unsaturated" contains at least one carbon-carbon multiple bond but is not aromatic.

[0035] "Heteroaryl" is as defined for aryl above where one or more of the ring members is a heteroatom. For example C_{1-10}heteroaryl, as used in this application, includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc. Heteroaryl may also include partially unsaturated ring systems such as 1,2,3,6-tetrahydropyridin-4-yl, and the like.

[0036] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

[0037] "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O)-, -S-, -S(O) - or -$S(O)_2$-, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, pyrrolidinyl-2-one, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, etc.

[0038] "Halogen" (or halo) preferably represents chloro or fluoro, but may also be bromo or iodo.

[0039] In general, any alkyl, alkenyl, alkynyl, acyl, or aryl or arylalkyl group or any heteroform of one of these groups that is contained in a substituent may itself optionally be substituted by additional substituents. The nature of these substituents is similar to those recited with regard to the primary substituents themselves if the substituents are not otherwise described. Thus, where an embodiment of, for example, R^7 is alkyl, this alkyl may optionally be substituted by the remaining substituents listed as embodiments for R^7 where this makes chemical sense, and where this does not undermine the size limit provided for the alkyl *per se*; *e.g.*, alkyl substituted by alkyl or by alkenyl would simply extend the upper limit of carbon atoms for these embodiments, and is not included. However, alkyl substituted by aryl, amino, alkoxy, =O, and the like would be included within the scope of the invention, and the atoms of these substituent groups are not counted in the number used to describe the alkyl, alkenyl, etc. group that is being described. Where no number of substituents is specified, each such alkyl, alkenyl, alkynyl, acyl, or aryl group may be substituted with a number of substituents according to its available valences; in particular, any of these groups may be substituted with fluorine atoms at any or all of its available valences, for example.

[0040] "Substituted" as used herein indicates that the particular group or groups being described will have one or more non-hydrogen substituents. "Optionally substituted" indicates that the group may or may not have non-hydrogen substituents. If not otherwise specified, the total number of such substituents that may be present is equal to the number of H atoms present on the unsubstituted form of the group being described. Where an optional substituent is attached via a double bond, such as a carbonyl oxygen (=O), the group takes up two available valences, so the total number of substituents that may be included is reduced according to the number of available valences.

[0041] "Kinase Panel" is a list of kinases comprising Abl(human), Abl(T315I), JAK2, JAK3, ALK, JNK1α1, ALK4, KDR, Aurora-A, Lck, Blk, MAPK1, Bmx, MAPKAP-K2, BRK, MEK1, CaMKII(rat), Met, CDK1/cyclinB, p70S6K, CHK2, PAK2, CK1, PDGFRα, CK2, PDK1, c-kit, Pim-2, c-RAF, PKA(h), CSK, PKBα, cSrc, PKCα, DYRK2, Plk3, EGFR, ROCK-I, Fes, Ron, FGFR3, Ros, Flt3, SAPK2α, Fms, SGK, Fyn, SIK,

GSK3β, Syk, IGF-1R, Tie-2, IKKß, TrKB, IR, WNK3, IRAK4, ZAP-70, ITK, AMPK(rat), LIMK1, Rsk2, Axl, LKB1, SAPK2β, BrSK2, Lyn (h), SAPK3, BTK, MAPKAP-K3, SAPK4, CaMKIV, MARK1, Snk, CDK2/cyclinA, MINK, SRPK1, CDK3/cyclinE, MKK4(m), TAK1, CDK5/p25, MKK6(h), TBK1, CDK6/cyclinD3, MLCK, TrkA, CDK7/cyclinH/MAT1, MRCKβ, TSSK1, CHK1, MSK1, Yes, CK1d, MST2, ZIPK, c-Kit (D816V), MuSK, DAPK2, NEK2, DDR2, NEK6, DMPK, PAK4, DRAK1, PAR-1Bα, EphA1, PDGFRβ, EphA2, Pim-1, EphA5, PKBβ, EphB2, PKCβI, EphB4, PKCδ, FGFR1, PKCη, FGFR2, PKCθ, FGFR4, PKD2, Fgr, PKG1β, Flt1, PRK2, Hck, PYK2, HIPK2, Ret, IKKα, RIPK2, IRR, ROCK-II(human), JNK2α2, Rse, JNK3, Rsk1(h), PI3 Kγ, PI3 Kδ and PI3-Kβ. Compounds of the invention are screened against the kinase panel (wild type and/or mutation thereof) and inhibit the activity of at least one of said panel members.

[0042] "Mutant forms of BCR-Abl" means single or multiple amino acid changes from the wild-type sequence. Mutations in BCR-ABL act by disrupting critical contact points between protein and inhibitor (for example, Gleevec, and the like), more often, by inducing a transition from the inactive to the active state, i.e. to a conformation to which BCR-ABL and Gleevec is unable to bind. From analyses of clinical samples, the repertoire of mutations found in association with the resistant phenotype has been increasing slowly but inexorably over time. Mutations seem to cluster in four main regions. One group of mutations (G250E, Q252R, Y253F/H, E255K/V) includes amino acids that form the phosphate-binding loop for ATP (also known as the P-loop). A second group (V289A, F311L, T315I, F317L) can be found in the Gleevec binding site and interacts directly with the inhibitor via hydrogen bonds or Van der Waals' interactions. The third group of mutations (M351T, E355G) clusters in close proximity to the catalytic domain. The fourth group of mutations (H396R/P) is located in the activation loop, whose conformation is the molecular switch controlling kinase activation/inactivation. BCR-ABL point mutations associated with Gleevec resistance detected in CML and ALL patients include: M224V, L248V, G250E, G250R, Q252R, Q252H, Y253H, Y253F, E255K, E255V, D276G, T277A, V289A, F311L, T315I, T315N, F317L, M343T, M315T, E355G, F359V, F359A, V379I, F382L, L387M, L387F, H396P, H396R, A397P, S417Y, E459K, and F486S (Amino acid positions, indicated by the single letter code, are those for the GenBank sequence, accession number AAB60394, and correspond to ABL type 1a; Martinelli et al., Haematologica/The

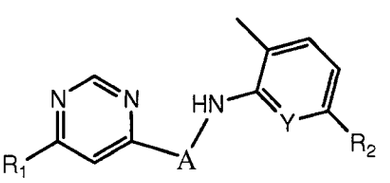
Hematology Journal, 2005, April; 90-4). Unless otherwise stated for this invention, Bcr-Abl refers to wild-type and mutant forms of the enzyme.

[0043] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

[0044] 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. The present invention provides compounds, compositions and methods for the treatment of kinase related disease, particularly Abl, ARG, BCR-Abl, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 and TrkB kinase related diseases. For example, leukemia and other proliferation disorders related to BCR-Abl can be treated through the inhibition of wild type and mutant forms of Bcr-Abl.

[0045] In one embodiment, with reference to compounds of Formula I, are compounds of Formula Ia:



Ia

[0046] in which: A is a 5 member, unsaturated or partially unsaturated, ring containing 1 to 3 heteroatoms selected from –N=, –NR_3–, –O– and –S–; wherein R_3 is selected from hydrogen, halo, halo-substituted-C_{1-6}alkyl, C_{1-6}alkyl, -XOR_{4a}, -XCN, -$XC(O)OR_{4a}$, -$XC(O)R_{4b}$, -$XNR_{4a}R_{4a}$, -$XNR_{4a}R_{4b}$, -$XNR_{4a}XNR_{4a}R_{4a}$, -$XC(O)NR_{4a}XNR_{4a}R_{4a}$, -$XC(O)NR_{4a}XR_{4b}$, -$XC(O)NR_{4a}XNR_{4a}R_{4b}$, -$XC(O)NR_{4a}XOR_{4a}$, -$XNR_{4a}XNR_{4a}R_{4b}$, -$XNR_{4a}XOR_{4a}$,-$XNR_{4a}XCF_3$, -$XC(O)NR_{4a}R_{4a}$, and -$XR_{4b}$; wherein X is selected from a bond and C_{1-4}alkylene; R_{4a} is selected from hydrogen and C_{1-6}alkyl; and R_{4b} is selected from C_{6-}

$_{10}$aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein any cycloalkyl, heterocycloalkyl, aryl or heteroaryl of R_{4b} is optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl and -$NR_{4c}R_{4d}$; wherein each R_{4c} and R_{4d} is independently selected from hydrogen and C_{1-6}alkyl; with the proviso that ring A is not imidazole; wherein any ring A can be optionally substituted with an R_3 radical;

[0047] R_1 is selected from $-XNR_5R_6$, $-XNR_5XNR_5R_6$, $-XNR_5XR_5$, $-XNR_5XOR_6$, $-XNR_6XC(O)OR_5$, $-XNR_6XC(O)NR_6R_6$, $-XOR_5$, $-XC(O)R_5$, $-XR_5$ and $-XS(O)_{0-2}R_5$; wherein X is selected from a bond and C_{1-4}alkylene optionally substituted by 1 to 2 C_{1-6}alkyl radicals; R_5 is selected from hydrogen, C_{1-6}alkyl, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; and each R_6 is independently selected from hydrogen and C_{1-6}alkyl; or R_5 and R_6 together with the nitrogen to which R_5 and R_6 are both attached form heteroaryl or heterocycloalkyl; or R_1 together with the N1 of the pyrimidine ring to which R_1 is attached forms 2,3-dihydroimidazo[1,2-f]pyrimidine;

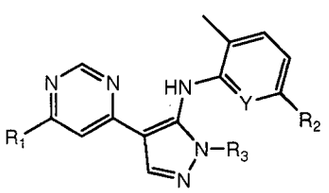
[0048] wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_5 or the combination of R_5 and R_6 can be optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-alkyl, halo-substituted-alkoxy, $-XNR_7R_8$, $-XOR_7$, $-XNR_7S(O)_2R_8$, $-XNR_7S(O)R_8$, $-XNR_7SR_8$, $-XC(O)NR_7R_8$, $-XC(O)NR_7XNR_7R_8$, $-XNR_7C(O)NR_7R_8$, $-XNR_7XNR_7R_8$, $-XNR_7XOR_7$, $-XNR_7C(=NR_7)NR_7R_8$, $-XS(O)_2R_9$, $-XNR_7C(O)R_8$, $-XNR_7C(O)R_9$, $-XR_9$, $-XC(O)OR_8$, $-XS(O)_2NR_7R_8$, $-XS(O)NR_7R_8$ and $-XSNR_7R_8$; wherein X is a bond or C_{1-4}alkylene; R_7 and R_8 are independently selected from the group consisting of hydrogen and C_{1-4}alkyl; and R_9 is selected from C_{3-10}heterocycloalkyl and C_{1-10}heteroaryl; wherein said heterocycloalkyl or heteroaryl of R_9 is optionally substituted with a radical selected from the group consisting of C_{1-4}alkyl, $-XNR_7XNR_7R_7$, XNR_7XOR_7 and $-XOR_7$;

[0049] R_2 is selected from $-R_{11}$, $-CONR_{10}R_{11}$, $-SO_2NR_{10}R_{11}$, $-NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}S(O)_{0-2}R_{11}$ and $-NR_{10}C(O)NR_{10}R_{11}$; R_{10} is selected from hydrogen and C_{1-6}alkyl; R_{11} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{11} is optionally substituted by 1 to 3 radicals selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-}

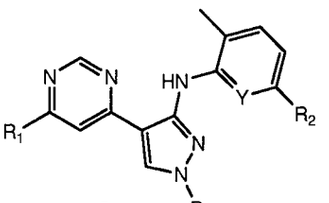
$_6$alkyl, halo-substituted-C_{1-6}alkoxy, -X_2R_{13}, –$X_2NR_{12}C(O)R_{13}$, –$X_2NR_{12}C(O)NR_{12}R_{13}$, –$X_2NR_{12}R_{12}$, –$X_2NR_{12}R_{13}$, –$X_2NR_{12}X_2R_{13}$, –$X_2NR_{12}NR_{12}R_{12}$, –$X_2NR_{12}X_2OR_{12}$, –$X_2C(O)NR_{12}R_{13}$, –$X_2NR_{12}S(O)_{0-2}R_{13}$ and –$X_2S(O)_{0-2}NR_{12}R_{13}$; wherein R_{12} is selected from hydrogen, C_{1-6}alkyl and hydroxy-substituted-C_{1-6}alkyl; wherein X_2 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{13} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{13} is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, hydroxy, nitro, amino, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, -$X_3NR_7R_8$, -$X_3NR_7X_3OR_7$, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl, C_{3-10}heterocycloalkyl-C_{0-4}alkoxy and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; wherein X_3 is selected from a bond and C_{1-4}alkyelene; R_7 and R_8 are as described above and wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituents of R_{13} is further optionally substituted by 1 to 3 radicals independently selected from halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-10}heterocycloalkyl and halo-substituted-C_{1-6}alkoxy; and

[0050] Y is selected from C and N.

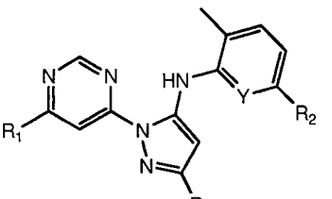
[0051] In another embodiment, is a compound selected from Formula Ib, Ic and Id:



Ib



Ic



Id

[0052] in which:

[0053] R_1 is selected from –XNR_5R_6, –$XNR_5XNR_5R_6$, –XNR_5XR_5, –XNR_5XOR_6, –$XNR_6XC(O)OR_5$, –$XNR_6XC(O)NR_6R_6$, –XOR_5, –$XC(O)R_5$, –XR_5 and –$XS(O)_{0-2}R_5$; wherein X is selected from a bond and C_{1-4}alkylene optionally substituted by 1 to 2 C_{1-6}alkyl radicals; R_5 is selected from hydrogen, C_{1-6}alkyl, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; and each R_6 is independently selected from hydrogen and C_{1-6}alkyl; or R_5 and R_6 together with

the nitrogen to which R_5 and R_6 are both attached form heteroaryl or heterocycloalkyl; or R_1 together with the N1 of the pyrimidine ring to which R_1 is attached forms 2,3-dihydroimidazo[1,2-f]pyrimidine;

[0054] wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_5 or the combination of R_5 and R_6 can be optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-alkyl, halo-substituted-alkoxy, $-XNR_7R_8$, $-XOR_7$, $-XNR_7S(O)_2R_8$, $-XNR_7S(O)R_8$, $-XNR_7SR_8$, $-XC(O)NR_7R_8$, $-XC(O)NR_7XNR_7R_8$, $-XNR_7C(O)NR_7R_8$, $-XNR_7XNR_7R_8$, $-XNR_7XOR_7$, $-XNR_7C(=NR_7)NR_7R_8$, $-XS(O)_2R_9$, $-XNR_7C(O)R_8$, $-XNR_7C(O)R_9$, $-XR_9$, $-XC(O)OR_8$, $-XS(O)_2NR_7R_8$, $-XS(O)NR_7R_8$ and $-XSNR_7R_8$; wherein X is a bond or C_{1-4}alkylene; each R_7 and R_8 are independently selected from the group consisting of hydrogen and C_{1-4}alkyl, or R_7 and R_8 together with the nitrogen to which R_7 and R_8 are both attached form heteroaryl or heterocycloalkyl;; and R_9 is selected from C_{3-10}heterocycloalkyl and C_{1-10}heteroaryl; wherein said heterocycloalkyl or heteroaryl of R_9 is optionally substituted with a radical selected from the group consisting of C_{1-4}alkyl, $-XNR_7XNR_7R_7$, XNR_7XOR_7 and $-XOR_7$;

[0055] R_2 is selected from $-R_{11}$, $-CONR_{10}R_{11}$, $SO_2NR_{10}R_{11}$, $-NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}S(O)_{0-2}R_{11}$ and $-NR_{10}C(O)NR_{10}R_{11}$; wherein R_{10} is selected from hydrogen and C_{1-6}alkyl; R_{11} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein R_{10} and R_{11} together with the nitrogen to which R_{10} and R_{11} are both attached can optionally form heteroaryl or heterocycloalkyl, and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{11} is optionally substituted by 1 to 3 radicals selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-X_2R_{13}$, $-X_2NR_{12}C(O)R_{13}$, $-X_2NR_{12}C(O)NR_{12}R_{13}$, $-X_2NR_{12}R_{12}$, $-X_2NR_{12}R_{13}$, $-X_2NR_{12}X_2R_{13}$, $-X_2NR_{12}NR_{12}R_{12}$, $-X_2NR_{12}X_2OR_{12}$, $-X_2C(O)NR_{12}R_{13}$, $-X_2S(O)_{0-2}R_{12}$, $-X_2NR_{12}S(O)_{0-2}R_{13}$ and $-X_2S(O)_{0-2}NR_{12}R_{13}$; wherein X_2 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{12} is selected from hydrogen, C_{1-6}alkyl and hydroxy-substituted-C_{1-6}alkyl; R_{13} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein two R_{12} of $NR_{12}R_{12}$ or R_{12} and R_{13} of $NR_{12}R_{13}$ together with the nitrogen to which both are attached optionally form heteroaryl or heterocycloalkyl, and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{13} is optionally substituted with 1 to 3 radicals independently

selected from halo, cyano, hydroxy, nitro, amino, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-X_3NR_7R_8$, $-X_3NR_7X_3OR_7$, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl, C_{3-10}heterocycloalkyl-C_{0-4}alkoxy and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; wherein X_3 is selected from a bond and C_{1-4}alkyelene; R_7 and R_8 are as described above and wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituents of R_{13} is further optionally substituted by 1 to 3 radicals independently selected from halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-10}heterocycloalkyl and halo-substituted-C_{1-6}alkoxy;

[0056] R_3 is selected from hydrogen, halo, halo-substituted-C_{1-6}alkyl, C_{1-6}alkyl, $-XOR_{4a}$, -XCN, $-XC(O)OR_{4a}$, $-XC(O)R_{4b}$, $-XNR_{4a}R_{4a}$, $-XNR_{4a}R_{4b}$, $-XNR_{4a}XNR_{4a}R_{4a}$, $-XC(O)NR_{4a}XNR_{4a}R_{4a}$, $-XC(O)NR_{4a}XR_{4b}$, $-XC(O)NR_{4a}XNR_{4a}R_{4b}$, $-XC(O)NR_{4a}XOR_{4a}$, $-XNR_{4a}XNR_{4a}R_{4b}$, $-XNR_{4a}XOR_{4a}$, $-XNR_{4a}XCF_3$, $-XC(O)NR_{4a}R_{4a}$, and $-XR_{4b}$; wherein X is selected from a bond and C_{1-4}alkylene; R_{4a} is selected from hydrogen and C_{1-6}alkyl; and R_{4b} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein two R_{4a} of $NR_{4a}R_{4a}$ together with the nitrogen to which both are attached optionally form heteroaryl or heterocycloalkyl, and any cycloalkyl, heterocycloalkyl, aryl or heteroaryl of R_{4b} is optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl and $-NR_{4c}R_{4d}$; wherein each R_{4c} and R_{4d} is independently selected from hydrogen and C_{1-6}alkyl, and R_{4c} and R_{4d} of $NR_{4c}R_{4d}$ together with the nitrogen to which R_{4c} and R_{4d} are attached optionally form a heteroaryl or heterocycloalkyl,; and Y is selected from CH and N.

[0057] In another embodiment, R_3 is selected from hydrogen, methyl, morpholino-ethyl, ethoxy-carbonyl, chloro, trifluoromethyl, (methyl-piperidinyl)(methyl)amino-methyl, methyl-amino-carbonyl, hydroxy-methyl, dimethyl-amino-methyl, methyl-amino-methyl, morpholino-methyl, diethyl-amino-ethyl-amino-methyl, methyl-piperazinyl-methyl, methyl-piperazinyl-ethyl-amino-methyl, dimethyl-amino-propyl-amino-methyl, ((2-hydroxyethyl)(methyl)amino)methyl, ethyl-amino-methyl, trifluoromethyl-amino-methyl, dimethyl-amino-ethyl-amino-carbonyl, piperidinyl-ethyl-amino-carbonyl, morpholino-ethyl-amino-carbonyl, morpholino-carbonyl, amino-carbonyl, dimethyl-amino-carbonyl, dimethyl-amino-pyrrolidinyl-methyl, dimethyl-amino-pyrrolidinyl-carbonyl, thiomorpholino-methyl, methoxy-ethyl-piperazinyl-methyl, methoxy-

ethyl-amino-carbonyl, cyano-methyl, (2,6-dimethylmorpholino)methyl, (2,6-dimethyl-piperidinyl)ethyl-amino-carbonyl and cyclopropyl-amino-carbonyl.

[0058] In another embodiment, R_1 is selected from morpholino-ethyl-amino, methyl-amino, methyl-piperazinyl-ethyl-amino, cyclopropyl-amino, hydroxy-ethyl-piperazinyl-amino, isopropyl-amino, dimethyl-amino-ethyl-amino, methyl-piperazinyl-amino, amino, 2,6-dimethyl-morpholino-ethyl-amino, hydroxy-pyridinyl-ethyl-amino, amino-ethyl-amino, 3-oxopiperazin-1-yl-ethyl-amino, hydroxy-ethyl-amino, hydroxy-propyl-amino, methyl-sulfanyl, methoxy, sulfanyl, pyridinyl-ethyl-amino, pyridinyl-methyl-amino, morpholino-methyl-pyridinyl-amino, carboxy-propyl-amino, carboxy-methyl-amino, azetidin-3-yl-amino, azetidin-3-yl-methyl-amino, carboxy-ethyl-amino and hydroxy-pyrrolidinyl.

[0059] In another embodiment, R_2 is selected from $-R_{11}$, $-CONHR_{11}$, SO_2NHR_{11}, $-NHR_{11}$, $-NHC(O)R_{11}$, $-NHS(O)_{0-2}R_{11}$ and $-NHC(O)NHR_{11}$; wherein R_{11} is selected from phenyl, pyridinyl, thiazolyl, benzimidazolyl, isoxazolyl, 1,2,3,4-tetrahydronaphthyl, benzothiazolyl, benzo[d][1,2,3]triazole, 2,3-dihydrobenzofuran and 2,3-dihydro-3,3-dimethylbenzofuran-5-yl; wherein said phenyl, pyridinyl, thiazolyl, isoxazolyl and 2,3-dihydro-3,3-dimethylbenzofuran-5-yl of R_2 are optionally substituted with 1 to 3 radicals independently selected from halo, isopropyl, methyl-sulfonyl, hydroxy, methyl-sulfonyl-amino, 1-(2-hydroxyethylamino)cyclopropyl, 3-(3-hydroxypropylamino)cyclobutyl, isopropyl-amino-cyclobutyl, 2-(2-hydroxyethylamino)propan-2-yl, 3-aminoprop-1-enyl, isopropyl-3-aminoprop-1-enyl, isopropyl-amino-propyl, isopropyl-amino-ethyl, hydroxyethyl-3-aminoprop-1-enyl, methyl-amino, 1,2-dihydroxyethyl, 2-hydroxy-ethyl, (3-hydroxyazetidin-1-yl)methyl, (3-methoxyazetidin-1-yl)methyl, 2-methyl-morpholino-methyl, (3-methoxypyrrolidin-1-yl)methyl, (2-hydroxy-2-methylpropylamino)methyl, 1-methyl-1,2,3,6-tetrahydropyridin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, piperidin-4-yl, (4-ethylpiperazin-1-yl)methyl, pyrrolidiny-1-yl-methyl, 1-(ethylamino)ethyl, 4-(2-hydroxypropyl)-1-piperazinyl, 3-trifluoromethyl-4-methyl-1-piperazinyl, difluoro-methyl, 4-methyl-1-imidazolyl, methyl-sulfonyl-ethyl-amino-carbonyl, hydroxy-propyl-amino-carbonyl, 4-t-butoxy-carbonyl-1-piperazinyl, 4-(1-carboxyethyl)piperazin-1-yl, 4,7-diazaspiro[2.5]octan-7-yl, ethoxy, 4-(tert-butoxycarbonyl)-2-oxopiperazin-1-yl, 4-methyl-2-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, methoxy, ethyl, pyrazolyl, trifluoromethyl, 2-cyanobutan-2-yl, 1-cyanocyclopropyl, 2-hydroxypropan-2-yl, difluoromethyl, 3-ethylpentan-

3-yl, methyl-piperazinyl, ethyl-piperazinyl, t-butyl, t-butoxy, 1,2-dihydroxypropyl, 2-hydroxymethyl-ethyl, cyclopropyl-1-piperazinyl, 4-methyl-sulfonyl-ethyl-1-piperazinyl, 2-hydroxy-propyl-amino-methyl, (tetrahydrofuran-2-ylamino)methyl, (2,3-dihydroxypropylamino)methyl), (1,3-dihydroxypropan-2-ylamino)methyl, (1-hydroxy-2-methylpropan-2-ylamino)methyl, cyclobutyl-amino-methyl, 4-hydroxy-piperidinyl, (1-hydroxypropan-2-ylamino)methyl, dimethyl-amino-amino-methyl, methoxy-amino-methyl,hydroxy-amino-methyl,2-hydroxy-methyl-pyrrolidin-1-yl-methyl, pyrrolidinyl-ethoxy, 3-hydroxy-pyrrolidinyl, 3-hydroxyazetidin-1-yl, 3-(methoxy-carbonyl)- 4-methylpiperazin-1-yl, 4-methylpiperazin-1-yl, 4-methyl-3-hydroxymethyl-piperazin-1-yl, 4-methoxy-carbonyl-piperidinyl, 4-carboxy-piperidinyl, piperazinyl, 4-(2,2,2-trifluoroethyl)piperazin-1-yl, 2-hydroxy-cyclopent-1-yl-amino-methyl, amino-carbonyl-methyl, dimethyl-amino-propyl(methyl)-amino, (2-(dimethylamino)ethyl)(methyl)amino, methoxy-ethyl(methyl)amino, dimethyl-amino-ethoxy, nitro, 1-methyl-4-piperidinyloxy, morpholino, 2-methyl-morpholino, 4-ethyl-piperazin-1-yl-methyl, ethyl-amino-methyl, cyclopropyl-amino-methyl, diethyl-amino-ethyl, azetidin-1-ylmethyl, 3-hydroxy-pyrrolidin-1-yl-methyl, hydroxy-ethyl-amino-methyl, propyl-amino-methyl, 3-hydroxy-azetidin-1-ylmethyl, 4-methoxyethyl-1-piperazinyl, methoxy-ethyl-amino-methyl, butyl-amino-ethyl, t-butyl-amino-methyl, hydroxy-cyclohexyl-amino-methyl, amino-methyl, hydroxy-propyl-amino-methyl, hydroxy-ethyl(methyl)amino-methyl, 4-hydroxypropyl-1-piperazinyl, 4-carboxy-methyl-piperazinyl, dimethyl-amino-methyl, isopropyl-amino-methyl, 4-dimethyl-amino-carbonyl-methyl-1-piperazinyl, 4-(2-hydroxypropyl)piperazin-1-yl, hydroxy-ethyl-piperazinyl, methyl, cyclopropyl, halo, trifluoromethoxy, difluoromethoxy, 2-fluoropropan-2-yl, 2-methoxy-propan-2-yl, 1,1-difluoroethyl, 1-methyl-1-fluoroethyl, 1-methyl-1-methoxy-ethyl, 2-hydroxypropan-2-yl, 2-methoxypropan-2-yl, 2-cyanopropan-2-yl, 3-cyanopropan-2-yl, 2,3-difluoropropan-2-yl and cyano-cyclopropyl.

[0060] Preferred compounds are selected from N-(4-Methyl-3-{2-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{1-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-

phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(5-methyl-2-{6-[2-(4-methyl-piperazin-1-yl)-ethylamino]-pyrimidin-4-yl}-2H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[4-(6-Cyclopropylamino-pyrimidin-4-yl)-2-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(2-methyl-4-{6-[2-(4-methyl-piperazin-1-yl)-ethylamino]-pyrimidin-4-yl}-2H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{2-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-{3-[4-(6-Cyclopropylamino-pyrimidin-4-yl)-1-methyl-1H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(1-methyl-4-{6-[2-(4-methyl-piperazin-1-yl)-ethylamino]-pyrimidin-4-yl}-1H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{1-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-{4-Methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(4-ethyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, 3-(4-Ethyl-piperazin-1-yl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-5-trifluoromethyl-benzamide, 3-(4-Ethyl-piperazin-1-yl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-5-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, 3-(4-Ethyl-piperazin-1-yl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-5-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 5-Methyl-6-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-pyridine-2-carboxylic acid (3-trifluoromethyl-phenyl)-amide, 5-Methyl-6-

[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-pyridine-2-carboxylic acid (3-trifluoromethyl-phenyl)-amide, 5-Methyl-6-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-pyridine-2-carboxylic acid (3-trifluoromethyl-phenyl)-amide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-[3-(2-{6-[2-(2,6-Dimethyl-morpholin-4-yl)-ethylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-3-trifluoromethyl-benzamide, N-[3-(2-{6-[2-(4-Hydroxy-piperidin-1-yl)-ethylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(5-methyl-2-{6-[2-(3-oxo-piperazin-1-yl)-ethylamino]-pyrimidin-4-yl}-2H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, N-(3-{2-[6-(2-Amino-ethylamino)-pyrimidin-4-yl]-5-methyl-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, 2-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-tert-Butyl-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, N-{4-Methyl-3-[4-(6-methylamino-pyrimidin-4-yl)-1H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[4-(6-methylamino-pyrimidin-4-yl)-1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[1-methyl-4-(6-methylamino-pyrimidin-4-yl)-1H-pyrazol-3-ylamino]-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, 3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-N-{4-methyl-3-[1-methyl-4-(6-methylamino-pyrimidin-4-yl)-1H-pyrazol-3-ylamino]-phenyl}-5-trifluoromethyl-benzamide, N-{3-[4-(6-Cyclopropylamino-pyrimidin-4-yl)-1-methyl-1H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-{3-[4-(6-Cyclopropylamino-pyrimidin-4-yl)-1-methyl-1H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-5-trifluoromethyl-benzamide, N-(3-{2-[6-(2-Hydroxy-ethylamino)-pyrimidin-4-yl]-5-methyl-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[5-methyl-2-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(2,3-Dihydro-imidazo[1,2-

c]pyrimidin-7-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, 2-tert-Butyl-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, N-{3-[2-(6-Methoxy-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Mercapto-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-pyridin-3-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 4-(6-{3-Methyl-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-pyrazol-1-yl}-pyrimidin-4-ylamino)-butyric acid, (6-{3-Methyl-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-pyrazol-1-yl}-pyrimidin-4-ylamino)-acetic acid, N-(3-{2-[6-(Azetidin-3-ylamino)-pyrimidin-4-yl]-5-methyl-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, 3-(6-{3-Methyl-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-pyrazol-1-yl}-pyrimidin-4-ylamino)-propionic acid, N-(3-{2-[6-(3-Hydroxy-pyrrolidin-1-yl)-pyrimidin-4-yl]-5-methyl-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, N-[3-(2-{6-[(Azetidin-3-ylmethyl)-amino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(5-methyl-2-{6-[(pyridin-2-ylmethyl)-amino]-pyrimidin-4-yl}-2H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, 4-Methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-N-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-phenyl]-benzamide, (4-Methyl-3-{5-methyl-2-[6-(5-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-carbamic acid tert-butyl ester, 5-Methyl-N-(4-methyl-3-{5-methyl-2-[6-(5-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 3-Cyclopropyl-isoxazole-5-carboxylic acid (4-methyl-3-{5-methyl-2-[6-(5-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-amide, 3,4-Dichloro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-Fluoro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-5-trifluoromethyl-

benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-4-trifluoromethyl-benzamide, 3,5-Dichloro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-Fluoro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethoxy-benzamide, 3-Bromo-4-chloro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-Difluoromethoxy-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-Chloro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 3-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Cyano-cyclopropyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3,3-Dimethyl-2,3-dihydro-benzofuran-5-carboxylic acid (4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-amide, 4-Methyl-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 3-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Cyano-cyclopropyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 2-(1-Cyano-cyclopropyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-

isonicotinamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid ethyl ester, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-hydroxymethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-dimethylaminomethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-methylaminomethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-(3-{2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[(2-diethylamino-ethylamino)-methyl]-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-(4-methyl-piperazin-1-ylmethyl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-[3-(2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-{[2-(4-methyl-piperazin-1-yl)-ethylamino]-methyl}-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-3-trifluoromethyl-benzamide, N-(3-{2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[(3-dimethylamino-propylamino)-methyl]-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-ethylaminomethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-(3-{2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[(2,2,2-trifluoro-ethylamino)-methyl]-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid (2-dimethylamino-ethyl)-amide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid (2-piperidin-1-yl-ethyl)-amide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide,

N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-(morpholine-4-carbonyl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid amide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid dimethylamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-(3-dimethylamino-pyrrolidine-1-carbonyl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid (2-methoxy-ethyl)-amide, 1-(6-Methylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, N-{4-Methyl-3-[5-methylaminomethyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, 1-(6-Methylamino-pyrimidin-4-yl)-5-{2-methyl-5-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzoylamino]-phenylamino}-1H-pyrazole-3-carboxylic acid methylamide, 1-(6-Methylamino-2-morpholin-4-yl-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1-Cyano-cyclopropyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, N-{3-[5-Cyanomethyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, 1-(6-Methylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 1-(6-Methylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid cyclopropylamide, 5-tert-Butyl-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-tert-Butyl-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, N-

[5-(1-Fluoro-1-methyl-ethyl)-pyridin-3-yl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-[5-(1-Methoxy-1-methyl-ethyl)-pyridin-3-yl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-[5-(1-Fluoro-1-methyl-ethyl)-pyridin-3-yl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-[5-(1-Methoxy-1-methyl-ethyl)-pyridin-3-yl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, 4-Methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-N-(4-trifluoromethyl-pyridin-2-yl)-benzamide, N-(3-tert-Butyl-phenyl)-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-(2-tert-Butyl-pyridin-4-yl)-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-(3-tert-Butyl-phenyl)-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-[3-(Cyano-dimethyl-methyl)-phenyl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, 4-Methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-N-(4-trifluoromethyl-pyridin-2-yl)-benzamide, (6-{5-[5-(6-tert-Butyl-1H-benzoimidazol-2-yl)-2-methyl-phenylamino]-3-methyl-pyrazol-1-yl}-pyrimidin-4-yl)-(4-methyl-piperazin-1-yl)-amine, (6-{3-Methyl-5-[2-methyl-5-(6-trifluoromethyl-1H-benzoimidazol-2-yl)-phenylamino]-pyrazol-1-yl}-pyrimidin-4-yl)-(4-methyl-piperazin-1-yl)-amine, N-[3-(1,1-Difluoro-ethyl)-phenyl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-[3-(1,1-Difluoro-ethyl)-phenyl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, 4-Fluoro-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, 4-Fluoro-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 5-[5-(4-Fluoro-3-trifluoromethyl-benzoylamino)-2-methyl-phenylamino]-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-[5-(4-Fluoro-3-trifluoromethyl-benzoylamino)-2-methyl-phenylamino]-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-[5-(4-Fluoro-3-trifluoromethyl-benzoylamino)-2-methyl-phenylamino]-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 5-[5-(2-tert-Butyl-pyridin-4-ylcarbamoyl)-2-

methyl-phenylamino]-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, N-(4-Methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 2-tert-Butyl-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 5-tert-Butyl-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(Cyano-dimethyl-methyl)-N-{3-[5-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-isonicotinamide, 3-(Cyano-dimethyl-methyl)-N-{3-[5-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-benzamide, 2-tert-Butyl-N-{3-[5-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-isonicotinamide, 2-tert-Butyl-N-{3-[5-[2-(2,6-dimethyl-piperidin-1-yl)-ethylcarbamoyl]-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-isonicotinamide, 2-(Cyano-dimethyl-methyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 3-(Cyano-dimethyl-methyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Cyano-cyclopropyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-(1-Cyano-cyclopropyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 3-(1-Cyano-1-methyl-propyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-tert-Butyl-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 3-(1,1-Difluoro-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-

4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Hydroxy-1-methyl-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Methoxy-1-methyl-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 5-tert-Butyl-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, 2-tert-Butyl-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2,2-Dimethyl-2,3-dihydro-benzofuran-7-carboxylic acid {4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-amide, 2-(1-Fluoro-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Fluoro-1-methyl-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Fluoro-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Methoxy-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Hydroxy-1-methyl-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 3-(1-Cyano-cyclopropyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(Cyano-dimethyl-methyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-(Cyano-dimethyl-methyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Cyano-cyclopropyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 3-(1,1-Difluoro-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Methoxy-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Hydroxy-1-

methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-(1-Fluoro-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Methoxy-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Hydroxy-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 5-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, N-[3-(Cyano-dimethyl-methyl)-phenyl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-(2-tert-Butyl-pyridin-4-yl)-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, 5-(1-Fluoro-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 2-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(1,1-difluoro-ethyl)-benzamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(5-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-2-tert-butyl-isonicotinamide, 2-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-tert-Butyl-N-[3-(2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-ylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-isonicotinamide, 5-tert-Butyl-N-[3-(2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-ylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-nicotinamide, N-(2-tert-Butyl-pyridin-4-yl)-3-(2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-ylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-benzamide, N-(5-tert-Butyl-pyridin-3-yl)-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-[2-(1-Methoxy-1-methyl-ethyl)-pyridin-4-yl]-4-methyl-3-{5-methyl-2-

[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-[3-(1,1-Difluoro-ethyl)-phenyl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-[2-(Cyano-dimethyl-methyl)-pyridin-4-yl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, 5-(1-Fluoro-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-2-tert-butyl-isonicotinamide, 3-(1,1-Difluoro-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-tert-Butyl-N-(3-{2-[6-(2-dimethylamino-acetylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-isonicotinamide, N-[2-(1,1-Difluoro-ethyl)-pyridin-4-yl]-4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 5-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, 5-tert-Butyl-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 1-(6-Methylamino-pyrimidin-4-yl)-5-{2-methyl-5-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzoylamino]-phenylamino}-1H-pyrazole-3-carboxylic acid methylamide, 1-(6-Methylamino-2-morpholin-4-yl-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1-Cyano-cyclopropyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 1-(6-Methylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid cyclopropylamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-

yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 2-tert-Butyl-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-tert-Butyl-N-{4-methyl-3-[2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-methylcarbamoyl-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 5-[5-(3-tert-Butyl-benzoylamino)-2-methyl-phenylamino]-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 2-Chloro-6-methoxy-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-Chloro-6-methoxy-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-Chloro-6-methoxy-N-{4-methyl-3-[2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-Chloro-6-methoxy-N-{4-methyl-3-[2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-Chloro-6-methoxy-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-Chloro-6-methoxy-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, N-(4-Methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-6-pyrazol-1-yl-nicotinamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-methylcarbamoyl-2H-pyrazol-3-ylamino]-phenyl}-6-pyrazol-1-yl-nicotinamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-6-pyrazol-1-yl-nicotinamide, N-(4-Methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-6-pyrazol-1-yl-nicotinamide, 5-[2-Methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1-[6-(2-morpholin-4-yl-ethylamino)-

pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 5-[2-Methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 1-[6-(4-Methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-6-trifluoromethoxy-nicotinamide, N-{4-Methyl-3-[2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-6-trifluoromethoxy-nicotinamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-methylcarbamoyl-2H-pyrazol-3-ylamino]-phenyl}-6-trifluoromethoxy-nicotinamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-6-trifluoromethoxy-nicotinamide, N-(4-Methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-6-trifluoromethoxy-nicotinamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 5-{5-[3-(1-Cyano-1-methyl-propyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 3-(1-Cyano-1-methyl-propyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 5-{5-[3-(1-Cyano-1-methyl-propyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1-Cyano-1-methyl-propyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1-Methoxy-1-methyl-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 3-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 5-tert-Butyl-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-

2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 2-tert-Butyl-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 4-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-Methanesulfonyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-Chloro-3-methanesulfonyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-tert-Butoxy-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-Methoxy-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 3-tert-Butoxy-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-Methanesulfonyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-4-trifluoromethoxy-benzamide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethoxy-benzamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 5-tert-Butyl-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 2-tert-Butyl-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-

phenyl)-isonicotinamide, 5-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, 1-Isopropyl-1H-benzotriazole-5-carboxylic acid {4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-amide, 5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid {4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-amide, 2-Methyl-benzothiazole-5-carboxylic acid {4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-amide, 3-(1,1-Diethyl-propyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-benzamide, N-{3-[5-(3-Dimethylamino-pyrrolidin-1-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[5-[4-(2-Methoxy-ethyl)-piperazin-1-ylmethyl]-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[5-(2,6-Dimethyl-morpholin-4-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[5-(2,6-Dimethyl-morpholin-4-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(2-(6-methylamino-pyrimidin-4-yl)-5-{[methyl-(1-methyl-piperidin-4-yl)-amino]-methyl}-2H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, N-{3-[5-(1,1-Dioxo-1l6-thiomorpholin-4-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-thiomorpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, 5-tert-butyl-N-(3-(3-(((2-hydroxyethyl)(methyl)amino)methyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)nicotinamide, -(2-(2-fluoropropan-2-yl)pyridin-4-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 5-tert-butyl-N-(3-(3-(((2-hydroxyethyl)(methyl)amino)methyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)nicotinamide, 5-tert-butyl-N-(3-(3-(2-(2,6-dimethylpiperidin-1-yl)ethylcarbamoyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)nicotinamide, 5-(2-methoxypropan-2-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)nicotinamide, 5-(2-fluoropropan-2-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)nicotinamide, N-(4-tert-butylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-

(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-(2-fluoropropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 5-(5-(2-tert-butylpyridin-4-ylcarbamoyl)-2-methylphenylamino)-1-(6-(isopropylamino)pyrimidin-4-yl)-N-methyl-1H-pyrazole-3-carboxamide, 5-(5-(2-tert-butylpyridin-4-ylcarbamoyl)-2-methylphenylamino)-N-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazole-3-carboxamide, N-(2-tert-butylpyridin-4-yl)-4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-(morpholinomethyl)-1H-pyrazol-5-ylamino)benzamide, N-(2-tert-Butyl-pyridin-4-yl)-3-[5-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-benzamide (see exmple 295), 2-tert-butyl-N-(3-(1-(6-(isopropylamino)pyrimidin-4-yl)-3-(methylcarbamoyl)-1H-pyrazol-5-ylamino)-4-methylphenyl)isonicotinamide, N-(2-tert-butylpyridin-4-yl)-3-(1-(6-(isopropylamino)pyrimidin-4-yl)-3-(morpholinomethyl)-1H-pyrazol-5-ylamino)-4-methylbenzamide, N-(2-tert-Butyl-pyridin-4-yl)-3-[5-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-2-(6-isopropylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-benzamide (see example 298), 2-tert-butyl-N-(3-(1-(6-(isopropylamino)pyrimidin-4-yl)-3-(morpholinomethyl)-1H-pyrazol-5-ylamino)-4-methylphenyl)isonicotinamide, N-(4-(2-fluoropropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(5-tert-butyl-4-methylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(5-tert-butyl-4-methylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-(2-cyanopropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(2-(2-methoxypropan-2-yl)pyridin-4-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-tert-butylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-(2-morpholinoethylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(5-tert-butyl-4-methylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-(2-morpholinoethylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, -(4-(1,1-difluoroethyl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-(1,1-difluoroethyl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-tert-butylpyridin-2-yl)-4-

methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-tert-butylpyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 3-(1-(6-aminopyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(5-tert-butyl-4-methylthiazol-2-yl)-4-methylbenzamide, 3-(1-(6-aminopyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(4-tert-butylthiazol-2-yl)-4-methylbenzamide, N-(4-(2-methoxypropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-(2-methoxypropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(6-methyl-5-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)-3-(trifluoromethyl)benzamide, N-(6-methyl-5-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)-3-(trifluoromethyl)benzamide, 2-tert-butyl-N-(6-methyl-5-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)isonicotinamide, 2-tert-butyl-N-(6-methyl-5-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)isonicotinamide, N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-(1-oxo-thiomorpholinomethyl)-1H-pyrazol-5-ylamino)phenyl)-3-(trifluoromethyl)benzamide, N-(3-(1-(6-aminopyrimidin-4-yl)-3-methyl-1H-pyrazol-5-ylamino)-4-methylphenyl)-3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)benzamide, 3-(4-hydroxypiperidin-1-yl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(4-hydroxypiperidin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1-methylpiperidin-4-yloxy)-5-(trifluoromethyl)benzamide, 3-(4-(2-hydroxyethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-morpholino-5-(trifluoromethyl)benzamide, (S)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(2-methylmorpholino)-5-(trifluoromethyl)benzamide, (R)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(2-methylmorpholino)-5-

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(trifluoromethyl)benzamide, 1-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(3-(trifluoromethyl)phenyl)urea, 1-(4-fluoro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(3-(4-ethylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1,1-dioxo-thiomorpholino)-5-(trifluoromethyl)benzamide, (R)-3-(3,4-dimethylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(3,4-dimethylpiperazin-1-yl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-(2-(dimethylamino)ethoxy)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(2-(pyrrolidin-1-yl)ethoxy)-5-(trifluoromethyl)phenyl)benzamide, N-(3-(3-hydroxypyrrolidin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-(3-hydroxyazetidin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 2-(1,1-difluoroethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)isonicotinamide, methyl 1-methyl-4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamido)-5-(trifluoromethyl)phenyl)piperazine-2-carboxylate, N-(3-((2-methoxyethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-((2-(dimethylamino)ethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 3-(1,1-difluoroethyl)-N-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)benzamide, N-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-

methylphenyl)-3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)benzamide, 4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-(trifluoromethyl)-1H-pyrazol-5-ylamino)-N-(3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)benzamide, methyl 1-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamido)-5-(trifluoromethyl)phenyl)piperidine-4-carboxylate, 1-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamido)-5-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid, N-(3-(3-(hydroxymethyl)-4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-((2-hydroxyethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-(4-(hydroxymethyl)piperidin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 1-(3-(1,1-difluoroethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(2-(1,1-difluoroethyl)pyridin-4-yl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, N-(3-fluoro-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(methylsulfonamido)-5-(trifluoromethyl)phenyl)benzamide, 2-methoxy-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-(trifluoromethyl)isonicotinamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(trifluoromethyl)phenyl)benzamide, N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-fluoro-3-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 3-((3-(dimethylamino)propyl)(methyl)amino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-nitro-5-(trifluoromethyl)benzamide, 3-amino-N-(4-methyl-

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3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((2-methoxyethyl)(methyl)amino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 1-(4-bromo-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(6-methyl-5-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)urea, 3-((2-(dimethylamino)ethyl)(methyl)amino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 1-(3-(4-(2-hydroxyethyl)piperazin-1-yl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)urea, methyl 3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamido)-5-(trifluoromethyl)benzoate, 3-(2-(dimethylamino)ethoxy)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(3-(dimethylamino)propoxy)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-hydroxy-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1-(6-(2-(dimethylamino)ethylamino)pyrimidin-4-yl)-3-methyl-1H-pyrazol-5-ylamino)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(1-(6-(2-(dimethylamino)ethylamino)pyrimidin-4-yl)-3-methyl-1H-pyrazol-5-ylamino)-4-methylphenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(2-morpholinoethylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 3-(1-(6-(3-hydroxypropylamino)pyrimidin-4-yl)-3-methyl-1H-pyrazol-5-ylamino)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide, 3-(difluoromethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-(difluoromethyl)-N-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)benzamide, 1-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-

pyrazol-5-ylamino)phenyl)urea, 3-(4-methyl-1H-imidazol-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide, N-(3-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(2-methyl-5-(trifluoromethyl)phenyl)benzamide, 1-(3-(1,1-difluoroethyl)phenyl)-3-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)urea, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(2-(methylsulfonyl)ethylcarbamoyl)-5-(trifluoromethyl)phenyl)benzamide, N-(3-(3-hydroxypropylcarbamoyl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-methyl-5-(trifluoromethyl)phenyl)benzamide, 1-(3-((2-methoxyethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(3-((2-(dimethylamino)ethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-(morpholinomethyl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(3-((dimethylamino)methyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)urea, 3-bromo-5-(1,1-difluoroethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, (R)-1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-((2-methylmorpholino)methyl)-1H-pyrazol-5-ylamino)phenyl)urea, tert-butyl 4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamoyl)-5-(trifluoromethyl)phenyl)piperazine-1-carboxylate, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(piperazin-1-yl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)-5-(trifluoromethyl)benzamide, 3-(4-(2-amino-2-

oxoethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(4-(2-methoxyethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(4-(3-hydroxypropyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 2-(4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamoyl)-5-(trifluoromethyl)phenyl)piperazin-1-yl)acetic acid, 3-(4-(2-(dimethylamino)-2-oxoethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(4-(2-hydroxypropyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)-5-(trifluoromethyl)benzamide, 3-(4-cyclopropylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-2-(4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamoyl)-5-(trifluoromethyl)phenyl)piperazin-1-yl)propanoic acid, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4,7-diazaspiro[2.5]octan-7-yl)-5-(trifluoromethyl)benzamide, 2-ethoxy-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-(trifluoromethyl)isonicotinamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(trifluoromethyl)-5-(3-(trifluoromethyl)piperazin-1-yl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-5-(trifluoromethyl)benzamide, tert-butyl 4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamoyl)-5-(trifluoromethyl)phenyl)-3-oxopiperazine-1-carboxylate, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(2-oxopiperazin-1-yl)-5-(trifluoromethyl)benzamide, 3-(4-methyl-2-oxopiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-

yl)-1H-pyrazol-5-ylamino)phenyl)-2-(methylamino)-6-(trifluoromethyl)isonicotinamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4-methyl-3-(trifluoromethyl)piperazin-1-yl)-5-(trifluoromethyl)benzamide, 2-(2-(dimethylamino)ethylamino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-(trifluoromethyl)isonicotinamide, 2-(2-hydroxyethylamino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-(trifluoromethyl)isonicotinamide, 3-(4-hydroxypiperidin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (*R*)-3-(4-(2-hydroxypropyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (*S*)-3-(4-(2-hydroxypropyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(3-((4-ethylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)phenyl)benzamide, N-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 3-((dimethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)benzamide, 3-((isopropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((methylamino)methyl)-5-(trifluoromethyl)benzamide, 1-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)phenyl)urea, 1-(3-((4-ethylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 3-((ethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-

(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((cyclopropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,1-difluoroethyl)-5-((isopropylamino)methyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-(1,1-difluoroethyl)-5-((isopropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((diethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(azetidin-1-ylmethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(azetidin-1-ylmethyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3-hydroxyazetidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3-hydroxypyrrolidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((2-hydroxyethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((propylamino)methyl)-5-(trifluoromethyl)benzamide, 3-(1,1-difluoroethyl)-5-((dimethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((cyclopropylamino)methyl)-5-(1,1-difluoroethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((3-hydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,1-difluoroethyl)-5-((ethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((2-methoxyethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((butylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-

(trifluoromethyl)benzamide, 3-((tert-butylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,1-difluoroethyl)-5-((4-hydroxycyclohexylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((cyclopropylamino)methyl)-5-(1,1-difluoroethyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-(aminomethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 2-((dimethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-(trifluoromethyl)isonicotinamide, 3-(((2-hydroxyethyl)(methyl)amino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,2-dihydroxyethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((1-hydroxypropan-2-ylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((1-hydroxypropan-2-ylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((2,2-dimethylhydrazinyl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((methoxyamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((hydroxyamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-((2-hydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(((tetrahydrofuran-2-yl)methylamino)methyl)-5-(trifluoromethyl)benzamide, (R)-3-((2,3-dihydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-

(trifluoromethyl)benzamide, (S)-3-((2,3-dihydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((1,3-dihydroxypropan-2-ylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((1-hydroxy-2-methylpropan-2-ylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((cyclobutylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((dimethylamino)methyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(((2-methoxyethyl)(methyl)amino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(((1S,2R)-2-hydroxycyclopentylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(((tetrahydrofuran-2-yl)methylamino)methyl)-5-(trifluoromethyl)benzamide, (R)-3-((2-hydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(morpholinomethyl)-5-(trifluoromethyl)benzamide, 3-((3-methoxyazetidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide
3-((3-methoxypyrrolidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3-hydroxyazetidin-1-yl)methyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-chloro-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((dimethylamino)methyl)-5-(trifluoromethyl)benzamide, N-(4-chloro-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((isopropylamino)methyl)-5-(trifluoromethyl)benzamide, N-(4-chloro-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(pyrrolidin-

1-ylmethyl)-5-(trifluoromethyl)benzamide, 3-((isopropylamino)methyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)benzamide, 3-(1-(ethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (*S*)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((2-methylmorpholino)methyl)-5-(trifluoromethyl)benzamide, (*R*)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((2-methylmorpholino)methyl)-5-(trifluoromethyl)benzamide, 3-((2-hydroxy-2-methylpropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(piperidin-4-yl)-5-(trifluoromethyl)benzamide, 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,2-dihydroxyethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1-hydroxyethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(3-(2-hydroxyethylamino)cyclobutyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(3-(isopropylamino)cyclobutyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (E)-3-(3-aminoprop-1-enyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (E)-3-(3-(isopropylamino)prop-1-enyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (E)-3-(3-(2-hydroxyethylamino)prop-1-enyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-

(trifluoromethyl)benzamide, 3-(3-(isopropylamino)propyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(2-(isopropylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(2-(2-hydroxyethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-(1-(ethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (*R*)-3-(1-(ethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(1-(dimethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-(1-(dimethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1-(pyrrolidin-1-yl)ethyl)-5-(trifluoromethyl)benzamide, (R)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1-(pyrrolidin-1-yl)ethyl)-5-(trifluoromethyl)benzamide, (S)-3-(1-(isopropylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(1-(isopropylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(4-(2,2-difluoroethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-chloro-5-(4-(2-methoxyethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-chloro-5-(4-(2-ethoxyethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-chloro-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(4-methylpiperazin-1-yl)benzamide, (S)-3-(4-(2-methoxyethyl)-2-methylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(4-(2-methoxyethyl)-2-methylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(2,4-dimethylpiperazin-1-yl)-

N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-(2,4-dimethylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3,3-difluoroazetidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3,3-difluoropyrrolidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(4-(2,2-difluoroethyl)-2-methylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, *rac*-3-(2-(3,3-difluoropyrrolidin-1-yl)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, *rac*-3-(2-(3,3-difluoroazetidin-1-yl)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, and 3-((2,2-difluoroethyl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide.

[0061] Further preferred compounds of the invention are detailed in the Examples and Table I, *infra*.

Pharmacology and Utility

[0062] Compounds of the invention modulate the activity of kinases and, as such, are useful for treating diseases or disorders in which kinases, contribute to the pathology and/or symptomology of the disease. Examples of kinases that are inhibited by the compounds and compositions described herein and against which the methods described herein are useful include, but are not limited to, Abl, BCR-Abl (wild-type and mutant forms), ARG, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 and TrkB.

[0063] 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. Overall, it appears that the Abl protein serves 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. BCR-Abl is critical 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 with the most common being G250E, E255V, T315I, F317L and M351T.

[0064] Compounds of the present invention inhibit abl kinase, especially v-abl kinase. The compounds of the present invention also inhibit wild-type BCR-Abl kinase and mutations of BCR-Abl kinase and are thus 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), and also shows effects on the subgroup of leukemic stem cells as well as potential 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).

[0065] Malaria is caused by protozoan parasites of the genus Plasmodium. Four species of Plasmodium can produce the disease in its various forms: Plasmodium falciparum; Plasmodium vivax; Plasmodium ovale; and Plasmodium malaria. P. falciparum, the most widespread and dangerous, can lead to fatal cerebral malaria if left untreated. Protein tyrosine kinase activity is distributed in all the stages of P. falciparum parasite maturation and kinase inhibitors of the present invention can be used for treating Plasmodium related diseases. The in vitro assay, infra, is used as a means to determine the activity of compounds of the invention against a variety of malarial parasite strains.

[0066] 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 it includes three members, A-Raf, B-Raf and c-Raf (or Raf-1). The focus on Raf being a drug target has centered on the relationship of Raf as a downstream effector of Ras. However, recent data suggests that 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 (01 Jul 2002). In particular, B-Raf mutations have been detected in a large percentage of malignant melanomas.

[0067] 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.

[0068] The compounds of the present invention also inhibit cellular processes involving c-Raf kinase. c-Raf is activated by the ras oncogene, which is mutated in a wide number of human cancers. Therefore inhibition of the kinase activity of c-Raf may provide a way to prevent ras mediated tumor growth [Campbell, S. L., Oncogene, 17, 1395 (1998)].

[0069] PDGF (Platelet-derived Growth Factor) is a very commonly occurring growth factor, which plays an important role both in normal growth and also in pathological cell proliferation, such as is seen in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis. Compounds of the invention can inhibit PDGF receptor (PDGFR) activity and are, therefore, suitable for the treatment of tumor diseases, such as gliomas, sarcomas, prostate tumors, and tumors of the colon, breast, and ovary.

[0070] Compounds of the present invention, can be used not only as a tumor-inhibiting substance, for example in small cell lung cancer, but also as an agent to treat non-malignant proliferative disorders, such as atherosclerosis, thrombosis, psoriasis, scleroderma and fibrosis, as well as for the protection of stem cells, for example to combat the hemotoxic effect of chemotherapeutic agents, such as 5-fluoruracil, and in asthma. Compounds of the invention can especially be used for the treatment of diseases, which respond to an inhibition of the PDGF receptor kinase.

[0071] Compounds of the present invention show useful effects in the treatment of disorders arising as a result of transplantation, for example, allogenic transplantation, especially tissue rejection, such as especially 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.

[0072] Compounds of the present invention are also effective in diseases associated with vascular smooth-muscle cell migration and proliferation (where PDGF and

PDGF-R 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* can 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*.

[0073] 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. TkrB is, moreover, 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).

[0074] 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.

[0075] The Tec family kinase, Bmx, a non-receptor protein-tyrosine kinase, controls the proliferation of mammary epithelial cancer cells.

[0076] 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, and 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. Inhibitors of FGFR3 activity are useful in the treatment of T-cell mediated inflammatory or autoimmune diseases including but not

limited to rheumatoid arthritis (RA), collagen II arthritis, multiple sclerosis (MS), systemic lupus erythematosus (SLE), psoriasis, juvenile onset diabetes, Sjogren's disease, thyroid disease, sarcoidosis, autoimmune uveitis, inflammatory bowel disease (Crohn's and ulcerative colitis), celiac disease and myasthenia gravis.

[0077] The activity of serum and glucocorticoid-regulated kinase (SGK), is correlated to perturbed ion-channel activities, in particular, those of sodium and/or potassium channels and compounds of the invention can be useful for treating hypertension.

[0078] Lin et al (1997) J. Clin. Invest. 100, 8: 2072-2078 and P. Lin (1998) PNAS 95,.8829-8834, have shown an inhibition of tumor growth and vascularization and also a decrease in lung metastases during adenoviral infections or during injections of the extracellular domain of Tie-2 (Tek) in breast tumor and melanoma xenograft models. Tie2 inhibitors can be used in situations where neovascularization takes place inappropriately (i.e. in diabetic retinopathy, chronic inflammation, psoriasis, Kaposi's sarcoma, chronic neovascularization due to macular degeneration, rheumatoid arthritis, infantile haemangioma and cancers).

[0079] 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.

[0080] JNKs, along with other MAPKs, have been implicated in having a role in mediating cellular response to cancer, thrombin-induced platelet aggregation, immunodeficiency disorders, autoimmune diseases, cell death, allergies, osteoporosis and heart disease. The therapeutic targets related to activation of the JNK pathway include chronic myelogenous leukemia (CML), rheumatoid arthritis, asthma, osteoarthritis, ischemia, cancer and neurodegenerative diseases. As a result of the importance of JNK activation associated with liver disease or episodes of hepatic ischemia, compounds of the invention may also be useful to treat various hepatic disorders. A role for JNK in cardiovascular disease such as myocardial infarction or congestive heart failure has also been reported as it has been shown JNK mediates hypertrophic responses to various forms of cardiac stress. It has been demonstrated that the JNK cascade also plays a role in T-cell activation, including activation of the IL-2 promoter. Thus, inhibitors of JNK may have

therapeutic value in altering pathologic immune responses. A role for JNK activation in various cancers has also been established, suggesting the potential use of JNK inhibitors in cancer. For example, constitutively activated JNK is associated with HTLV-1 mediated tumorigenesis [Oncogene 13:135-42 (1996)]. JNK may play a role in Kaposi's sarcoma (KS). Other proliferative effects of other cytokines implicated in KS proliferation, such as vascular endothelial growth factor (VEGF), IL-6 and TNFα, may also be mediated by JNK. In addition, regulation of the c-jun gene in p210 BCR-ABL transformed cells corresponds with activity of JNK, suggesting a role for JNK inhibitors in the treatment for chronic myelogenous leukemia (CML) [Blood 92:2450-60 (1998)].

[0081] Certain abnormal proliferative conditions are believed to be associated with raf expression and are, therefore, believed to be responsive to inhibition of raf expression. Abnormally high levels of expression of the raf protein are also implicated in transformation and abnormal cell proliferation. These abnormal proliferative conditions are also believed to be responsive to inhibition of raf expression. For example, expression of the c-raf protein is believed to play a role in abnormal cell proliferation since it has been reported that 60% of all lung carcinoma cell lines express unusually high levels of c-raf mRNA and protein. Further examples of abnormal proliferative conditions are hyper-proliferative disorders such as cancers, tumors, hyperplasia, pulmonary fibrosis, angiogenesis, psoriasis, atherosclerosis and smooth muscle cell proliferation in the blood vessels, such as stenosis or restenosis following angioplasty. The cellular signaling pathway of which raf is a part has also been implicated in inflammatory disorders characterized by T-cell proliferation (T-cell activation and growth), such as tissue graft rejection, endotoxin shock, and glomerular nephritis, for example.

[0082] The stress activated protein kinases (SAPKs) 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. Therefore, agents that inhibit SAPK activity in a cell prevent DNA repair and sensitize the cell to agents that induce DNA damage or inhibit DNA synthesis and induce apoptosis of a cell or that inhibit cell proliferation.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] BTK plays a role in autoimmune and/or inflammatory disease such as systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, and asthma.. Because of BTK's role in B-cell activation, inhibitors of BTK are useful as inhibitors of B-cell mediated pathogenic

activity, such as autoantibody production, and are useful for the treatment of B-cell lymphoma and leukemia.

[0087] CHK2 is a member of the checkpoint kinase family of serine/threonine protein kinases and is involved in a mechanism used for surveillance of DNA damage, such as damage caused by environmental mutagens and endogenous reactive oxygen species. As a result, it is implicated as a tumor suppressor and target for cancer therapy.

[0088] CSK influences the metastatic potential of cancer cells, particularly colon cancer.

[0089] Fes is a non-receptor protein tyrosine kinase that has been implicated in a variety of cytokine signal transduction pathways, as well as differentiation of myeloid cells. Fes is also a key component of the granulocyte differentiation machinery.

[0090] Flt3 receptor tyrosine kinase activity is implicated in leukemias and myelodysplastic syndrome. In approximately 25% of AML the leukemia cells express a constitutively active form of auto-phosphorylated (p) FLT3 tyrosine kinase on the cell surface. The activity of p-FLT3 confers growth and survival advantage on the leukemic cells. Patients with acute leukemia, whose leukemia cells express p-FLT3 kinase activity, have a poor overall clinical outcome. Inhibition of p-FLT3 kinase activity induces apoptosis (programmed cell death) of the leukemic cells.

[0091] Inhibitors of IKKα and IKKβ (1 & 2) are therapeutics for diseases which include rheumatoid arthritis, transplant rejection, inflammatory bowel disease, osteoarthritis, asthma, chronic obstructive pulmonary disease, atherosclerosis, psoriasis, multiple sclerosis, stroke, systemic lupus erythematosus, Alzheimer's disease, brain ischemia, traumatic brain injury, Parkinson's disease, amyotrophic lateral sclerosis, subarachnoid hemorrhage or other diseases or disorders associated with excessive production of inflammatory mediators in the brain and central nervous system.

[0092] Met is associated with most types of the major human cancers and expression is often correlated with poor prognosis and metastasis. Inhibitors of Met are therapeutics for diseases which include cancers such as lung cancer, NSCLC (non small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e. g.,

uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e. g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e. g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (e. g., primary CNS lymphoma, spinal axis tumors, brain stem glioma or pituitary adenomas), cancers of the blood such as acute myeloid leukemia, chronic myeloid leukemia, etc, Barrett's esophagus (pre-malignant syndrome) neoplastic cutaneous disease, psoriasis, mycoses fungoides and benign prostatic hypertrophy, diabetes related diseases such as diabetic retinopathy, retinal ischemia and retinal neovascularization, hepatic cirrhosis, cardiovascular disease such as atherosclerosis, immunological disease such as autoimmune disease and renal disease. Preferably, the disease is cancer such as acute myeloid leukemia and colorectal cancer.

[0093] The Nima-related kinase 2 (Nek2) is a cell cycle-regulated protein kinase with maximal activity at the onset of mitosis that localizes to the centrosome. Functional studies have implicated Nek2 in regulation of centrosome separation and spindle formation. Nek2 protein is elevated 2- to 5-fold in cell lines derived from a range of human tumors including those of cervical, ovarian, prostate, and particularly breast.

[0094] p70S6K-mediated diseases or conditions include, but are not limited to, proliferative disorders, such as cancer and tuberous sclerosis.

[0095] In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of Formula I or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Administration and Pharmaceutical Compositions

[0096] 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 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, 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 50mg active ingredient.

[0097] Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Suitable formulations for transdermal applications

include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. 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. Matrix transdermal formulations may also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0098] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations). For example, synergistic effects can occur with other immunomodulatory or anti-inflammatory substances, for example when used in combination with cyclosporin, rapamycin, or ascomycin, or immunosuppressant analogues thereof, for example cyclosporin A (CsA), cyclosporin G, FK-506, rapamycin, or comparable compounds, corticosteroids, cyclophosphamide, azathioprine, methotrexate, brequinar, leflunomide, mizoribine, mycophenolic acid, mycophenolate mofetil, 15-deoxyspergualin, immunosuppressant antibodies, especially monoclonal antibodies for leukocyte receptors, for example MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, CD58 or their ligands, or other immunomodulatory compounds, such as CTLA41g. Where the compounds of the invention are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

[0099] The invention also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

[00100] The terms "co-administration" or "combined administration" or the like as utilized 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.

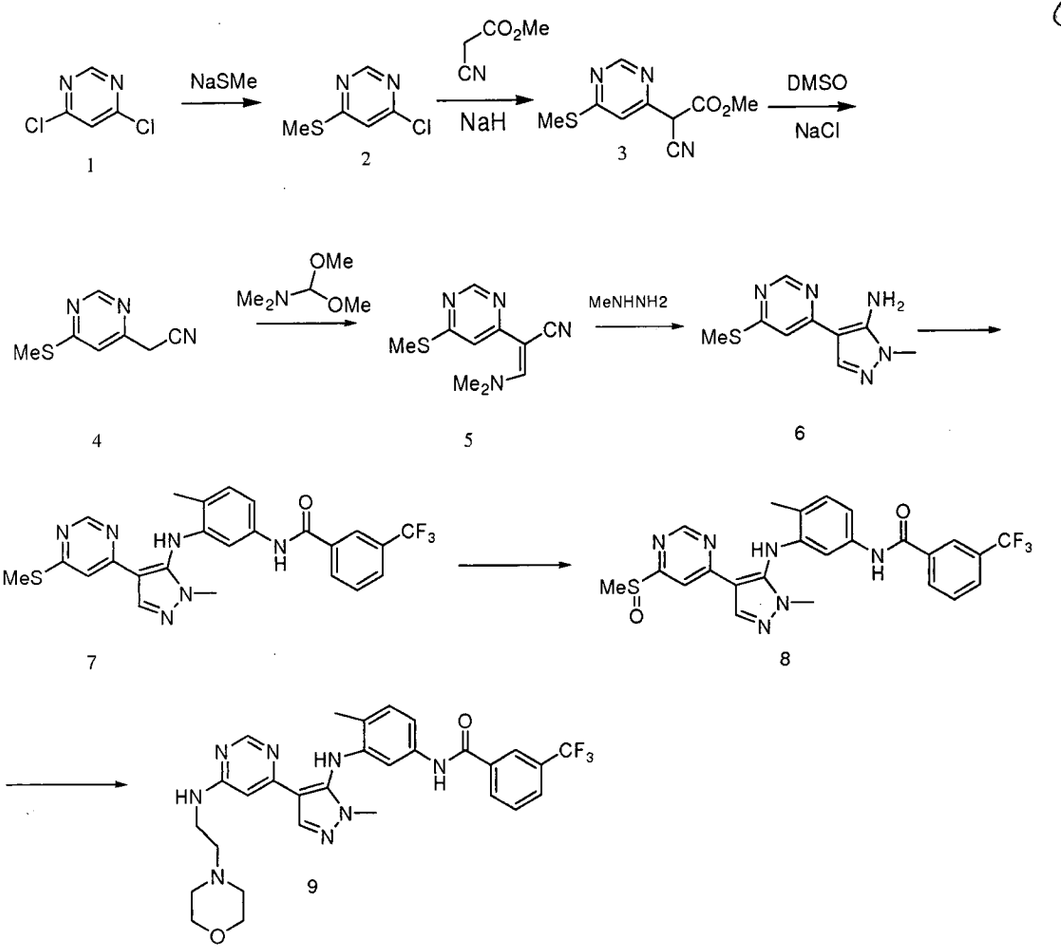
[00101] The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a 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 I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Processes for Making Compounds of the Invention

[00102] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, 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.

[00103] Compounds of Formula I can be prepared by proceeding as in the following Reaction Schemes I - V:

Reactions Scheme I

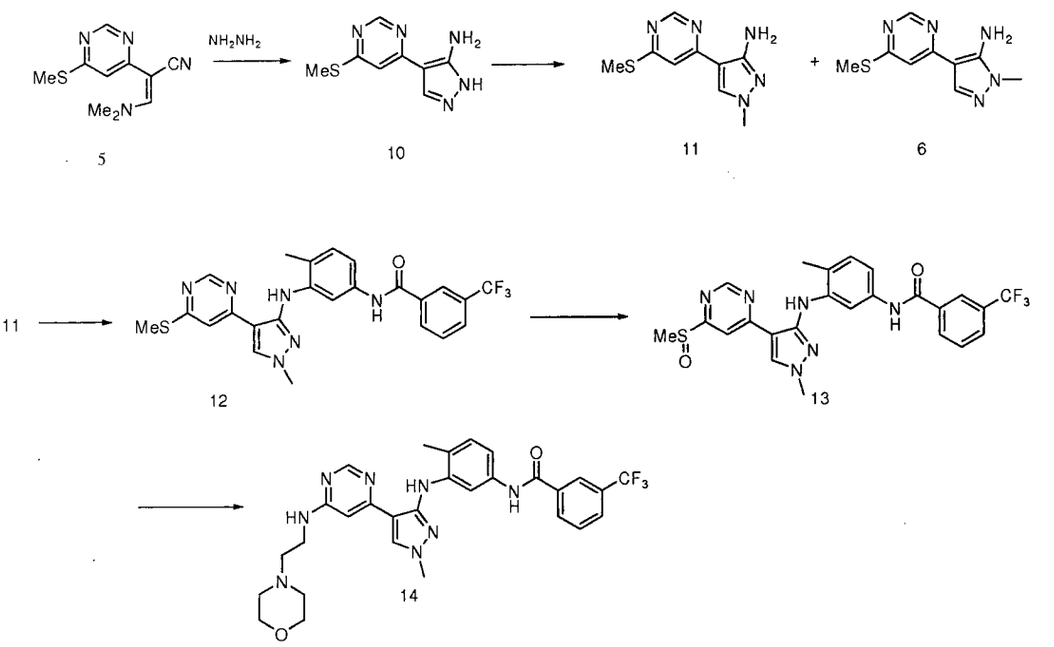


[00104] A compound of Formula 2 can be prepared by reacting of a compound of formula 1 with NaSMe in the presence of a suitable solvent (e.g., THF). A compound of formula 3 can be prepared by reacting of a compound of formula 2 and methyl cyanoacetate in the presence of a solvent (e.g., DMSO, DMF and the like) using an appropriate base (e.g., sodium hydride (NaH)).

[00105] A compound of formula 4 can be prepared by decarboxylation of a compound of formula 3 with NaCl in a suitable solvent (e.g., a mixture of DMSO and water) and in a temperature range of about 120 to about 180°C can take up to 4 hours to complete. A compound of formula 4 can be converted to give a compound of formula 5 with a suitable eneamine formation reagent (e.g., N,N-dimethylformamide dimethyl acetal) and can take up to 24 hours to complete. The reaction of the resulting eneamine 5 with an appropriate hydrazine affords a compound of formula 6. A compound of formula 7 can be prepared by

reacting a compound of formula 6 with an appropriate halide (e.g., N-(3-bromo-4-methyl-phenyl)-3-trifluoromethyl-benzamide). The reaction proceeds in the presence of a suitable catalyst (e.g., Pd (II) salt, or the like), a suitable ligand (e.g., Xantphos, or the like) and a suitable solvent (e.g., 1,4-dioxane, or the like), in a temperature range of about 80 to about 150°C and can take up to about 20 hours to complete. A compound of formula 7 can be further oxidized to give a compound of formula 8 with a suitable oxidizing agent (e.g., *m*-chloroperoxybenzoic acid (mCPBA), or the like) and can take up to 6 hours to complete. A compound of formula 9 can be prepared by reacting a compound of formula 8 with an appropriate amine or aniline. The reaction is carried out in a temperature range of 100-150°C and can take up to 10 hours to complete. The reaction conditions for alkyl amine displacement involves heating a compound of formula 9 with 5-10 equivalents of amine in a suitable solvent (e.g. DMSO, DMF, or the like).

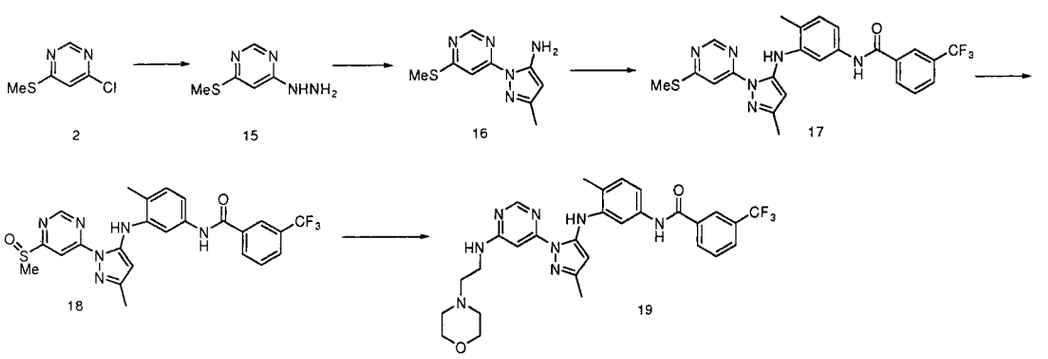
Reactions Scheme II



[00106] The reaction of the eneamine 5 with a hydrazine affords a compound of formula 10. A compound of formula 11 can be prepared by reacting of a compound of formula 10 with alkylating reagents (e.g., methyl iodide) in the presence of a solvent (e.g., DMSO, DMF and the like) using an appropriate base (e.g., sodium hydride (NaH)).

[00107] A compound of formula 12 can be prepared by reacting a compound of formula 11 with an appropriate halide (e.g., N-(3-bromo-4-methyl-phenyl)-3-trifluoromethyl-benzamide). The reaction proceeds in the presence of a suitable catalyst (e.g., Pd (II) salt, or the like), a suitable ligand (e.g., Xantphos, or the like) and a suitable solvent (e.g., 1,4-dioxane, or the like), in a temperature range of about 80 to about 150°C and can take up to about 20 hours to complete. A compound of formula 12 can be further oxidized to give a compounds of formula 13 with a suitable oxidizing agent (e.g., *m*-chloroperoxybenzoic acid (mCPBA), or the like) and can take up to 6 hours to complete. A compound of formula 14 can be prepared by reacting a compound of formula 13 with an appropriate amine or aniline. The reaction is carried out in a temperature range of 100-150°C and can take up to 10 hours to complete. The reaction conditions for alkyl amine displacement involves heating a compound of formula 13 with 5-10 equivalents of amine in a suitable solvent (e.g. DMSO, DMF, or the like).

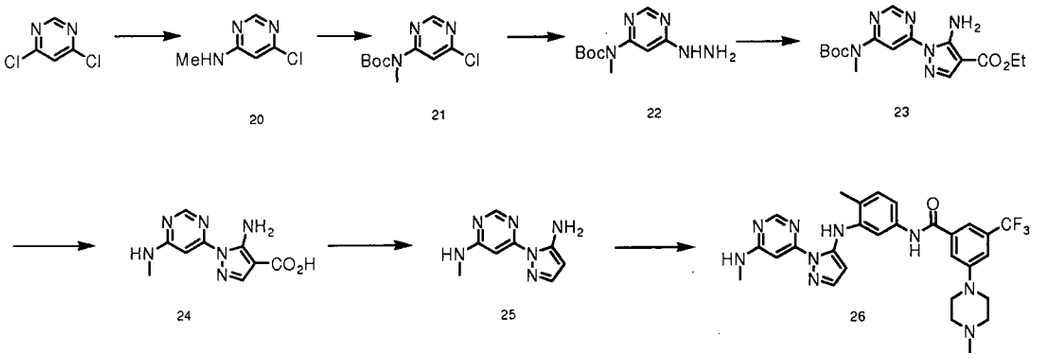
Reactions Scheme III



[00108] A compound of formula 15 can be prepared by reacting of a compound of formula 2 and hydrazine in the presence of a solvent (e.g., ethanol, DMSO, DMF and the like). Cyclization of a compound of formula 15 with an appropriate nitrile (e.g. 3-aminocrotononitrile) affords a compound of formula 16. A compound of formula 17 can be prepared by reacting a compound of formula 16 with an appropriate halide (e.g., N-(3-bromo-4-methyl-phenyl)-3-trifluoromethyl-benzamide). The reaction proceeds in the presence of a suitable catalyst (e.g., Pd (II) salt, or the like), a suitable ligand (e.g., Xantphos, or the like) and a suitable solvent (e.g., 1,4-dioxane, or the like), in a temperature range of about 80 to about 150°C and can take up to about 20 hours to complete. A compound of

formula 17 can be further oxidized to give a compound of formula 18 with a suitable oxidizing agent (e.g., *m*-chloroperoxybenzoic acid (mCPBA), or the like) and can take up to 6 hours to complete. A compound of formula 19 can be prepared by reacting a compound of formula 18 with an appropriate amine or aniline. The reaction is carried out in a temperature range of 100-150°C and can take up to 10 hours to complete. The reaction conditions for alkyl amine displacement involves heating a compound of formula 18 with 5-10 equivalents of amine in a suitable solvent (e.g. DMSO, DMF, or the like).

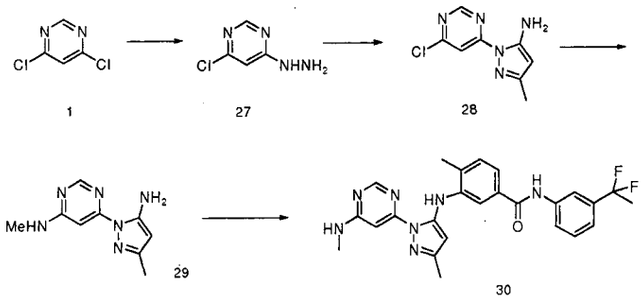
Reactions Scheme IV



[00109] A compound of Formula 20 can be prepared by reacting of 4,6-dichloro pyrimidine with an appropriate amine (e.g. methyl amine) in the presence of a suitable solvent (e.g., ethanol, THF and the like). A compound of formula 21 can be prepared by reacting of a compound of formula 20 and Boc_2O in the presence of a solvent (e.g., THF, DCM and the like) using an appropriate base (e.g.,DMAP). A compound of formula 22 can be prepared by reacting of a compound of formula 21 and hydrazine in the presence of a solvent (e.g., ethanol, THF, DMF and the like). Cyclization of a compound of formula 22 with an appropriate nitrile (e.g. ethyl(ethoxymethylene)cyanoacetate) affords a compound of formula 23. Cyclization of a compound of formula 22 with an appropriate nitrile (e.g. ethyl(ethoxymethylene)cyanoacetate) affords a compound of formula 23. Hydrolysis of compound of formula 23 with an appropriate base (e.g. NaOH) affords a compound of formula 24. A compound of formula 25 can be prepared by decarboxylation of a compound of formula 24 in a temperature range of about 150 to about 180°C can take up to 4 hours to complete. A Compound of formula 26 can be prepared by reacting a compound of formula 25 with an appropriate halide (e.g., N-(3-bromo-4-methyl-phenyl)-3-(4-methyl-piperazin-1-

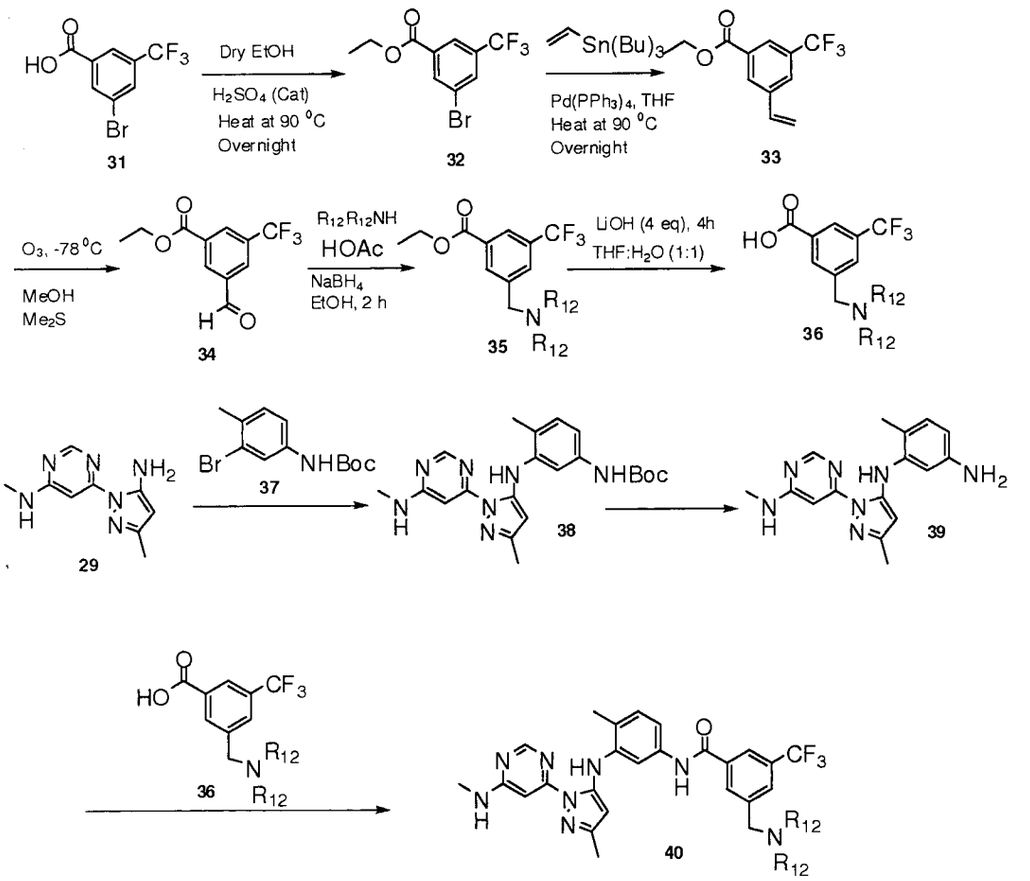
yl)-5-trifluoromethyl-benzamide). The reaction proceeds in the presence of a suitable catalyst (e.g., Pd (II) salt, or the like), a suitable ligand (e.g., Xantphos, or the like) and a suitable solvent (e.g., 1,4-dioxane, or the like), in a temperature range of about 80 to about 150°C and can take up to about 20 hours to complete.

Reactions Scheme V



[00110] A compound of formula 27 can be prepared by reacting of a compound of formula 1 and hydrazine in the presence of a solvent (e.g., ethanol, DMSO, DMF and the like). Cyclization of a compound of formula 27 with an appropriate nitrile (e.g. 3-aminocrotononitrile) affords a compound of formula 28. A compound of formula 29 can be prepared by reacting a compound of formula 28 with an appropriate amine. The reaction is carried out in a temperature range of 50-100°C and can take up to 10 hours to complete. A compound of formula 30 can be prepared by reacting a compound of formula 29 with an appropriate halide (e.g., N-[3-(1,1-difluoro-ethyl)-phenyl]-3-iodo-4-methyl-benzamide). The reaction proceeds in the presence of a suitable catalyst (e.g., Pd (II) salt, or the like), a suitable ligand (e.g., Xantphos, or the like) and a suitable solvent (e.g., 1,4-dioxane, or the like), in a temperature range of about 80 to about 150°C and can take up to about 20 hours to complete.

Reactions Scheme VI



[00111] In which R_{12} is as defined in the Summary of the Invention. A compound of formula 33 can be prepared by reacting of a compound of formula 32 and trialkyyl(vinyl)stannane in the presence of a suitable catalyst (e.g., Pd(0) complex or Pd (II) salt, or the like), a suitable phosphor-ligand (or the like), and a solvent (e.g., 1,4-dioxane, THF or the like). Cleavage of the vinyl group using conditions well known in the fields (Ozonolysis, $OsO_4/NaIO_4$, or the like) provides compound of formula 34. Reductive amination using primary or secondary amines in the presence of a reducing reagent ($NaBH_4$, $Na(OAc)_3BH$, $Na(CN)BH_3$, or the like) and suitable solvent (ethanol, 1,2-dichloroethane, DMF, or the like) affords compound of formula 35. Saponification of compound of formula 35 then gives the carboxylic acid of formula 36. Reacting of compound of formula 29 with compound of formula 37 in the presence of a suitable catalyst (e.g., Pd (II) salt, or the like), a suitable ligand (e.g., Xantphos, or the like) and a suitable solvent (e.g., 1,4-dioxane, or the like), in a temperature range of about 80 to about 150°C, provides compound of formula 38.

De-protection of the Boc group under acidic conditions such as trifluoroacetic acid /DCM affords compound of formula 39. Amide bond formation between carboxylic acid of formula 36 and the amine of formula 39 under the standard peptide coupling reaction conditions (HATU/DIEA, EDCI/HOBT, or the like) yields compound of formula 40.

[00112] A detailed example of the synthesis of a compound of formula I can be found in the Examples, *infra*.

Additional Processes for Making Compounds of the Invention

[00113] A compound of the invention can 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 can 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 can be prepared using salts of the starting materials or intermediates.

[00114] The free acid or free base forms of the compounds of the invention can 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 can 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 can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

[00115] Compounds of the invention in unoxidized form can 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.

[00116] Prodrug derivatives of the compounds of the invention can 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 can 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).

[00117] Protected derivatives of the compounds of the invention can 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.

[00118] Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[00119] Compounds of the invention can 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. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, 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.

[00120] In summary, the compounds of Formula I can be made by a process, which involves:

(a) those of reaction schemes I to V, 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.

[00121] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

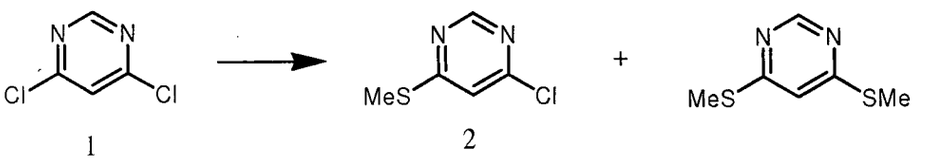
[00122] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

[00123] The present invention is further exemplified, but not limited, by the following examples that illustrate the preparation of compounds of Formula I according to the invention.

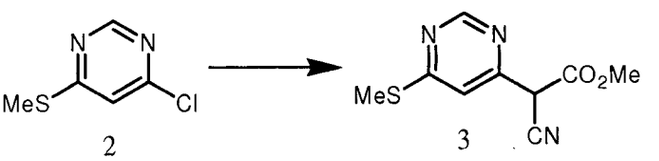
Example 1

N-(4-Methyl-3-{2-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide



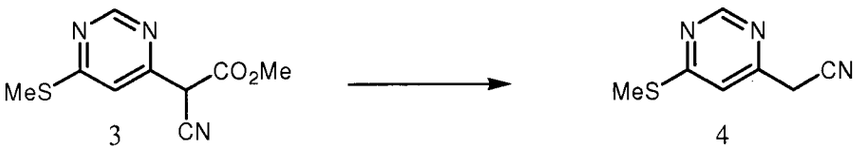
1 2

[00124] A mixture of 4,6-dichrolo-pyrimidine 1 (20.93 g, 140 mmol), sodium thiomethoxide (10.34 g, 147 mmol) in THF (100 mL) is stirred at room temperature, overnight. The reaction mixture is concentrated. The residue is partitioned between ethyl acetate and brine. The organic layer is separated and washed with brine, dried over Na_2SO_4. The crude product is purified by recrystallization from hexanes (60 mL) to afford 4-chloro-6-methylsulfanyl-pyrimidine. The mother liquor is concentrated and the residue is purified by silica gel flash chromatography eluting with ethyl acetate in hexanes from 0% to 10% to give 4-chloro-6-methylsulfanyl-pyrimidinecontaining and a small amount of byproduct 4,6-bis methylthio-pyrimidine, which is easily removed in the next step. ^{1}H NMR 400 MHz ($CDCl_3$) δ 8.72 (*s*, 1H), 7.21 (*s*, 1H), 2.58 (*s*, 3H).

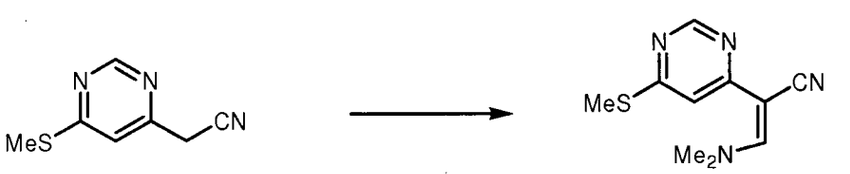


2 3

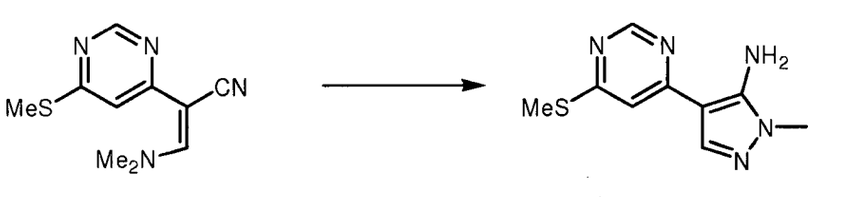
[00125] To the suspension of NaH (2.19 g, 55 mmol, 60% in oil) in DMSO (20 mL) is added methyl cyanoacetate (4.88 mL, 51 mmol) at 23°C (cooled by ice-water if necessary). After the evolution of hydrogen has ceased, 4-chloro-6-methylsulfanyl-pyrimidine (3.56 g, 22 mmol) is added. The reaction is heated at 80°C for 5 hours. The reaction mixture is then cooled to room temperature and quenched with ice-cooled saturated NH_4Cl (50 mL). The solid is filtered and washed with water. 100 mL of hexanes is added to the solid and heated at 60°C for 1 hour and then cooled to room temperature. The solid is filtered and washed with hexanes to afford cyano-(6-methylsulfanyl-pyrimidin-4-yl)-acetic acid methyl ester. ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.42 (*d*, 1H), 6.64 (*s*, 1H), 3.71 (*s*, 3H), 2.55 (*s*, 3H). MS *m/z* 224.10 (M + 1).



[00126] A Smith vial (10-20 mL) is charged with cyano-(6-methylsulfanyl-pyrimidin-4-yl)-acetic acid methyl ester (0.83 g, 3.72 mmol), NaCl (1.0 g), water (1mL) and DMSO. The vial is sealed and irradiated at 160°C for 50 minutes in Smith Synthesizer. The reaction mixture is partitioned between ethyl acetate and brine, and then filtered through a pad of celite and washed with ethyl acetate. The organic layer is separated and washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by silica gel flash chromatography eluting with ethyl acetate in hexanes from 10% to 100% to afford (6-methylsulfanyl-pyrimidin-4-yl)-acetonitrile: ^1H NMR 400 MHz ($CDCl_3$) δ 8.93 (*s*, 1H), 7.47 (*s*, 1H), 4.20 (*s*, 2H), 2.56 (*s*, 3H); MS *m/z* 166.00 (M + 1).

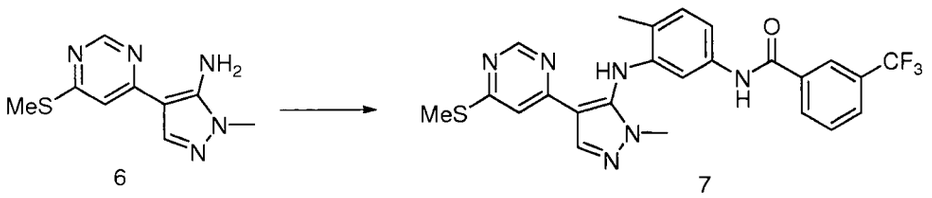


[00127] *tert*-butoxy-bis (dimethylamino)methane (0.60 mL, 2.9 mmol.) is added to a mixture of (6-methylsulfanyl-pyrimidin-4-yl)-acetonitrile (0.397 g, 2.4 mmol) in DMF (10 mL) at 0°C. After 2 hours, the reaction mixture is concentrated, and the residue is used for next reaction without further purification.



[00128] A mixture of crude 5 and methyl hydrazine (0.414 mL, 8.53 mmol) in ethanol (15 ml) is heated at 80°C for 16 hours. The reaction mixture is cooled to room temperature and concentrated. The reaction mixture is partitioned between ethyl acetate and brine. The organic layer is separated and washed with brine, dried over Na_2SO_4, filtered and

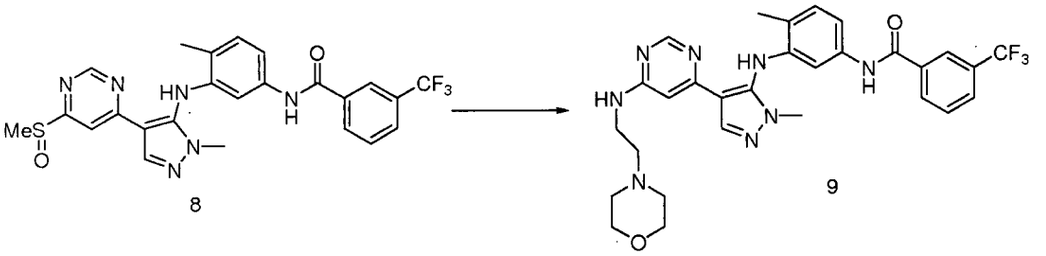
concentrated. The crude product is purified by silica gel flash chromatography eluting with ethyl acetate in hexanes from 10% to 100% to afford 2-methyl-4-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamine: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.70 (*s*, 1H), 7.93 (*s*, 1H), 7.43 (*s*, 1H), 6.69 (*s*, *br* 2H), 3.57 (*s*, 3H), 2.53 (*s*, 3H); MS *m/z* 222.00 (M + 1).



[00129] 2-Methyl-4-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamine (120mg, 0.54mmol) is mixed with N-(3-Bromo-4-methyl-phenyl)-3-trifluoromethyl-benzamide (290mg, 0.81mmol), palladium acetate (25mg, 0.1mmol), Xantophos (100mg, 0.17mmol) and cesium carbonate (530mg, 1.63mmol). 10 mL of anhydrous 1,4-dioxane is added under a nitrogen environment and the mixture is subjected to microwave irradiation to 150°C for one hour. The reaction mixture is then cooled to room temperature, treated with 100 mL THF, passed through a celite column and concentrated. The crude product is purified by ISCO chromatography eluting with ethyl acetate in hexanes from 10% to 100% to afford N-{4-Methyl-3-[2-methyl-4-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide: MS *m/z* 499.1 (M + 1).

[00130] A suspension of N-{4-Methyl-3-[2-methyl-4-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide (175mg, 0.35 mmol) in 40mL CH_2Cl_2 is treated with 3-choloroperoxybenzoic acid (77% max, 150mg, 0.67mmol, 1.9eq) at 0°C. The reaction mixture is allowed to warm to room temperature with stirring for 3 hours. After oxidation is complete, the reaction mixture is quenched with saturated sodium thiosulfate solution 15mL and vigorously stirred for 30 minutes, then treated with

100mL dichloromethane. The reaction mixture is partitioned between dichloromethane and the aqueous layer. The organic layer is washed with saturated $NaHCO_3$ solution, water, and brine sequentially, then dried over Na_2SO_4, concentrated to give N-{3-[4-(6-Methanesulfinyl-pyrimidin-4-yl)-2-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide as yellow solid. The crude product is used directly in the next step: MS *m/z* 515.1 (M + 1).

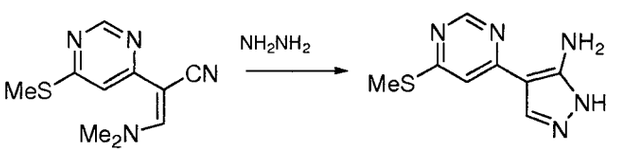


8 9

[00131] The mixture of N-{3-[4-(6-Methanesulfinyl-pyrimidin-4-yl)-2-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide (40mg, 0.078mmol) and 2-Morpholin-4-yl-ethylamine (100μL) in 2-propanol is heated to 80 ^{o}C for 3 hours. The reaction mixture is cooled to room temperature and concentrated. The crude product is then treated with 1mL DMSO and purified by LC/MS to afford N-(4-Methyl-3-{2-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide.

Example 2

N-(4-Methyl-3-{1-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide

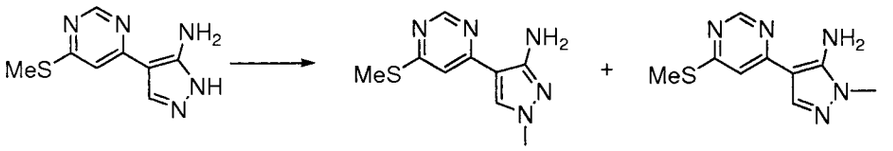


5 10

[00132] *Tert*-butoxybis(dimethylamino)methane (0.665 mL, 3.22 mmol.) is added to a mixture of (6-methylsulfanyl-pyrimidin-4-yl)-acetonitrile (0.484 g, 2.93 mmol) in DMF

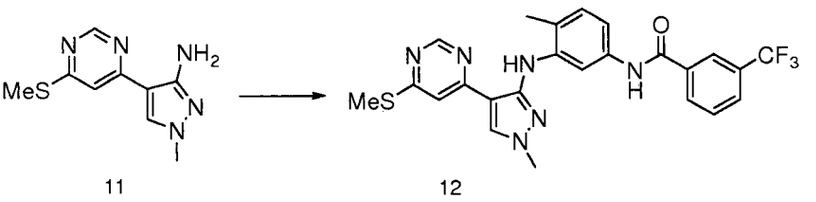
(10 mL) 0°C. After 2 hours, the reaction mixture is concentrated, and the residue is used for the next reaction without further purification.

[00133] A mixture of the above crude mixture and hydrazine monohydrate (0.426 mL, 8.78 mmol) in ethanol (15 ml) is heated at 80°C for 3 hours. The reaction mixture is cooled to room temperature and concentrated. The reaction mixture is partitioned between ethyl acetate and brine. The organic layer is separated and washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by silica gel flash chromatography eluting with ethyl acetate in hexanes from 10% to 100% to afford 2-methyl-4-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamine: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.70 (*s*, 1H), 7.92 (*bs*, 1H), 7.44 (*bs*, 1H), 6.45 (*bs*, 2H), 5.78 (*bs*, 1H), 2.53 (*s*, 3H); MS *m/z* 208.06 (M + 1).



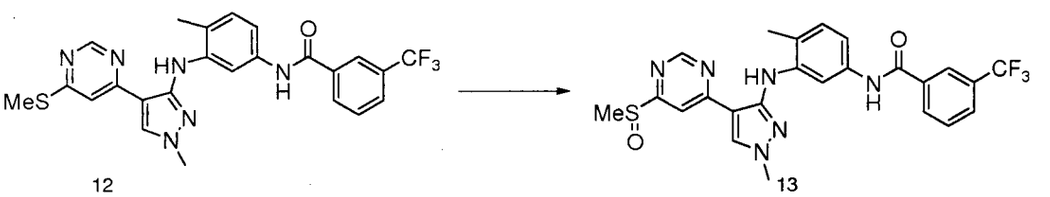
10 11

[00134] To the solution of 4-(6-Methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamine (245mg, 1.18 mmol) is added with NaOMe solution (25 wt% in MeOH, 425 μL, 1.53 mmol) dropwise. The reaction mixture is kept stirring for 30 minutes. Then Iodomethane (110uL, 1.76 mmol) is added into the reaction mixture drop wise. After stirring overnight at room temperature, the reaction mixture is concentrated, treated with 75 mL ethyl acetate, and washed with water. Filtration removes the undissolved solid. The obtained filtrate is separated, and the collected organic layer is dried over sodium sulfate, and concentrated. The crude product is purified by ISCO chromatography eluting with ethyl acetate in hexanes from 25% to 100% to afford 1-Methyl-4-(6-methylsulfanyl-pyrimidin-4-yl)-1H-pyrazol-3-ylamine: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.73 (*s*, 1H), 8.27 (*s*, 1H), 7.44 (*s*, 1H), 5.81 (*s*, 1H), 3.65 (*s*, 3H), 2.53 (*s*, 3H); MS *m/z* 222.07 (M + 1).



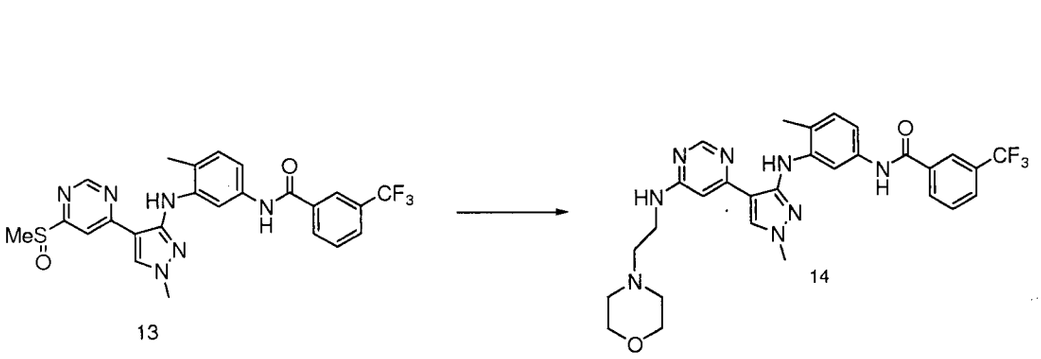
11 12

[00135] Methyl-4-(6-methylsulfanyl-pyrimidin-4-yl)-1H-pyrazol-3-ylamine (61mg, 0.27mmol) is mixed with N-(3-Bromo-4-methyl-phenyl)-3-trifluoromethyl-benzamide (161mg, 0.45mmol), palladium acetate (20mg, 0.089mmol), Xantophos (78mg, 0.135mmol) and cesium carbonate (280mg, 0.86mmol). 2 mL anhydrous 1,4-dioxane is added under nitrogen environment and the mixture is subjected to microwave irradiation to 150°C for 45 minutes. The reaction mixture is then cooled to room temperature, treated with 100 mL THF, passed through a celite column and concentrated. The crude product is purified by ISCO chromatography eluting with ethyl acetate in hexanes from 10% to 100% to afford N-{4-Methyl-3-[1-methyl-4-(6-methylsulfanyl-pyrimidin-4-yl)-1H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide.



12 13

[00136] To the suspension of N-{4-Methyl-3-[1-methyl-4-(6-methylsulfanyl-pyrimidin-4-yl)-1H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide (128mg, 0.26 mmol) in 25 mL CH_2Cl_2 is treated with 3-choloroperoxybenzoic acid (77% max, 86mg, 0.38mmol) at 0 °C. The reaction mixture is allowed to warm to room temperature and kept stirring for 3 hours. After oxidation is complete, the reaction mixture is quenched with saturated sodium thiosulfate solution 10 mL and vigorously stirred for 30 minutes, then treated with 75 mL dichloromethane. The reaction mixture is partitioned between dichloromethane and aqueous layer. The organic layer is washed with saturated $NaHCO_3$ solution, water, and brine sequentially, then dried over Na_2SO_4, concentrated to give N-{3-[4-(6-Methanesulfinyl-pyrimidin-4-yl)-1-methyl-1H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide as yellow solid. The crude product is directly used in the next step.

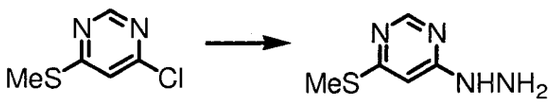


13 14

[00137] The mixture of N-{3-[4-(6-Methanesulfinyl-pyrimidin-4-yl)-1-methyl-1H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide (30mg, 0.058 mmol) and 2-Morpholin-4-yl-ethylamine (100uL) in 2-propanol is heated to 80 °C for 3 hours. The reaction mixture is cooled to room temperature and condensed. The crude product is then treated with 1mL DMSO and purified by LC/MS to afford N-(4-Methyl-3-{1-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide.

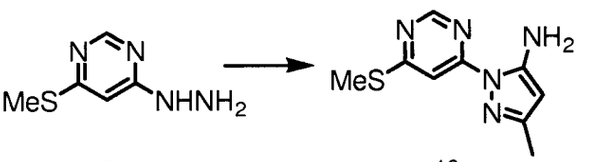
Example 3

N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide



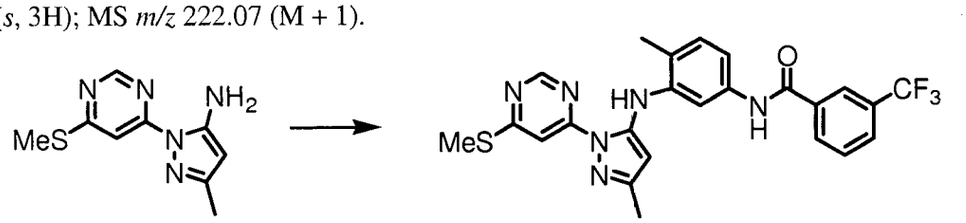
2 15

[00138] A mixture of 4-Chloro-6-methylsulfanyl-pyrimidine (1.1g, 6.85mmol), hydrazine monohydrate (1.2g, 23.5mmol), and 2-propanol (10mL) is heated to 90 °C for 4 hours. The reaction mixture is then cooled to room temperature, concentrated, triturated with water, and filtered. The undissolved solid is washed with water, air-dried to give (6-Methylsulfanyl-pyrimidin-4-yl)-hydrazine as light yellow solid: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.29 (*s*, 1H), 8.16 (*s*, 1H), 6.55 (*s*, 1H), 4.34 (*s*, 2H), 2.43 (*s*, 3H); MS *m/z* 157.05 (M + 1).

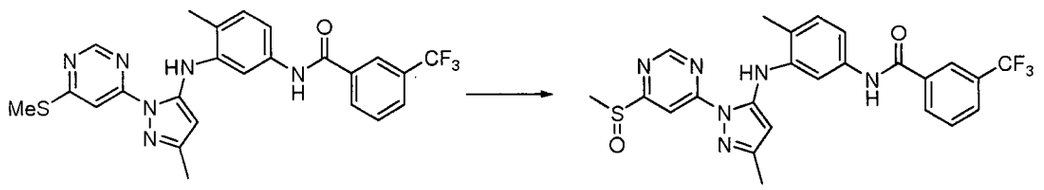


15 16

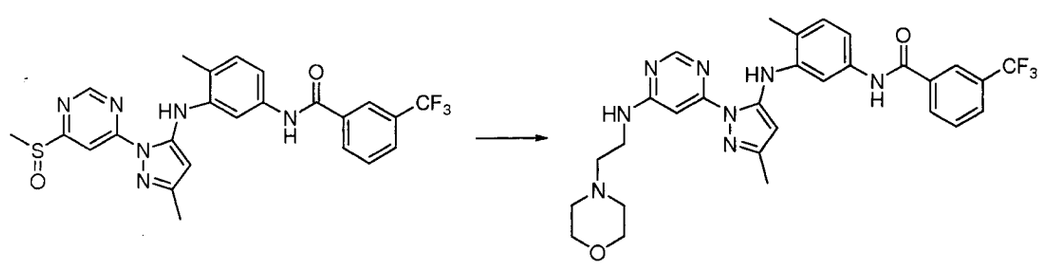
[00139] The mixture of (6-Methylsulfanyl-pyrimidin-4-yl)-hydrazine (1.0g, 6.4 mmol), 3-Imino-butyronitrile (1.1g, 12.8 mmol), and ethanol (30mL) is heated to 85°C for overnight. The reaction mixture is then cooled to room temperature, condensed, and treated with 75mL ethyl acetate. The reaction mixture is partitioned between ethyl acetate and aqueous layer. The organic layer is dried over Na_2SO_4 and concentrated. The crude product is purified by ISCO chromatography eluting with ethyl acetate in hexanes from 10% to 80% to afford 5-Methyl-2-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamine: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.72 (*s*, 1H), 7.53 (*s*, 1H), 6.90 (*s*, 1H), 5.26 (*s*, 1H), 2.57(*s*, 3H), 2.08(*s*, 3H); MS *m/z* 222.07 (M + 1).



[00140] 5-Methyl-2-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamine (90mg, 0.40mmol) is mixed with N-(3-Bromo-4-methyl-phenyl)-3-trifluoromethyl-benzamide (228mg, 0.64mmol), palladium acetate (20mg, 0.089mmol), Xantophos (75mg, 0.13mmol) and cesium carbonate (420mg, 1.28mmol). 4 mL anhydrous 1,4-dioxane is added under a nitrogen environment and the mixture is subjected to microwave irradiation to 150°C for 30 minutes. The reaction mixture is then cooled to room temperature, treated with 100 mL THF, passed through a celite column and concentrated. The crude product is purified by ISCO chromatography eluting with ethyl acetate in hexanes from 0% to 40% to afford N-{4-Methyl-3-[5-methyl-2-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 10.65 (*s*, 1H), 10.46 (*s*, 1H), 8.89 (*s*, 1H), 8.30-8.25 (*m*, 2H), 7.98 (*d*, *J* = 7.5 Hz, 1H), 7.89 (*s*, 1H), 7.80 (*t*, *J* = 7.5 Hz, 1H), 7.67 (*s*, 1H), 7.40 (*d*, *J* = 7.5 Hz, 1H), 7.25 (*d*, *J* = 8.2 Hz, 1H), 6.12 (*s*, 1H), 2.61 (*s*, 3H), 2.34 (*s*, 3H), 2.25 (*s*, 3H); MS *m/z* 499.14 (M + 1).



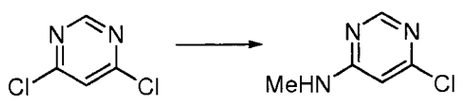
[00141] To the suspension of N-{4-Methyl-3-[5-methyl-2-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide (240mg, 0.48mmol) in 25 mL CH_2Cl_2 is treated with 3-choloroperoxybenzoic acid (77% max, 162mg, 0.72mmol, 1.5 eq) at 0°C. The reaction mixture is allowed to warm to room temperature with stirring for 3 hours. After oxidation is complete, the reaction mixture is quenched with saturated sodium thiosulfate solution 10 mL and vigorously stirred for 30 minutes, then treated with 75 mL dichloromethane. The reaction mixture is partitioned between dichloromethane and aqueous layer. The organic layer is washed with saturated $NaHCO_3$ solution, water, and brine sequentially, then dried over Na_2SO_4, concentrated to give N-{3-[2-(6-Methanesulfinyl-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide as a green solid. The crude product is directly used in the next step. MS *m/z* 515.1 (M + 1).



[00142] The mixture of N-{3-[2-(6-Methanesulfinyl-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide (20mg, 0.04mmol) and 2-Morpholin-4-yl-ethylamine (100uL) in 2-propanol is heated to 80 °C for 3 hours. The reaction mixture is cooled to room temperature and condensed. The crude product is then treated with 1mL DMSO and purified by LC/MS to afford N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide.

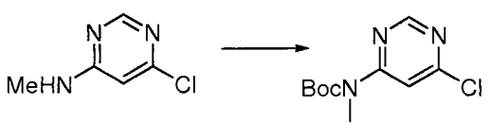
Example 4

N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide



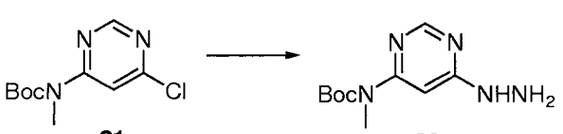
20

[00143] A mixture of 4,6-dichloro-pyrimidine(3.53g, 23.7mmol) and methylamine (33wt % in ethanol, 10ml, 80mmol) in ethanol is kept stirring overnight at room temperature. The reaction mixture is concentrated, triturated with water and filtered. The crude product is washed with water, a small amount of ethanol and ethyl ether sequentially, and air-dried to give (6-Chloro-pyrimidin-4-yl)-methyl-amine as white powder: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.36-8.16 (*m*, 1H), 7.69 (*s*, 1H), 6.50 (*s*, 1H), 2.90-2.68 (*m*, 3H); MS *m/z* 144.00 (M + 1).



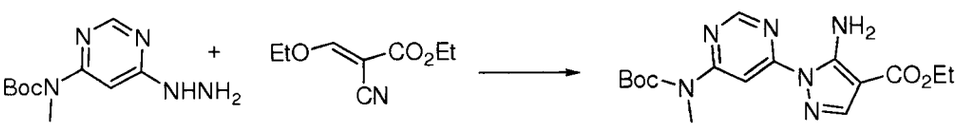
20 21

[00144] A mixture of (6-chloro-pyrimidin-4-yl)-methyl-amine (10g, 69.7mmol), triethylamine (15mL, 106.7mmol), and dimethylaminopyridine (8.5g, 69.5mmol) in 100mL dichloromethane is added *di-t*-butyl dicarbonate (18.75g, 85.9mmol) potion wise. The reaction mixture is kept stirring at room temperature for 4 hours and concentrated. The resultant crude product is treated with water and filtered. The obtained solid is dried under vacuum to give (6-Chloro-pyrimidin-4-yl)-methyl-carbamic acid tert-butyl ester: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.80 (*s*, 1H), 8.04 (*s*, 1H), 3.37 (*s*, 3H), 1.52 (*s*, 9H); MS *m/z* 244.10 (M + 1).



21 **22**

[00145] A mixture of (6-Chloro-pyrimidin-4-yl)-methyl-carbamic acid tert-butyl ester (10g, 41.1mmol), hydrazine monohydrate (6.5g, 130.0mmol), and 2-propanol (50mL) is heated to 90 °C for 4 hours. The reaction mixture is then cooled to room temperature, and concentrated. The resultant crude product is treated with a mixture of water (80mL) and ethanol (15 mL), heated for 30 minutes, and slowly cooled to room temperature. White precipitate forms. After filtration, the undissolved solid is washed with water, dried under vacuum overnight to give (6-Hydrazino-pyrimidin-4-yl)-methyl-carbamic acid tert-butyl ester as white powder in needle form: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.23 (*s*, 1H), 8.19 (*s*, 1H), 7.14 (*s*, 1H), 4.29 (*s*, 2H), 3.23 (*s*, 3H), 1.49 (*s*, 9H); MS *m/z* 240.10 (M + 1).



22 23

[00146] A mixture of (6-hydrazino-pyrimidin-4-yl)-methyl-carbamic acid tert-butyl ester (4.0g, 16.7mmol), 2-cyano-3-ethoxy-acrylic acid ethyl ester (3.02g, 17.5mmol) and ethanol (25mL) is heated to reflux for 4 hours. The reaction mixture is then concentrated and triturated with water (10mL). White precipitate forms. After filtration, the undissolved solid is further washed with water, then air-dried to give 5-amino-1-[6-(tert-butoxycarbonyl-methyl-amino)-pyrimidin-4-yl]-1H-pyrazole-4-carboxylic acid ethyl ester as white powder.

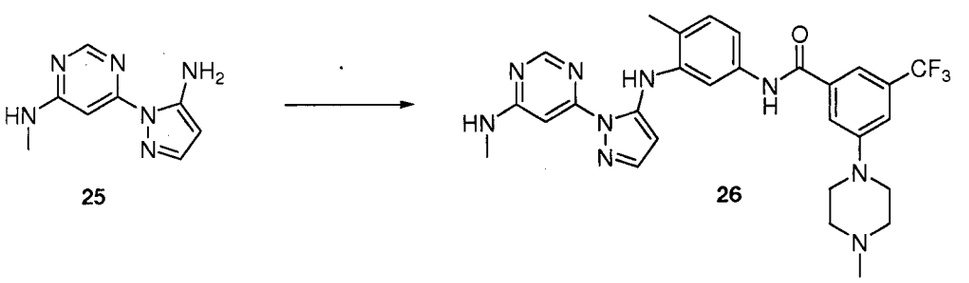
23 24

[00147] A mixture of 5-amino-1-[6-(tert-butoxycarbonyl-methyl-amino)-pyrimidin-4-yl]-1H-pyrazole-4-carboxylic acid ethyl ester (5.5 g, 15.2mmol), lithium hydroxide (1.82g, 75.8 mmol) dissolved in a mixture of 1,4-Dioxane (20mL) and water (5 mL) is heated to 85°C for 8 hours. The reaction mixture is then neutralized with 2 M HCl aqueous solution until pH~4-5 causing a white precipitate to form. After filtration, the undissolved solid is washed with small amount of water, air-dried to give 5-amino-1-[6-(tert-butoxycarbonyl-methyl-amino)-pyrimidin-4-yl]-1H-pyrazole-4-carboxylic acid as white

powder: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.41 (*s*, 1H), 8.00-7.40 (*m*, 4H), 6.86-6.58 (*m*, 1H), 2.86 (*s*, 3H); MS *m/z* 235.10 (M + 1).

24 25

[00148] The 5-amino-1-[6-(tert-butoxycarbonyl-methyl-amino)-pyrimidin-4-yl]-1H-pyrazole-4-carboxylic acid (230mg, 0.98mmol) is heated to 160 °C for 1.5 hours on a hot plate in powder form. The crude product is purified by ISCO chromatography eluting with ethyl acetate in hexanes from 20% to 100% to afford [6-(5-Amino-pyrazol-1-yl)-pyrimidin-4-yl]-methyl-amine: ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.33 (*s*, 1H), 7.53 (*s*, 1H), 7.35 (*s*, 1H), 7.00-6.60 (*m*, 3H), 5.34 (*s*, 1H), 2.83 (*bs*, 3H); MS *m/z* 191.10 (M + 1).

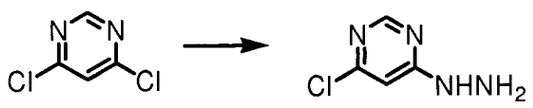


25 26

[00149] [6-(5-Amino-pyrazol-1-yl)-pyrimidin-4-yl]-methyl-amine (200mg, 1.05mmol) is mixed with N-(3-bromo-4-methyl-phenyl)-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide (640mg, 1.40mmol), palladium acetate (60mg, 0.27mmol), Xantophos (235mg, 0.41mmol) and cesium carbonate (1.03g, 3.15mmol). 10 mL of anhydrous 1,4-dioxane is added under nitrogen environment and the mixture is subjected to microwave irradiation to 160°C for 25 minutes. The reaction mixture is treated with 150 mL THF, passed through a celite column and condensed. The crude product is purified by ISCO chromatography eluting with THF and methanol (v/v =1:1) in methylene chloride from 0% to 10% to afford N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide.

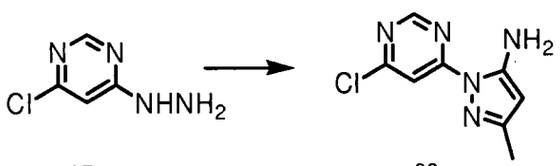
Example 5

N-[5-(1-Fluoro-1-methyl-ethyl)-pyridin-3-yl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide



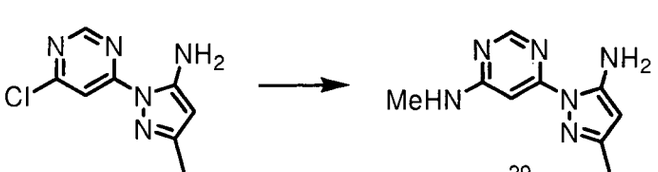
1 27

[00150] A mixture of 4,6-dichloro-pyrimidine (18.68 g, 125 mmol), hydrazine monohydrate (18.28 mL, 376 mmol), and 2-propanol (300 mL) was stirred at room temperature for 3 hours. The reaction mixture was concentrated, triturated with water, and filtered. The solid was washed with water, air-dried to give (6-chloro-pyrimidin-4-yl)-hydrazine (16.97 g, Yield 94%): ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.83 (*s*, 1H), 8.17 (*s*, 1H), 6.76 (*s*, 1H), 4.50 (*s*, 2H); MS *m/z* 145.02 (M + 1).



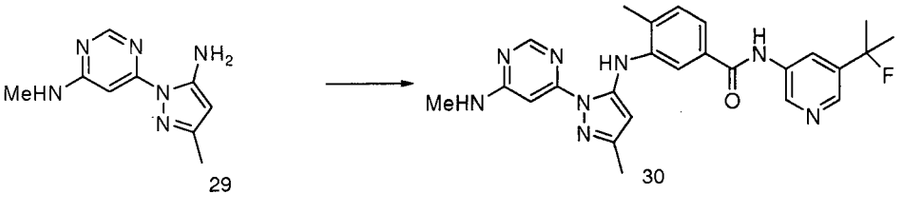
27 28

[00151] The mixture of (6-chloro-pyrimidin-4-yl)-hydrazine (16.97 g, 117 mmol), 3-imino-butyronitrile (28.88 g, 352 mmol), and 2-propanol (500 mL) was heated to 85°C for 5 h. The reaction mixture was then cooled to room temperature, condensed, and recrystallized from ethanol/water (1 : 1, 400 mL). The solid was filtered and washed with water (200 mL), then ethanol/water (1 : 1, 100 mL), dried to afford the desired product 20 .66 g. An additional product (0.9 g) was isolated from the filtrate after standing overnight at room temperature. MS *m/z* 210.05 (M + 1).



28 29

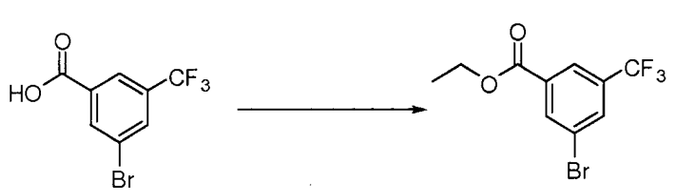
[00152] 5-Methyl-2-(6-chloro-pyrimidin-4-yl)-2H-pyrazol-3-ylamine (2.09 g, 10 mmol) was mixed with methyl amine (40 % in water, 9 mL) and 2-propanol (30 mL). The mixture was heated at 50 °C in a sealed tube. After 4 h, the reaction mixture was cooled to room temperature and condensed, triturated with water, and filtered. The solid was washed with water, air-dried to give [6-(5-amino-3-methyl-pyrazol-1-yl)-pyrimidin-4-yl]-methyl-amine (2.08 g, Yield 97%): ^{1}H NMR 400 MHz (*d6*-DMSO) δ 8.80 (*s*, 1H), 7.44 (*s*, 1H), 6.82 – 6.74 (*m*, 3H), 5.19 (*s*, 1H), 2.83 (*s*, 3H), 2.06 (*s*, 3H); MS *m/z* 210.64 (M + 1).



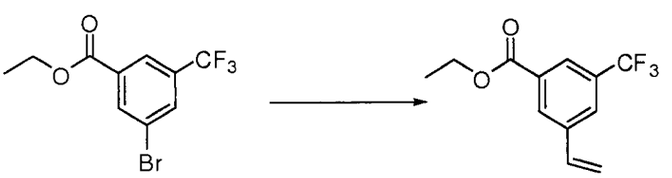
[00153] A suspension of [6-(5-amino-3-methyl-pyrazol-1-yl)-pyrimidin-4-yl]-methyl-amine (17 mg, 0.083 mmol), *N*-[5-(1-fluoro-1-methyl-ethyl)-pyridin-3-yl]-3-iodo-4-methyl-benzamide (41 mg, 0.104 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), Xantphos (9 mg, 0.0166 mmol) and Cs_2CO_3 (54 mg, 0.166 mmol) in anhydrous 1,4-dioxane (2 mL) in a pressure vial was degassed by a stream of argon and sealed. The reaction was stirred at 150 °C for 1 hour. LCMS showed completion of the reaction. A solution of 5% diethyl dithiocarbomic acid sodium salt (3 mL) was added to the reaction. A light yellow precipitate was collected by filtration, washed with water and dried. The crude was purified by column (SiO_2, EtOAc/hexanes: 30 to 100%) to give a white solid (25 mg, 64%): m/z 475.2 (M+1).

Example 426

3-((isopropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide

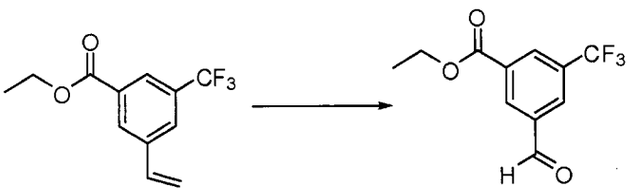


[00154] 100g (371 .71 mmol) of 3-bromo-5-(trifluoromethyl)benzoic acid **31** is dissolved in dry ethanol (300 mL) and 19 mL of conc. H_2SO_4 (Catalytic) is added drop by drop over a 15 minutes time period at room temperature. The reaction mixture is stirred at 90 °C overnight. An aliquot is taken out and checked via LC/MS and a big product peak is observed and no starting material is detected. The reaction mixture is poured into ice-cold water (200 mL) and is extracted with ethyl acetate (3 X 100 mL). The organic layers are combined and dried over magnesium sulfate and is pure enough to be carried over to the next step without further purification. Product is ethyl 3-bromo-5-(trifluoromethyl)-benzoate **32**. MS: *m/z* [M + H+]) 296.80, ^{1}H NMR: 8.36 (s, 1H), 8.24, (s, 1H), 7.95, (s, 1H), 4.41-4.47 (q, 2H, *J* =7.21 Hz), 1.42-1.45 (t, 3H, *J* = 7.21 Hz).



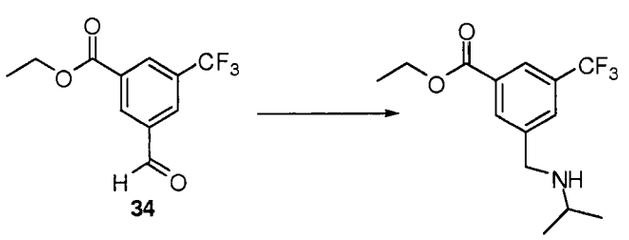
32 **33**

[00155] 50g of ethyl 3-bromo-5-(trifluoromethyl)benzoate **32** is dissolved in dry THF (100 mL), and tributyl vinyl tin (56.85g, 185.14 mmol, 1.09 eq) is added followed by tetrakistriphenylphosphine palladium (0) (2.5g, 2.16 mmol, 0.013eq). The reaction is heated at 90 °C for 18 hours. Next day the reaction mixture is tested via LC/MS and only product peak is detected without any trace of starting materials. The reaction mixture is filtered over celite to remove the palladium and then extra solvent is removed under vacuo. The desired compound is then isolated via flash column chromatography using straight hexane followed by 10 % EtoAc/Hex) to afford ethyl 3-(trifluoromethyl)-5-vinylbenzoate **33**. MS: *m/z* [M + H+]) 245.10, ^{1}H NMR 8.26 (s, 1H), 8.19 (s, 1H), 7.82 (s, 1H), 6.76-6.80 (dd, *J* = 4, 16 Hz, 1H), 5.91-5.95 (dd, *J* = 4, 16Hz, 1H), 5.45-5.48 (dd, *J* = 4, 16Hz), 4.41-4.47 (q, 2H, *J* = 7.21 Hz), 1.42-1.62 (t, 3H, *J* = 7.21 Hz).



33 34

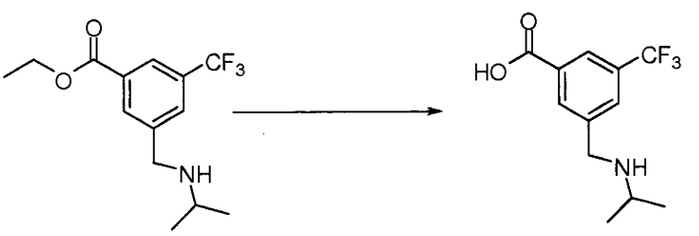
[00156] 25.39 g (103.96 mmol) of ethyl 3-(trifluoromethyl)-5-vinylbenzoate **33** is dissolved in dry MeOH (200 mL) and reaction vessel Is cooled down to -78 °C. Then O_3 is bubbled through for 1.5 hours until the reaction mixture turned dark blue. Then ozone is turned off and nitrogen is bubbled through the reaction mixture to remove extra ozone from the solution. 9.6 g of dimethyl sufide (155.95 mmol, 1.5 eq) is added and the reaction mixture is stirred at -78 °C for 2 hours followed by at room temperature for another hour. All the solvents are removed and ethyl 3-formyl-5-(trifluoromethyl)benzoate **34** is isolated via flash column chromatography (5-10 % EtOAc/Hex). MS: *m/z* [M + H+]) 247.18, ^{1}H NMR 10.16 (s, 1H), 8.73 (s, 1H), 8.56, (s, 1H), 8.35 (s, 1H), 4.46-4.51(q, 2H, J = 7.21 Hz), 1.45-1.49 (t, 3H, J = 7.21 Hz).



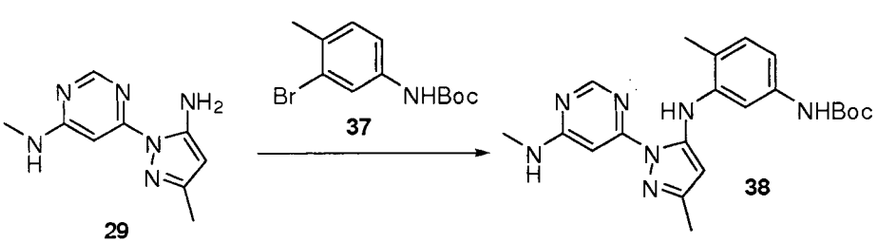
34

[00157] 1g (4.06 mmol, 1 eq) of 3-formyl-5-(trifluoromethyl)benzoate **34** is dissolved in dry EtOH (20 mL). To this reaction flask 287mg isopropyl amine (4.87 mmol, 1.2 eq) and acetic acid (5 drops) are added. This reaction mixture is heated at 50 °C for 2 hours under sealed condition. The reaction mixture is then cooled down to 0 °C and sodium borohydride (184 mg, 4.87 mmol, 1.2 eq) is added in one portion. The reaction vessel is sealed once again and the mixture is stirred at 0 °C for half an hour followed by at room temperature for another 2 hours. The reaction mixture is checked by LC/MS and a single product peak is found without any trace of starting materials. The reaction mixture is poured into ice-cold $NaHCO_3$ solution and extracted with Ethyl Acetate (3 X 20 mL). The organic layers are combined and dried over

magnesium sulfate. After purification using a flash column chromatography (5-20 % Ethyl Acetate/Hex) the pure compound ethyl 3-((isopropylamino)-methyl)-5-(trifluoromethyl)benzoate is isolated as a light yellow oil. MS: *m/z* [M + H+]) 290.20. ^{1}H NMR: 8.10 (m, 2H), 7.74 (s, 1H), 4.31-4.37 (q, 2H, *J* = 7.20 Hz), 3.88 (s, 2H), 2.75-2.82 (m, 1H), 1.33-1.38 (t, 3H, *J* = 7.20 Hz), 1.03-1.05 (m, 6H).



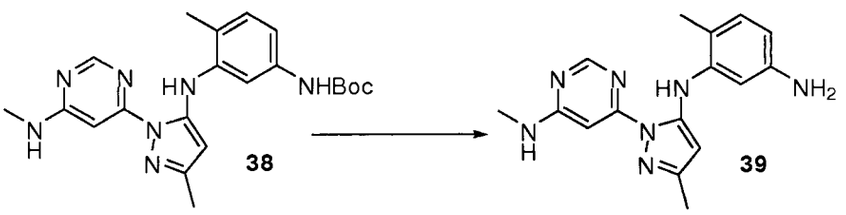
[00158] Ethyl 3-((isopropylamino)methyl)-5-(trifluoromethyl)benzoate (1.01g, 3.49 mmol, 1 eq) is dissolved in THF/H_2O (1:1) 10 mL and LiOH 0.39g (16.32 mmol, 4.6 eq) is added. The mixture is stirred at room temperature for 4 hours and then checked via LC/MS for a zero starting material peak. The organic solvent is removed and some more water is added to the reaction vessel. The reaction mixture is cooled and 1M HCl solution in ether is added drop-wise until the pH is between 4 and 5. The lithium chloride salts start to precipitate out of solution. Extra organic solvents are removed and the precipitate is transferred to small vials and freeze dried. MS: *m/z* [M + H+]) 262.20, ^{1}H NMR: 8.45 (s, 1H), 8.27 (s, 1H), 8.15 (s, 1H), 4.26 (s, 2H), 3.25-3.38 (m, 2H), 1.33-1.34 (m, 2H).



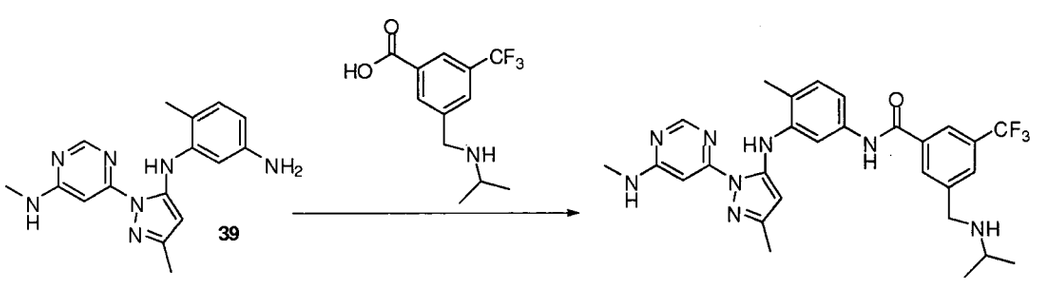
29 **37** **38**

[00159] To a high pressure tube is added 6-(5-amino-3-methyl-1H-pyrazol-1-yl)-N-methylpyrimidin-4-amine **29** (2.0 g, 9.8 mmol), 3-bromo-4-methylphenyl carbamic acid *tert*-butyl ester **37** (2.4 g, 10.8 mmol), $Pd(OAc)_2$ (132 mg, 0.59 mmol), Cs_2CO_3 (3.5 g, 10.8 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (340 mg, 0.59 mmol) and 1,4-dioxane (30

mL). The mixture is flushed with N_2 at 0 ℃ for a few minutes, then heated to 120 ℃ for 2 days. The mixture is poured into water and extracted with EtOAc. The organic layer is separated, dried with $MgSO_4$, then concentrated *in vacuo*. The residue is purified by flash chromatography [silica gel, hexane:EtOAc/5:5] to provide tert-butyl 4-methyl-3-(3-methyl-1-(6-(methylamino)-pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamate **38.**



[00160] Tert-butyl 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamate **38** (2.0 g) is dissolved in a mixed solvent of TFA:DCM/1:1 (20 mL). The mixture is stirred at room temperature for 4 hours, then concentrated *in vacuo*. The residue is dissolved in EtOAc and washed with aqueous $NaHCO_3$. The organic layer is separated, dried with $MgSO_4$, then concentrated *in vacuo* to provide 6-methyl-N1-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-yl)benzene-1,3-diamine **39.**

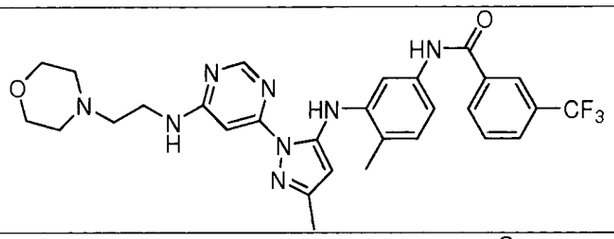
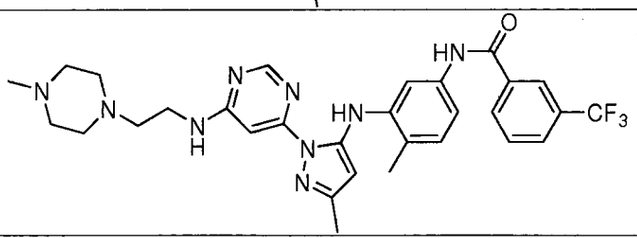
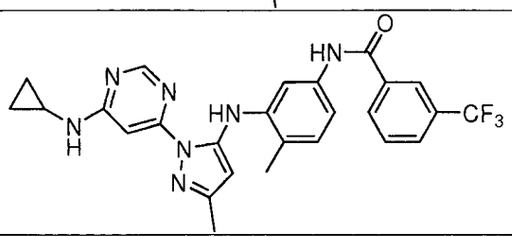


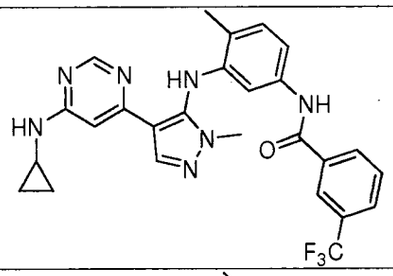
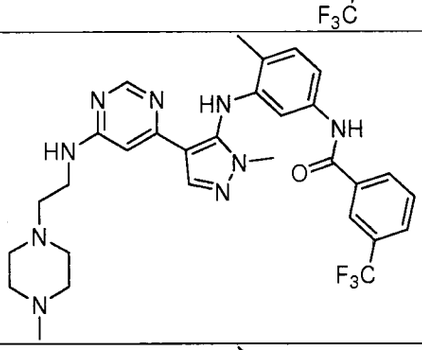
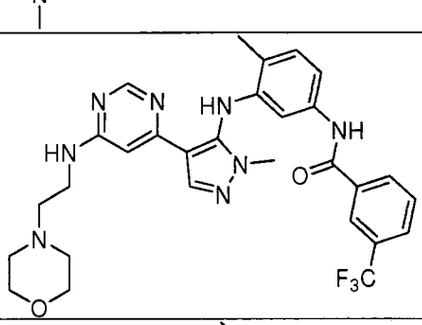
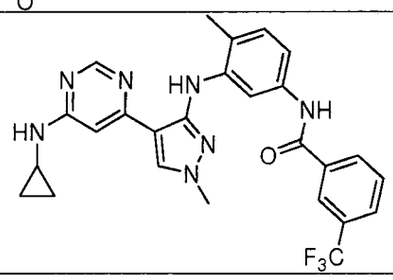
[00161] 6-methyl-N1-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-yl)benzene-1,3-diamine **39** (360 mg, 1.16 mmol, 1 eq) is dissolved in dry DMF (10 mL), followed by 3-((isopropylamino)methyl)-5-(trifluoromethyl)benzoic acid (0.504 mg, 1.02 mmol, 0.9 eq), HATU (663 mg, 1.74 mmol, 1.5 eq), and DIEA (0.5 mL, 3.49 mmol, 3 eq). The reaction mixture is stirred at room temperature for about 4 hours until the reaction is complete as evidenced by the LC/MS product peak. The reaction mixture is then quenched by $NaHCO_3$ solution and extracted with ethyl acetate. The organic layers are combined and dried over

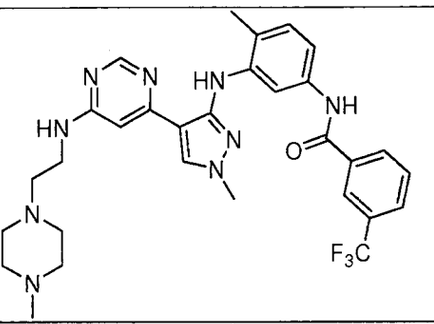
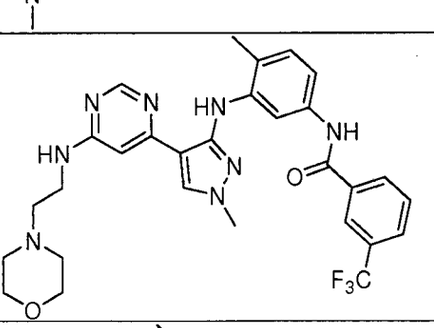
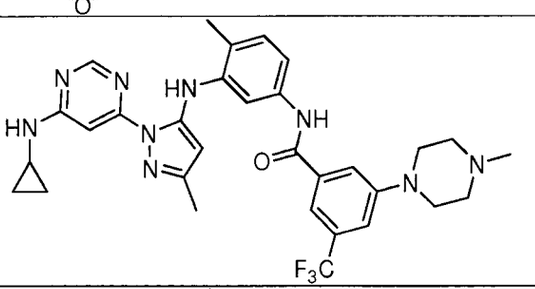
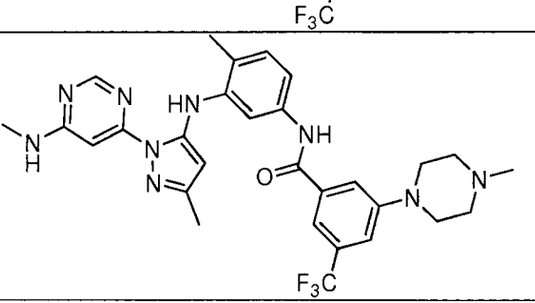
magnesium sulfate. The solvents are removed under vacuo and the residue is purified by flash column chromatography to afford 3-((isopropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide. MS: *m/z* [M + H+]) 553.20, ^{1}H NMR: 11.07 (s, 1H), 10.61 (s, 1H), 9.17 (bs, 1H), 8.58 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 7.95 (s, 1H), 7.69 (s, 1H), 7.39 (m, 1H), 7.24 (m, 1H), 6.88 (s, 1H), 6.16 (s, 1H), 4.36 (m, 2H), 3.34-3.48 (m, 1H), 2.87 (m, 3H), 2.49(m, 3H), 2.22 (m, 3H), 1.33-1.34 (m, 6H).

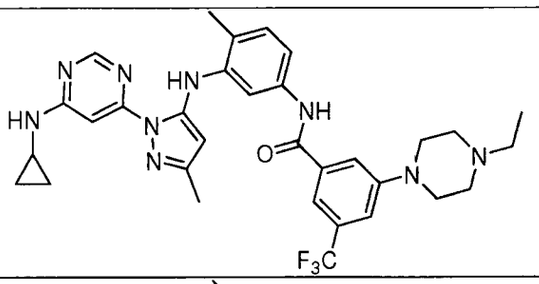
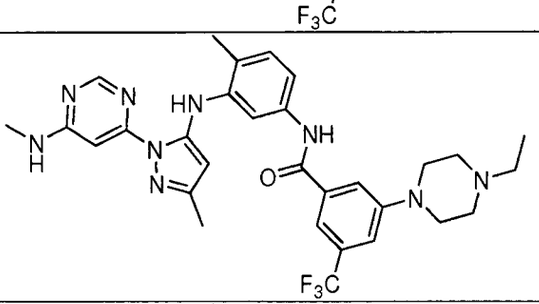
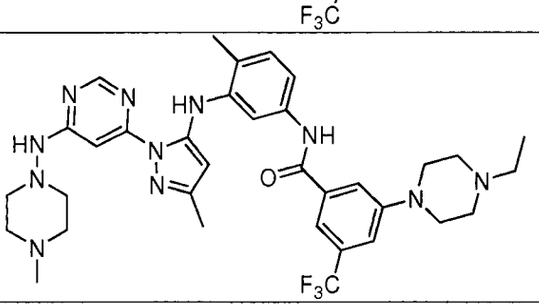
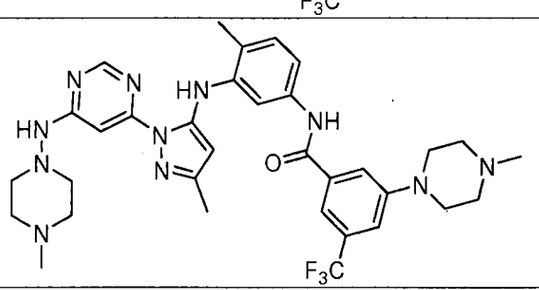
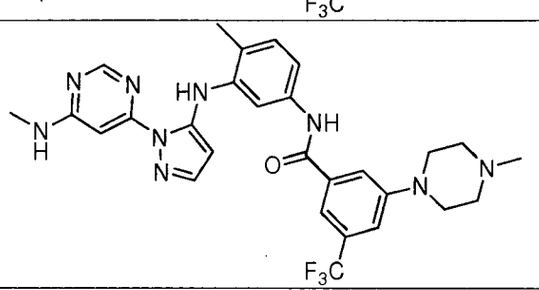
[00162] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

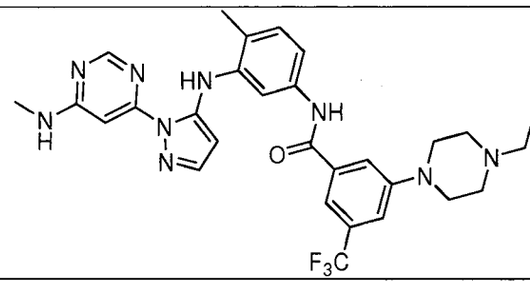
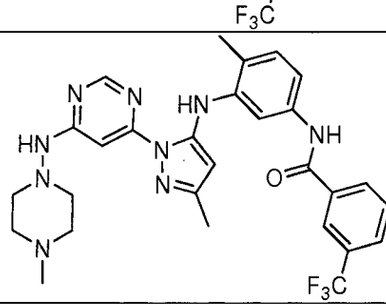
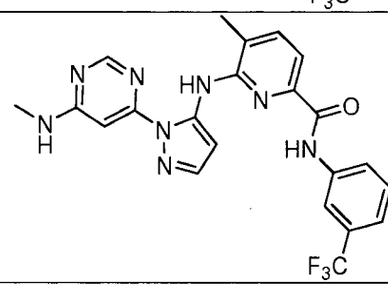
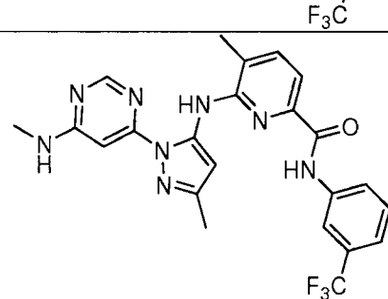
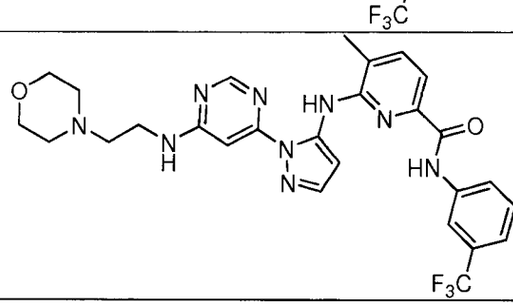
Table 1

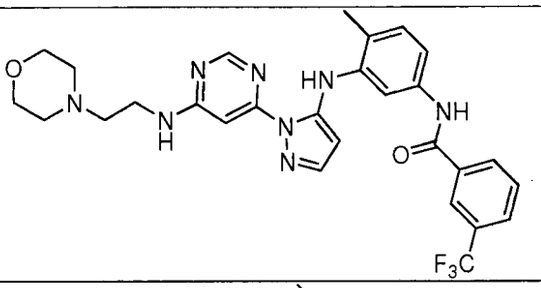
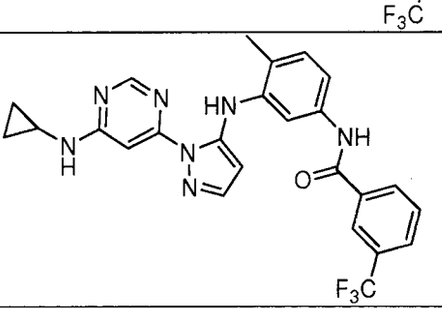
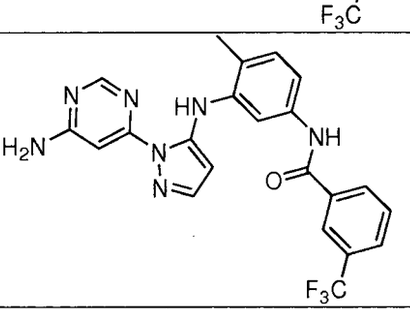
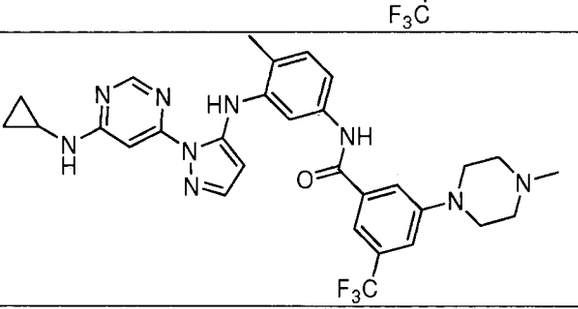
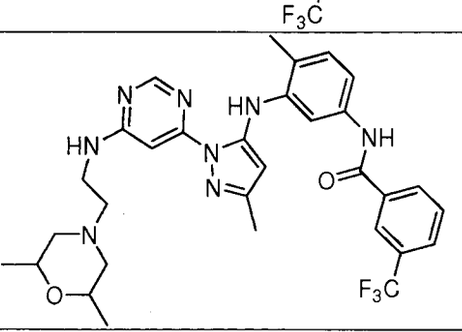
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
5		MS *m/z* 581.3 (M + 1)
6		MS *m/z* 594.3 (M + 1)
7		MS *m/z* 508.2 (M + 1)

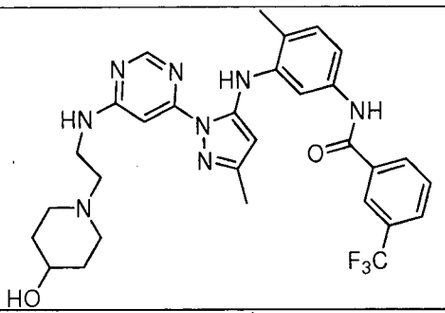
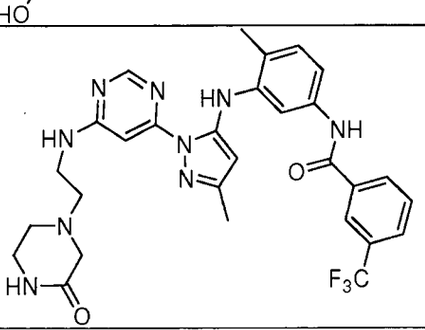
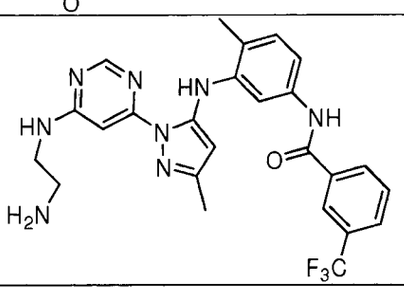
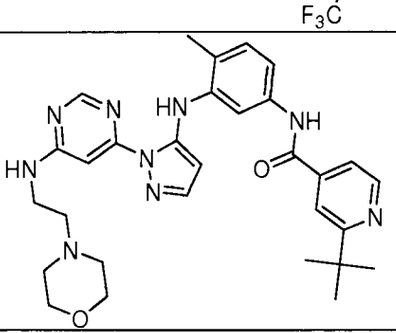
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
8		MS *m/z* 508.2 (M + 1)
9		MS *m/z* 594.3 (M + 1)
10		MS *m/z* 581.3 (M + 1)
11		MS *m/z* 508.2 (M + 1)

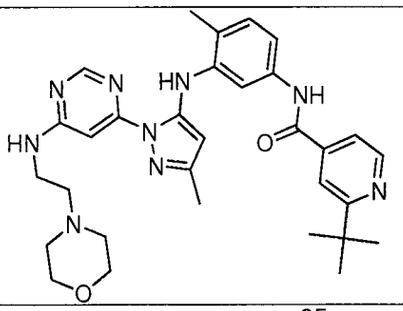
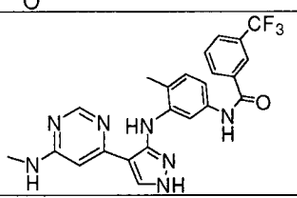
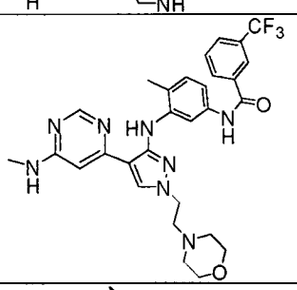
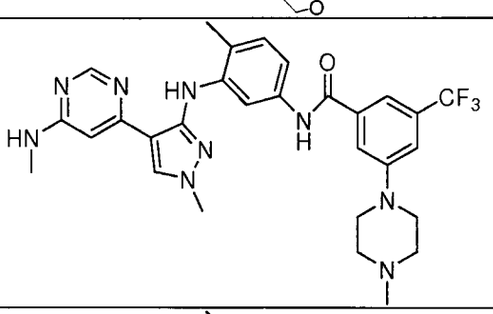
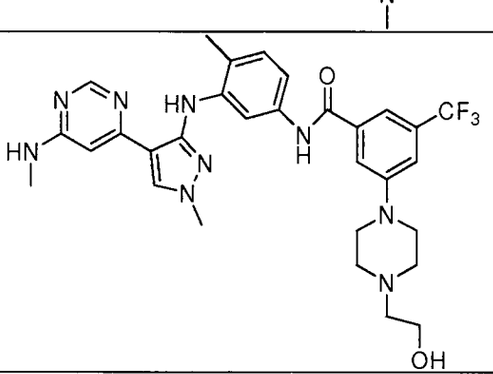
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
12		MS *m/z* 594.3 (M + 1)
13		MS *m/z* 581.3 (M + 1)
14		MS *m/z* 606.3 (M + 1)
15		MS *m/z* 580.3 (M + 1)

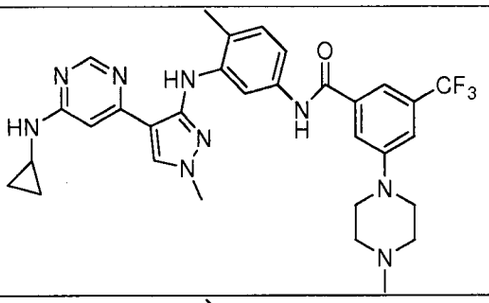
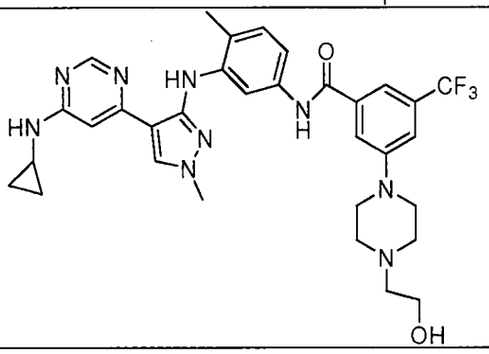
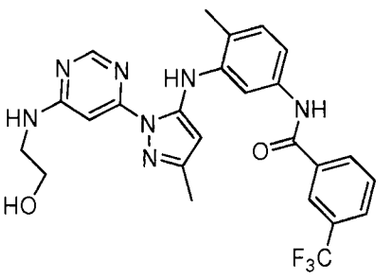
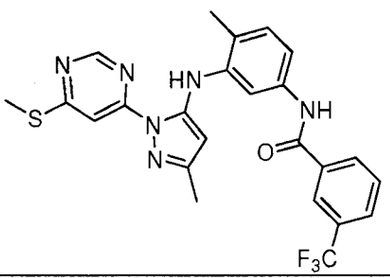
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
16		MS *m/z* 620.3 (M + 1)
17		MS *m/z* 594.3 (M + 1)
18		MS *m/z* 678.4 (M + 1)
19		MS *m/z* 664.3 (M + 1)
20		MS *m/z* 566.3 (M + 1)

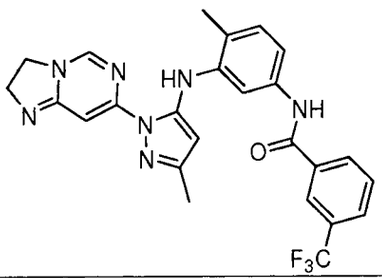
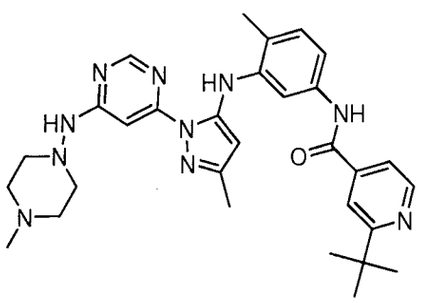
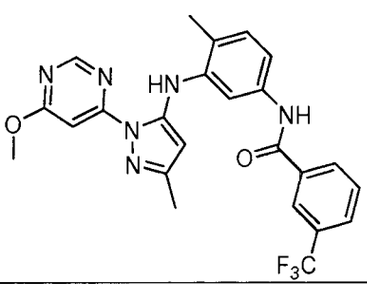
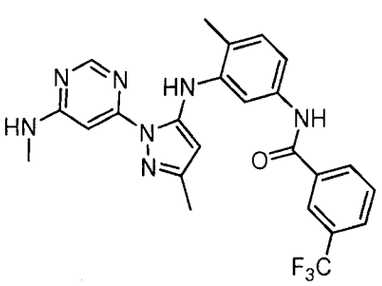
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
21		MS *m/z* 580.3 (M + 1)
22		MS *m/z* 566.3 (M + 1)
23		MS *m/z* 469.2 (M + 1)
24		MS *m/z* 483.2 (M + 1)
25		MS *m/z* 568.2 (M + 1)

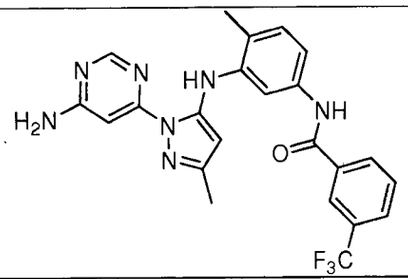
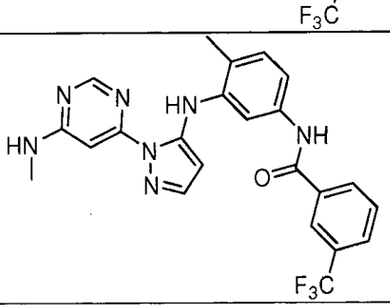
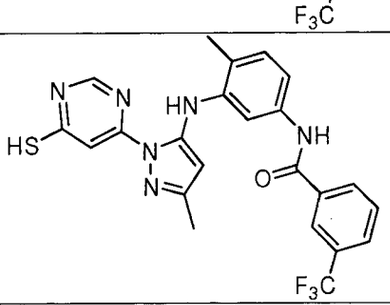
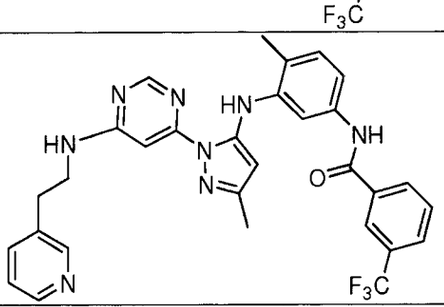
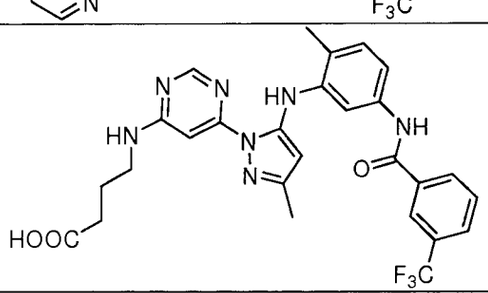
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
26		MS *m/z* 567.2 (M + 1)
27		MS *m/z* 494.2 (M + 1)
28		MS *m/z* 454.2 (M + 1)
29		MS *m/z* 592.3 (M + 1)
30		MS *m/z* 609.3 (M + 1)

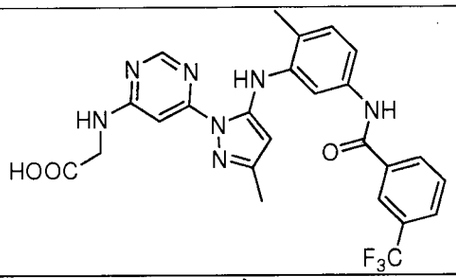
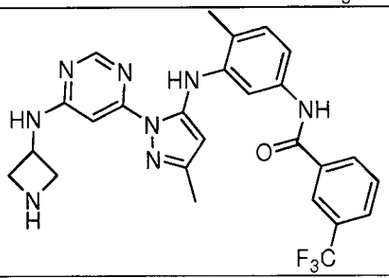
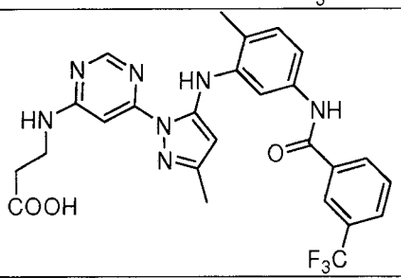
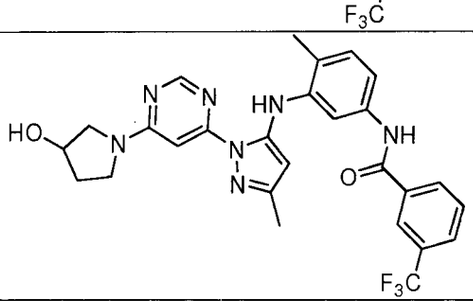
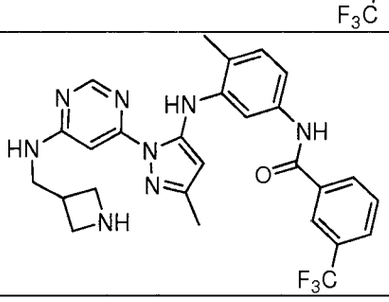
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
31		MS *m/z* 595.3 (M + 1)
32		MS *m/z* 594.3 (M + 1)
33		MS *m/z* 511.2 (M + 1)
34		MS *m/z* 511.2 (M + 1)

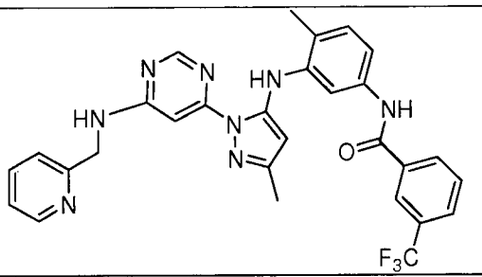
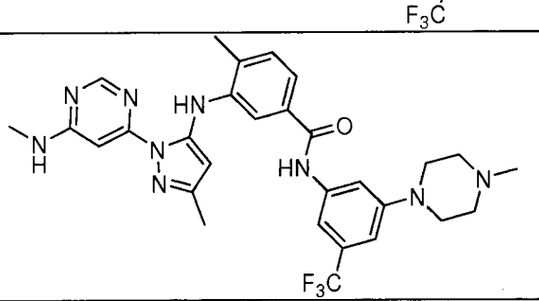
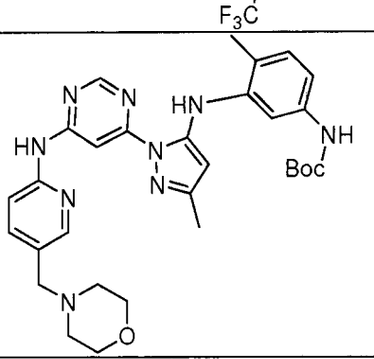
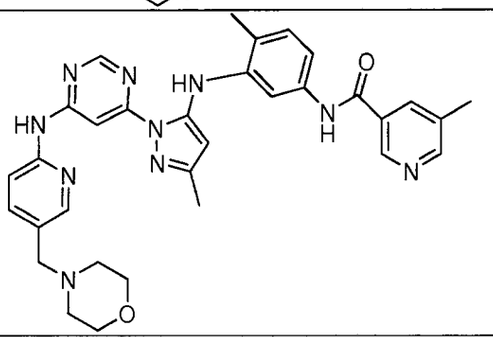
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
35		MS *m/z* 570.3 (M + 1)
36		MS *m/z* 468.2 (M + 1)
37		MS *m/z* 581.3 (M + 1)
38		MS *m/z* 580.3 (M + 1)
39		MS *m/z* 610.3 (M + 1)

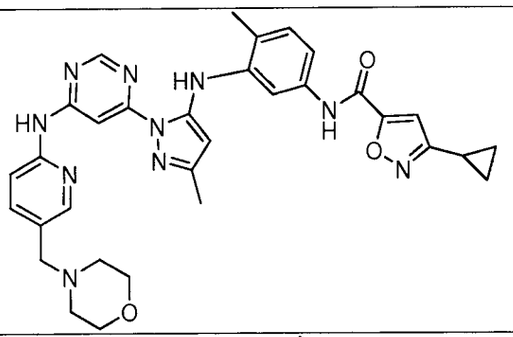
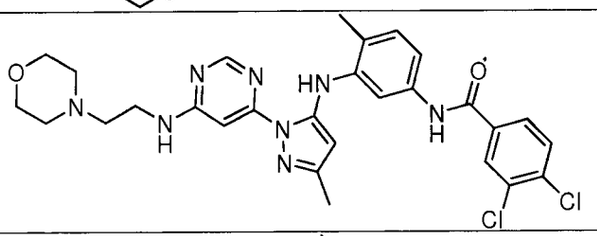
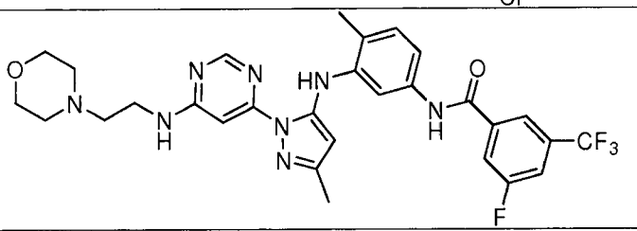
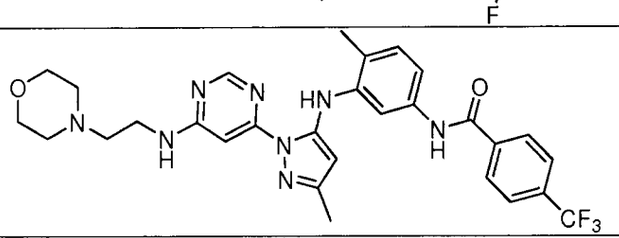
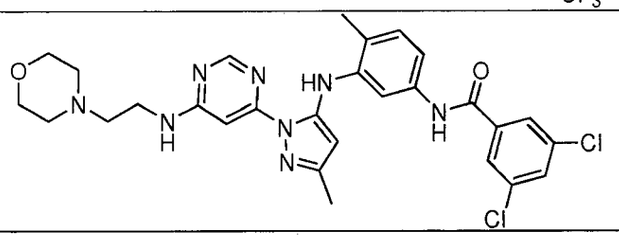
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
40		MS *m/z* 606.3 (M + 1)
41		MS *m/z* 636.3 (M + 1)
42		MS *m/z* 512.2 (M + 1)
43		MS *m/z* 499.1 (M + 1)

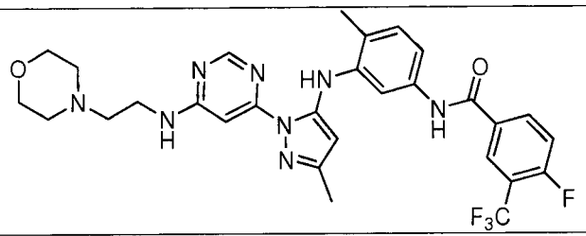
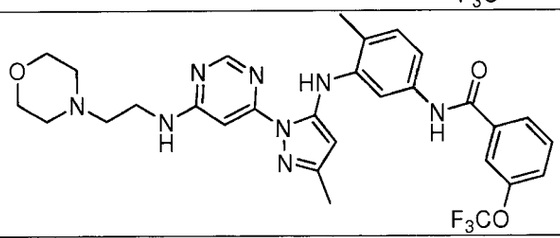
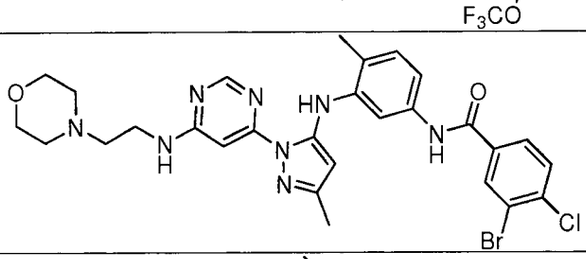
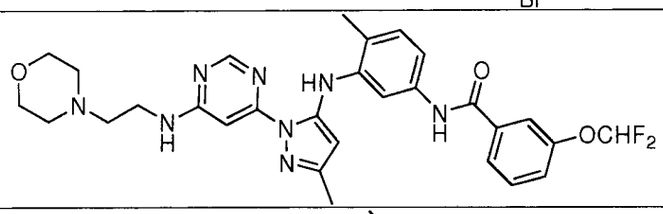
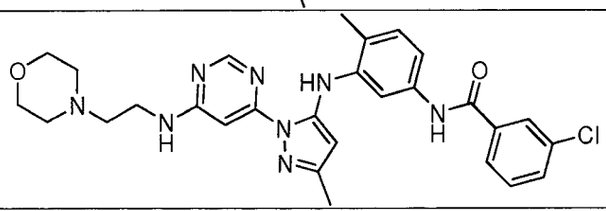
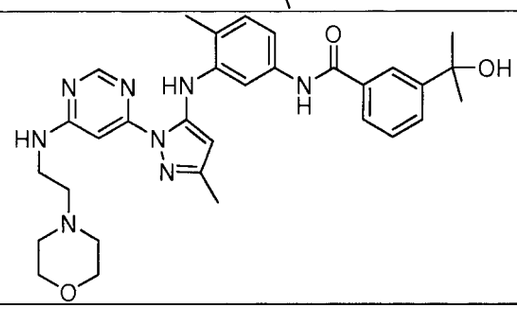
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
44		MS *m/z* 494.2 (M + 1)
45		MS *m/z* 555.3 (M + 1)
46		MS *m/z* 483.2 (M + 1)
47		MS *m/z* 482.2 (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
48		MS *m/z* 468.2 (M + 1)
49		MS *m/z* 468.2 (M + 1)
50		MS *m/z* 484.1 (M + 1)
51		MS *m/z* 573.2 (M + 1)
52		MS *m/z* 554.2 (M + 1)

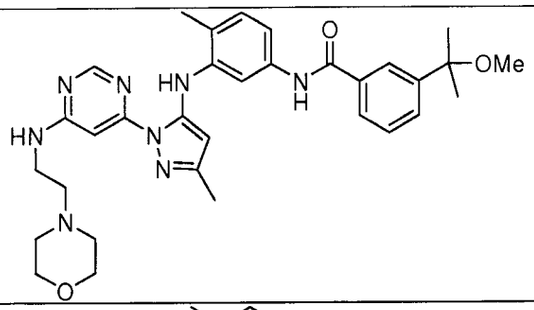
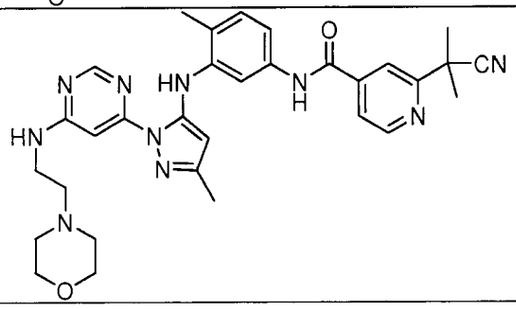
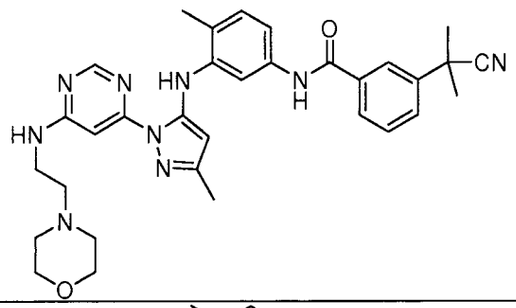
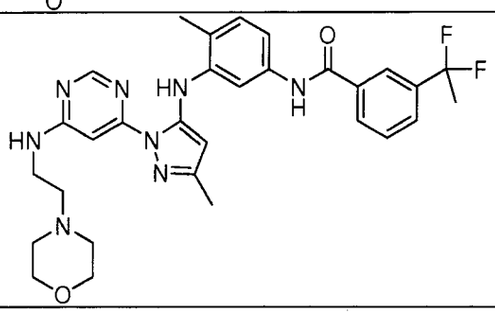
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
53		MS *m/z* 556.2 (M + 1)
54		MS *m/z* 523.2 (M + 1)
55		MS *m/z* 540.2 (M + 1)
56		MS *m/z* 538.2 (M + 1)
57		MS *m/z* 537.2 (M + 1)

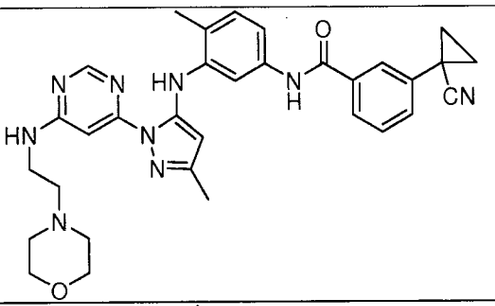
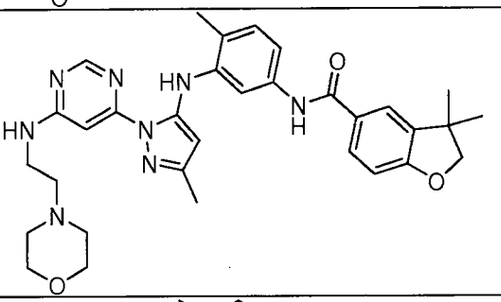
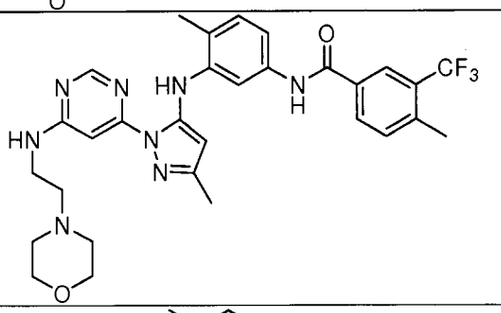
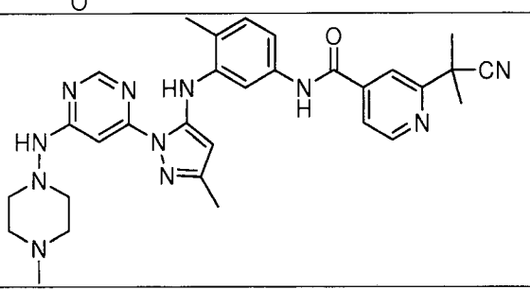
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
58		MS *m/z* 559.2 (M + 1)
59		MS *m/z* 580.3 (M + 1)
60		MS *m/z* 572.3 (M + 1)
61		MS *m/z* 591.3 (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
62		MS *m/z* 607.3 (M + 1)
63		MS *m/z* 581.2 (M + 1)
64		MS *m/z* 599.2 (M + 1)
65		MS *m/z* 581.3 (M + 1)
66		MS *m/z* 581.2 (M + 1)

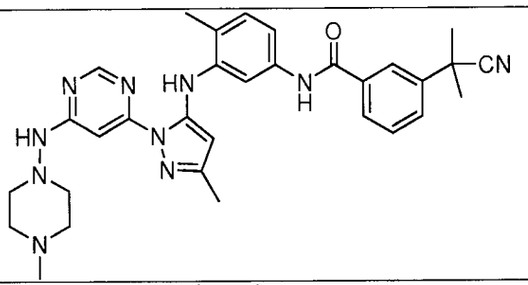
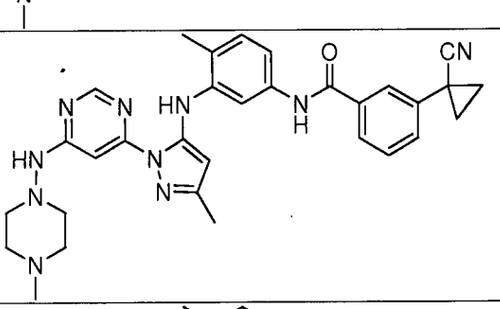
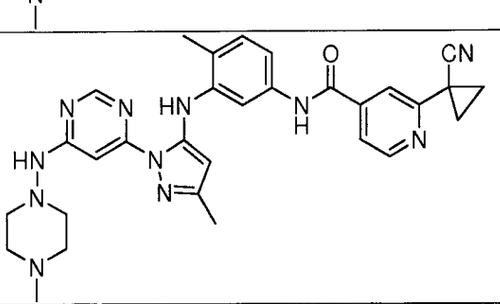
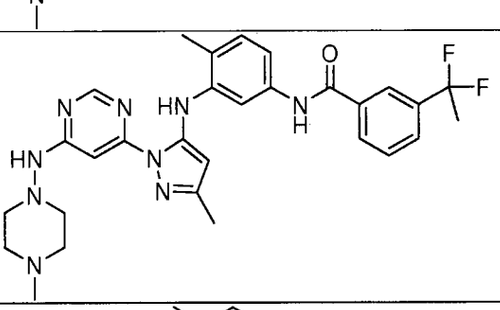
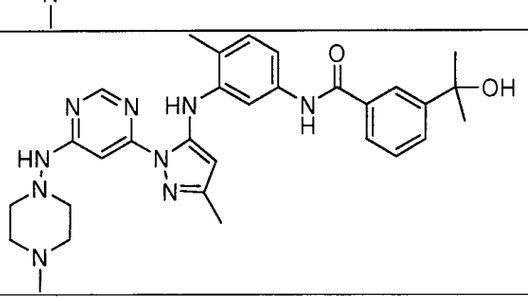
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
67		MS *m/z* 599.2 (M + 1)
68		MS *m/z* 597.3 (M + 1)
69		MS *m/z* 625.1 (M + 1)
70		MS *m/z* 579.3 (M + 1)
71		MS *m/z* 547.2 (M + 1)
72		MS *m/z* 571.3 (M + 1)

178

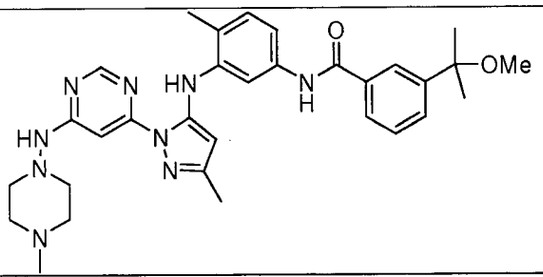
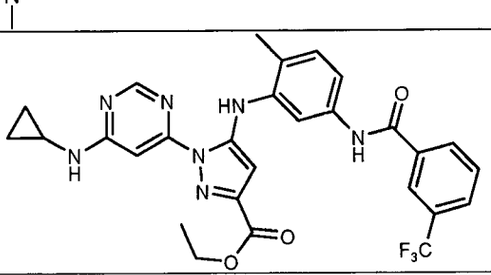
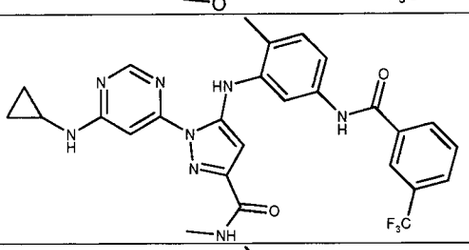
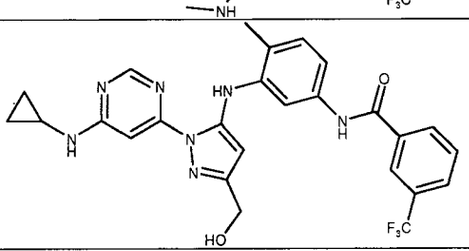
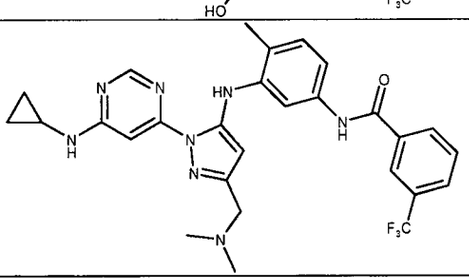
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
73		MS *m/z* 585.3 (M + 1)
74		MS *m/z* 581.3 (M + 1)
75		MS *m/z* 580.3 (M + 1)
76		MS *m/z* 577.3 (M + 1)

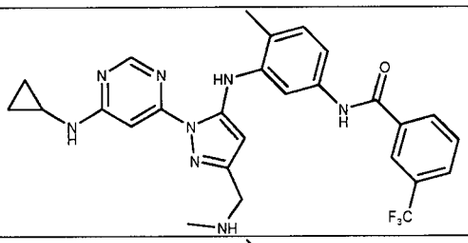
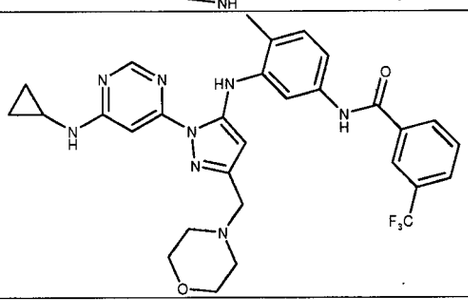
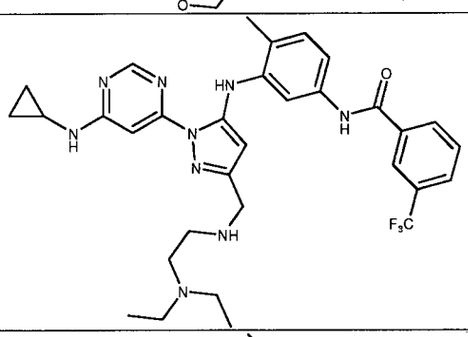
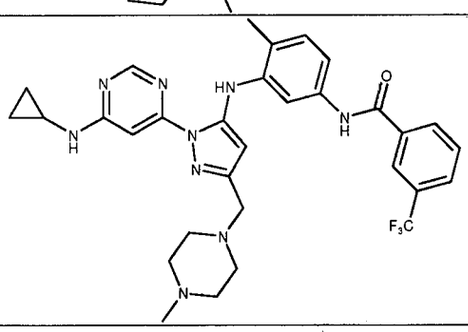
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
77		MS *m/z* 578.3 (M + 1)
78		MS *m/z* 583.3 (M + 1)
79		MS *m/z* 595.3 (M + 1)
80		MS *m/z* 566.3 (M + 1)

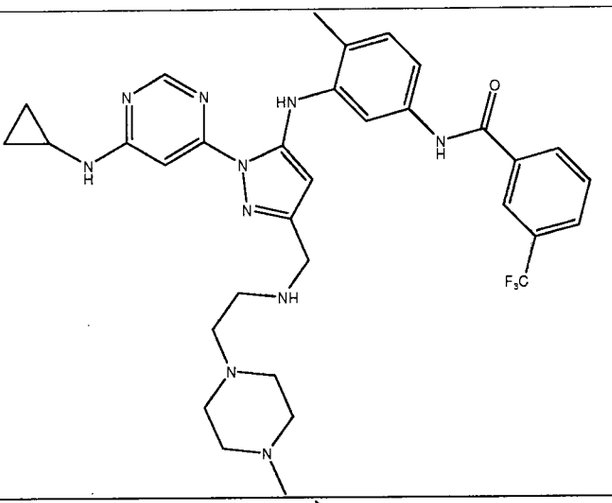
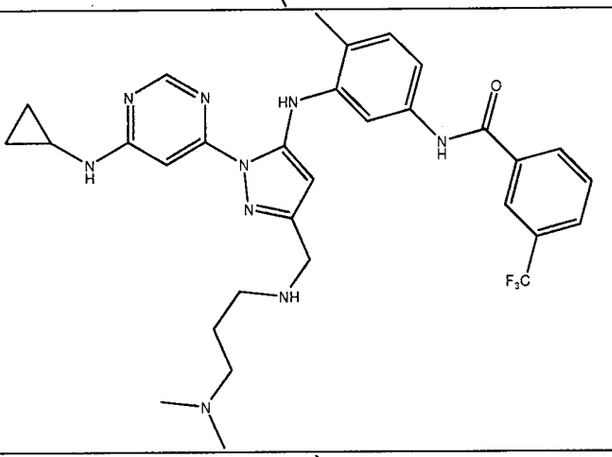
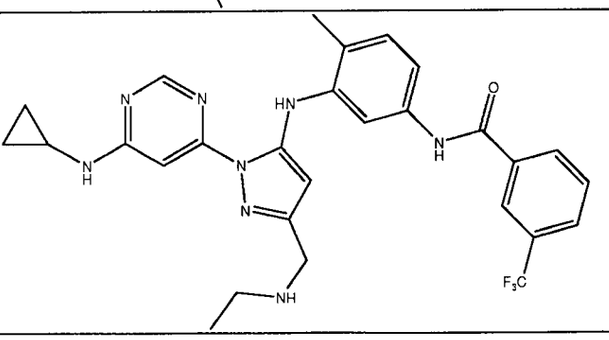
120

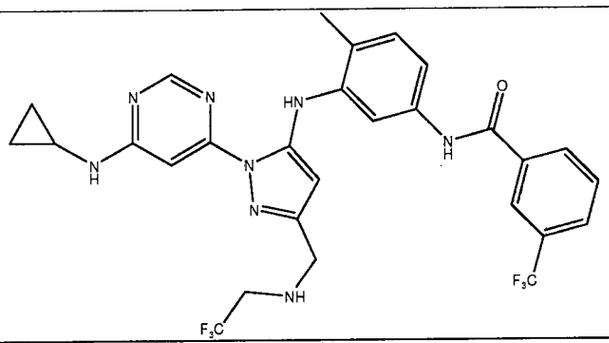
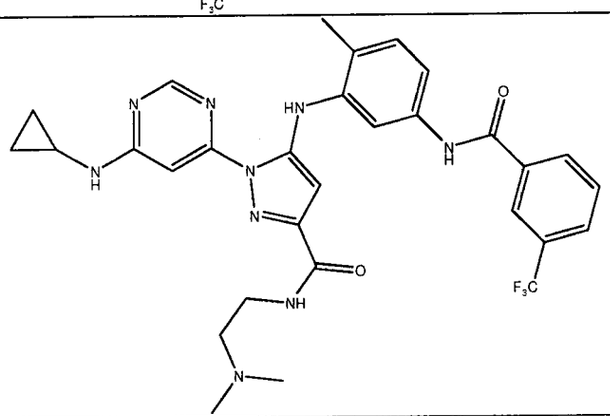
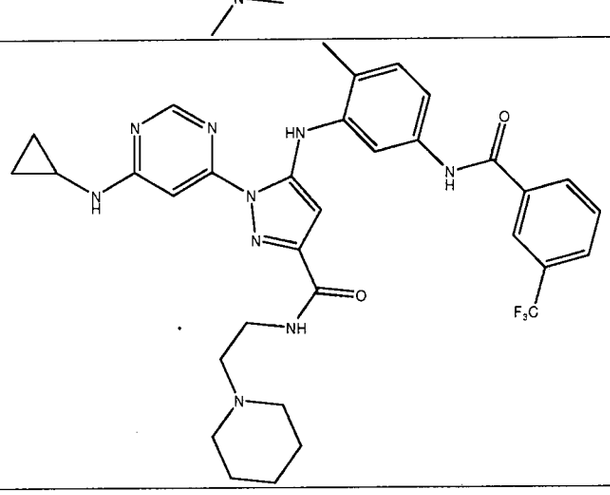
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
81		MS *m/z* 565.3 (M + 1)
82		MS *m/z* 563.3 (M + 1)
83		MS *m/z* 564.3 (M + 1)
84		MS *m/z* 562.3 (M + 1)
85		MS *m/z* 556.3 (M + 1)

121

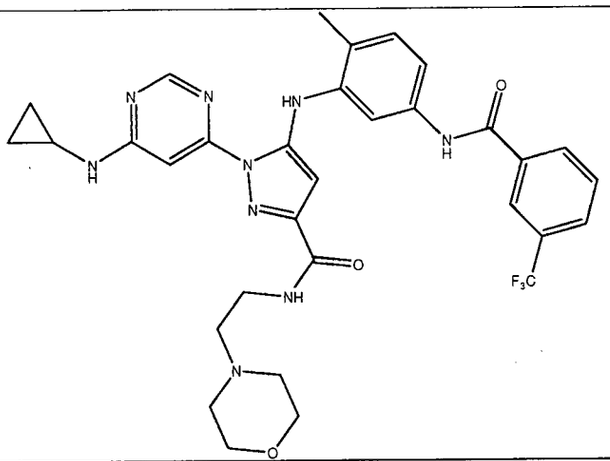
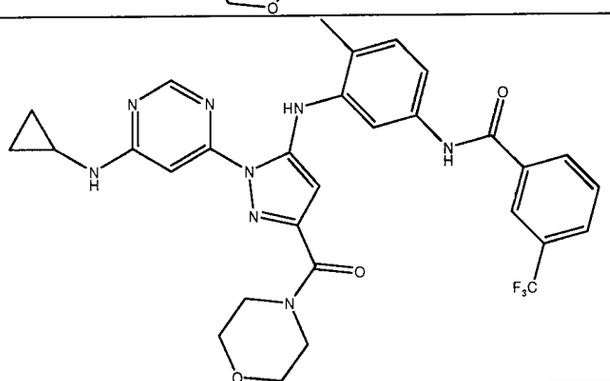
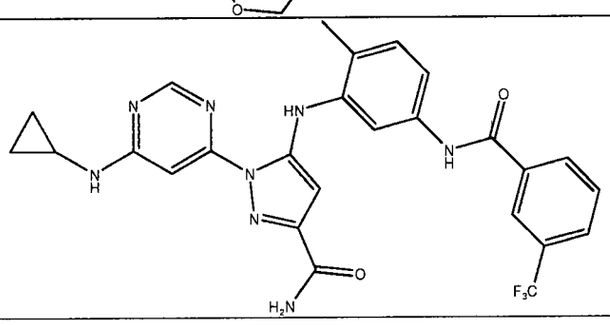
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
86		MS *m/z* 570.3 (M + 1)
87		MS *m/z* 566.2 (M + 1)
88		MS *m/z* 551.2 (M + 1)
89		MS *m/z* 524.2 (M + 1)
90		MS *m/z* 551.2 (M + 1)

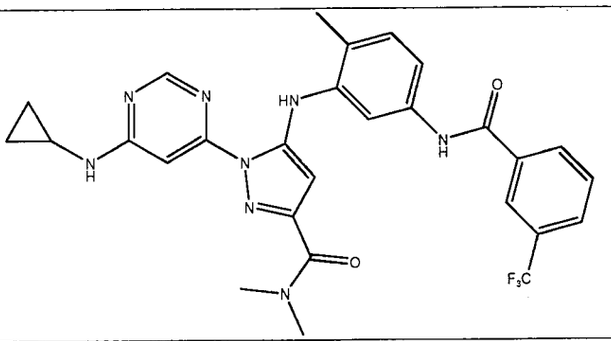
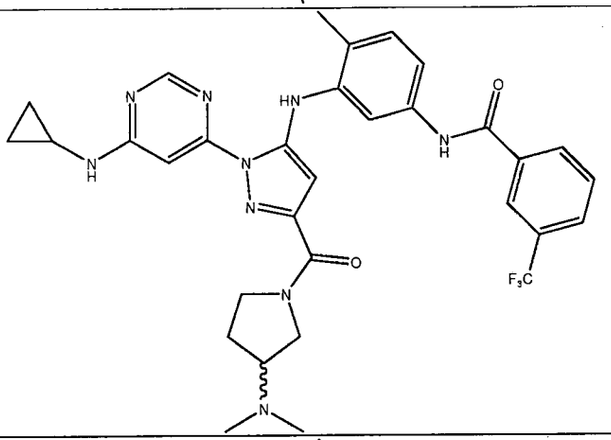
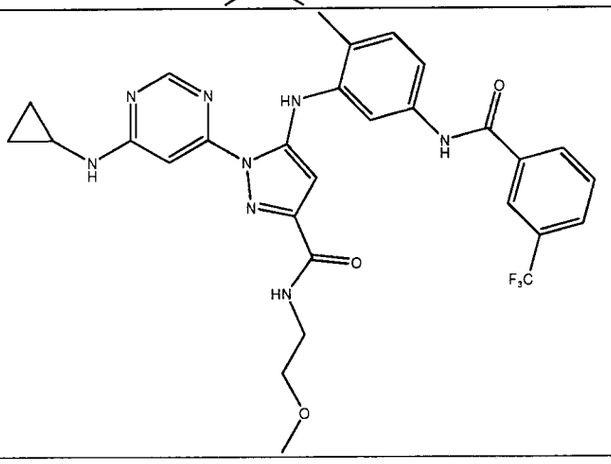
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
91		MS *m/z* 537.2 (M + 1)
92		MS *m/z* 593.3 (M + 1)
93		MS *m/z* 622.3 (M + 1)
94		MS *m/z* 606.3 (M + 1)

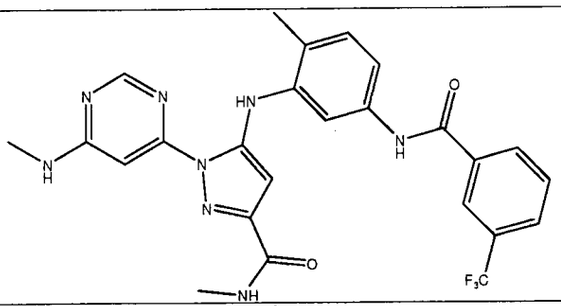
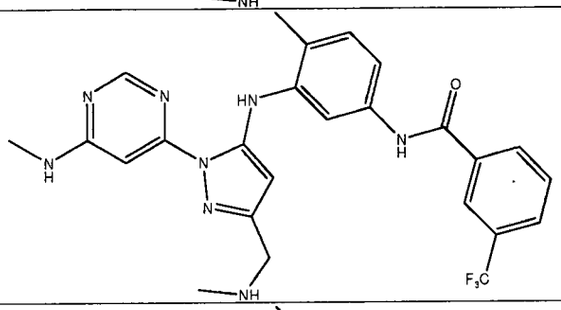
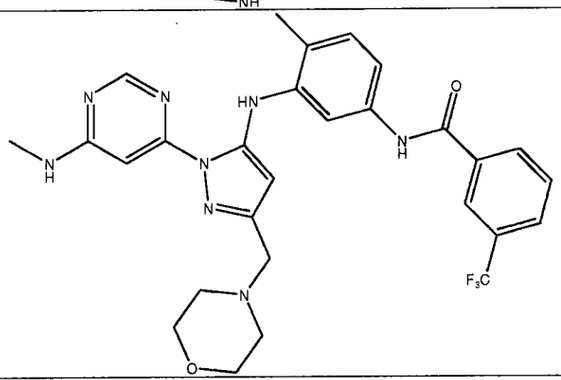
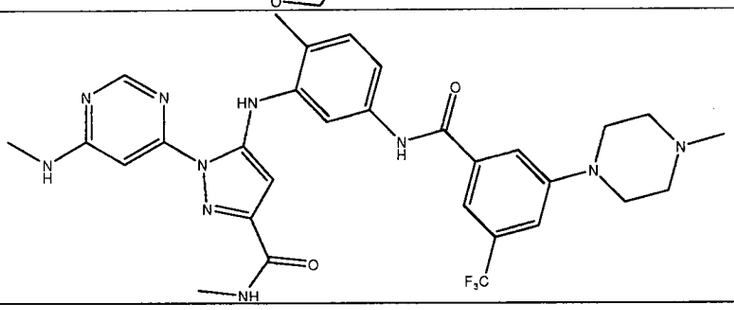
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
95		MS *m/z* 649.3 (M + 1)
96		MS *m/z* 608.3 (M + 1)
97		MS *m/z* 551.2 (M + 1)

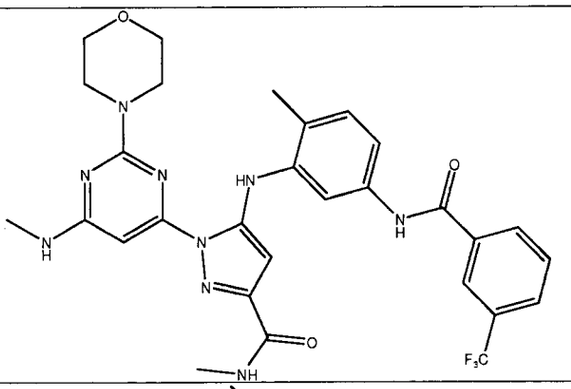
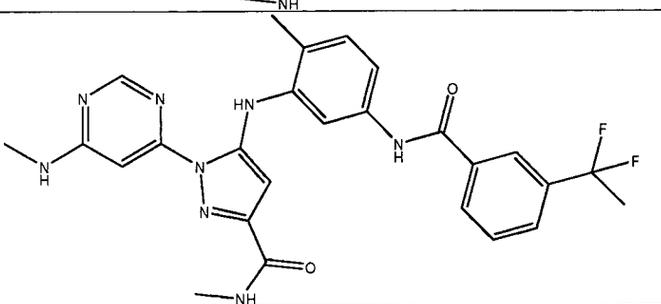
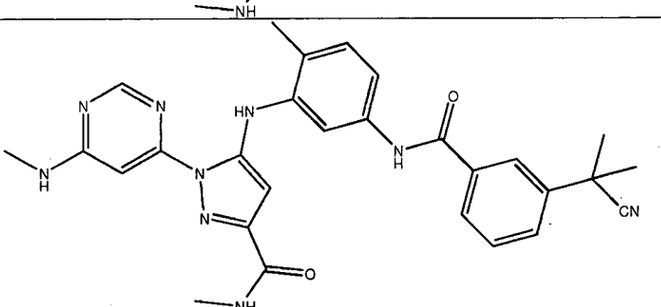
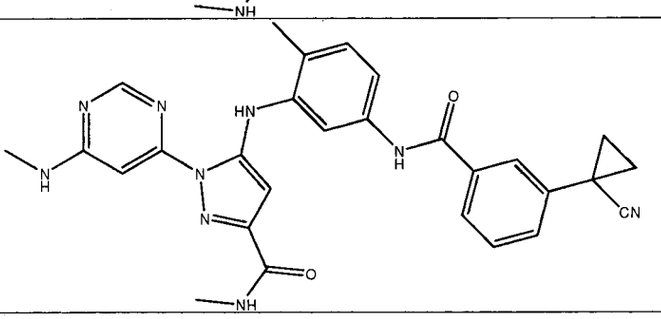
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
98		MS *m/z* 605.2 (M + 1)
99		MS *m/z* 608.3 (M + 1)
100		MS *m/z* 648.3 (M + 1)

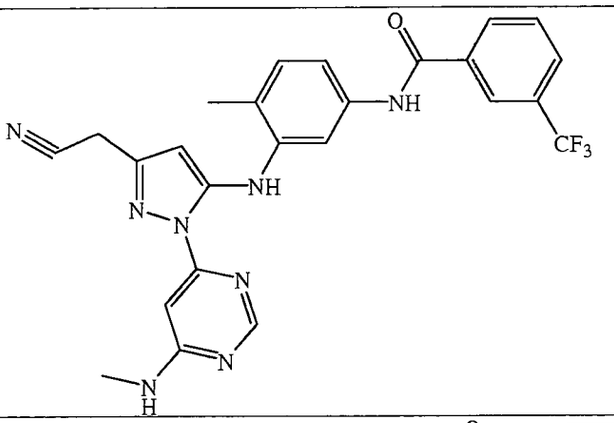
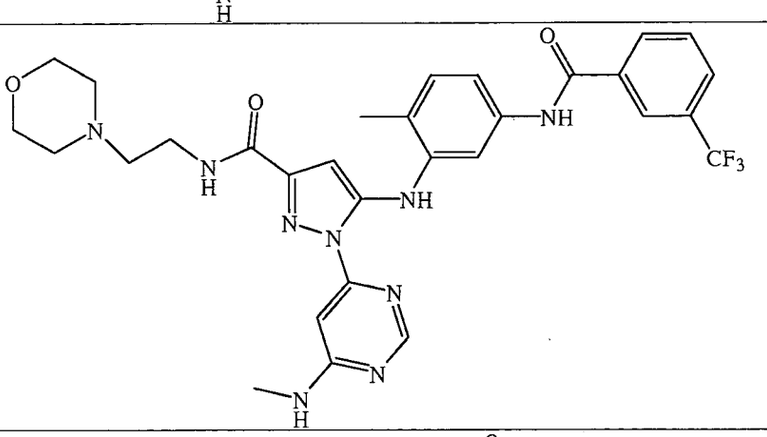
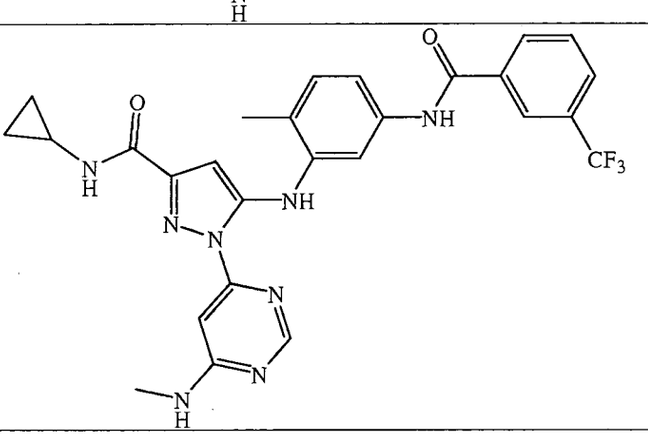
125

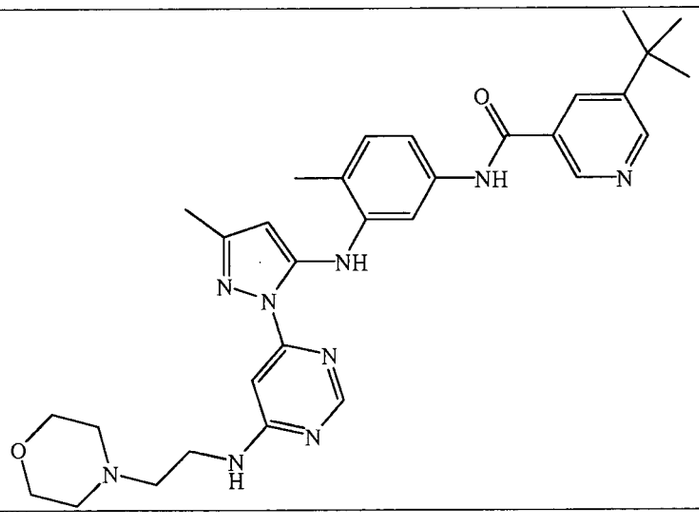
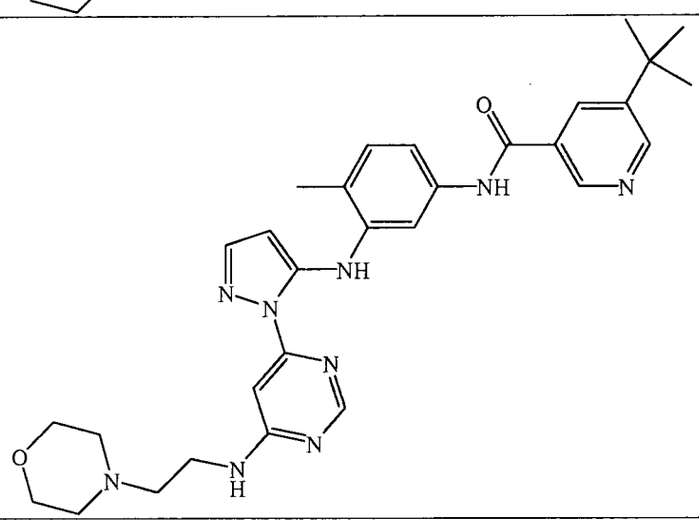
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
101		MS *m/z* 650.3 (M + 1)
102		MS *m/z* 607.2 (M + 1)
103		MS *m/z* 537.2 (M + 1)

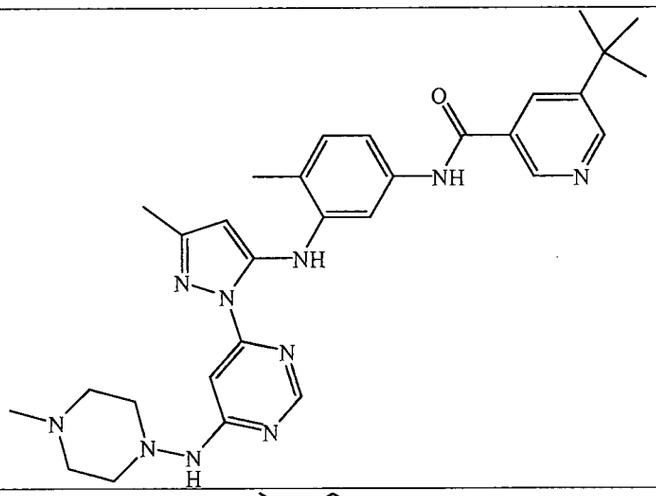
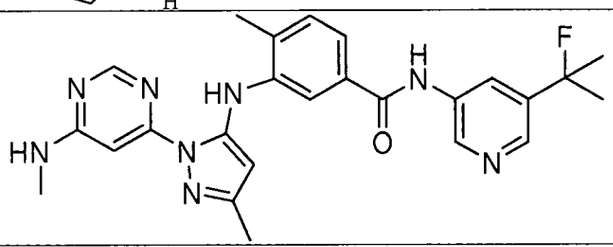
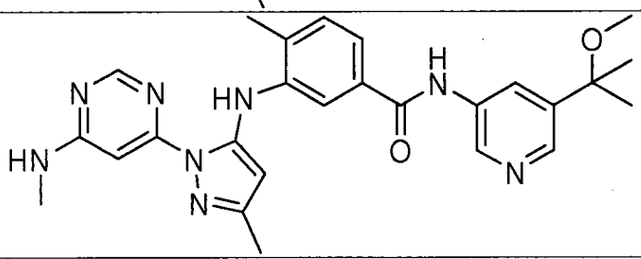
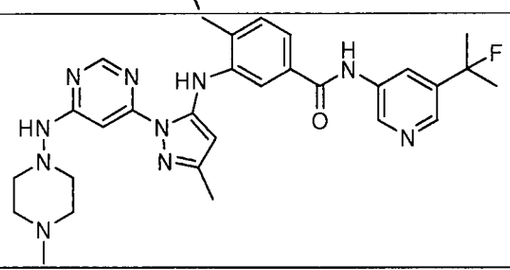
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
104		MS *m/z* 562.2 (M + 1)
105		MS *m/z* 634.3 (M + 1)
106		MS *m/z* 595.3 (M + 1)

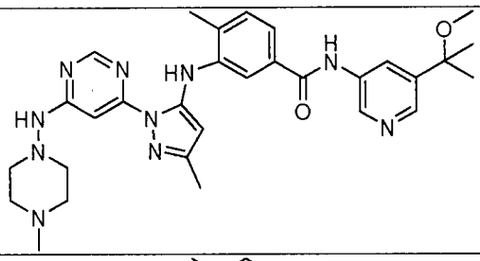
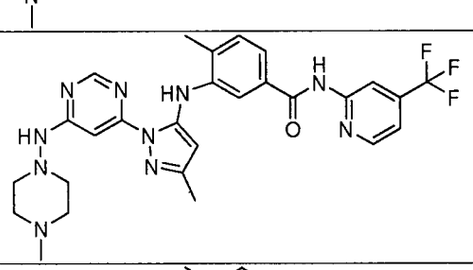
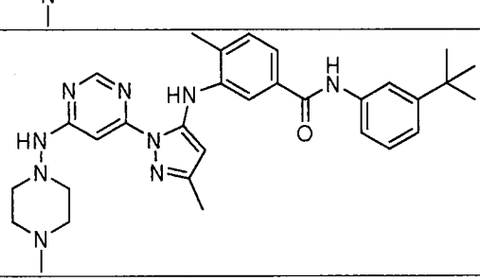
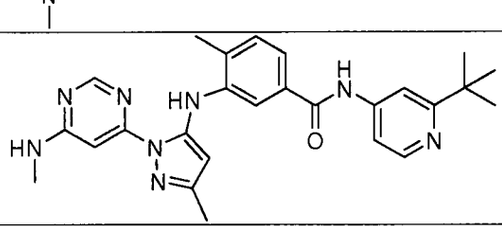
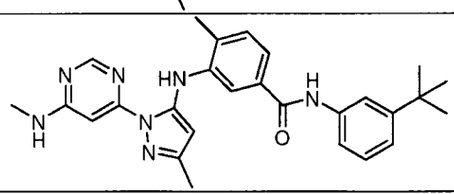
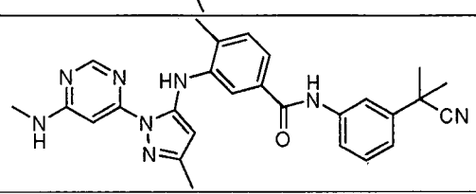
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
107		MS *m/z* 525.3 (M + 1)
108		MS *m/z* 511.2 (M + 1)
109		MS *m/z* 567.2 (M + 1)
110		MS *m/z* 623.3 (M + 1)

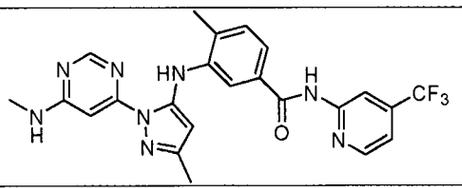
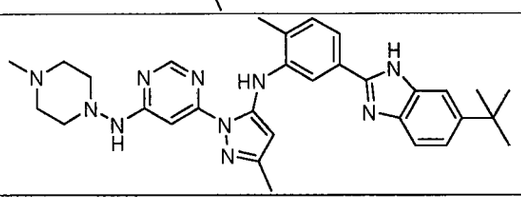
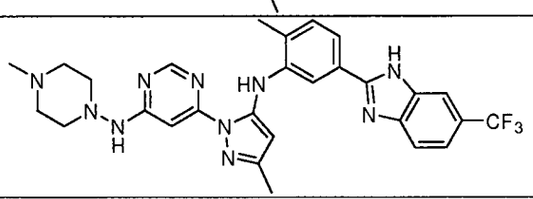
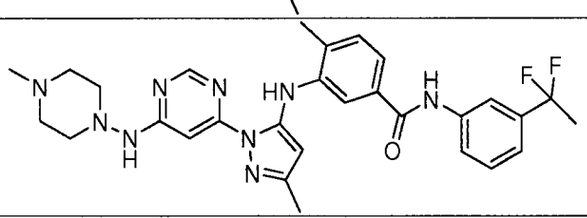
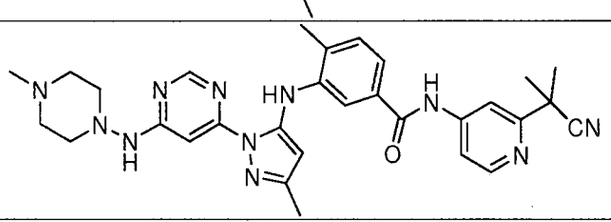
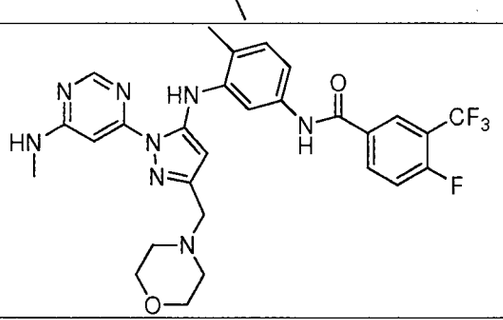
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
111		MS *m/z* 610.2 (M + 1)
112		MS *m/z* 521.2 (M + 1)
113		MS *m/z* 524.2 (M + 1)
114		MS *m/z* 507.2 (M + 1)

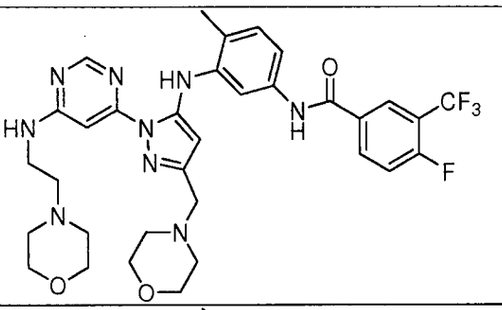
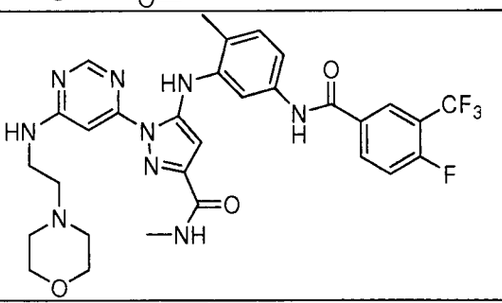
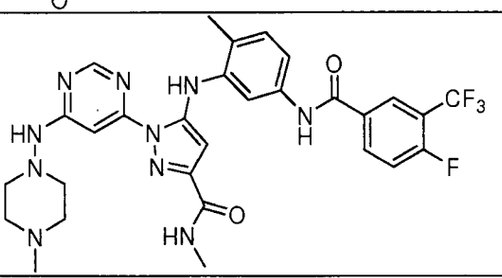
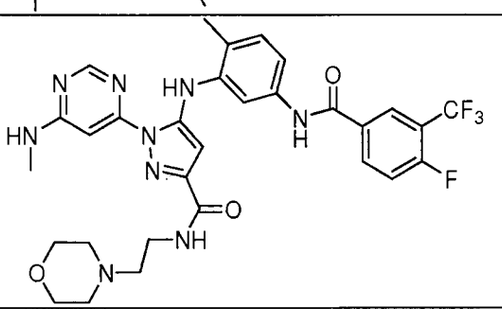
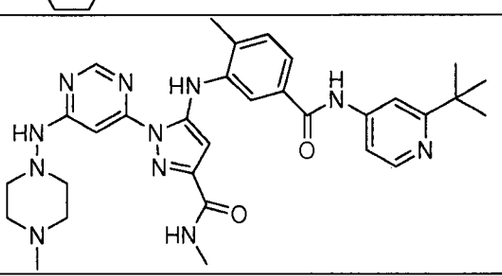
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
115		MS *m/z* 522.2 (M + 1)
116		MS *m/z* 624.3 (M + 1)
117		MS *m/z* 551.2 (M + 1)

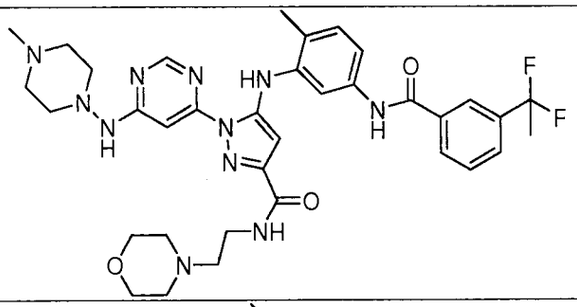
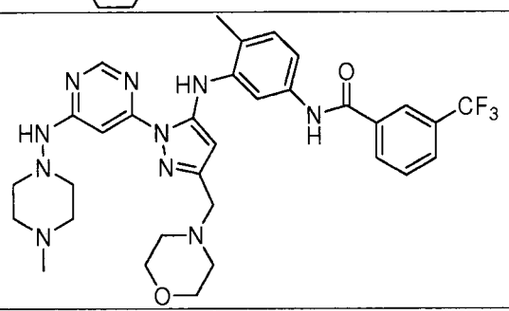
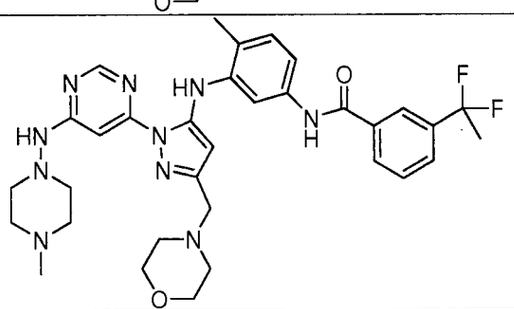
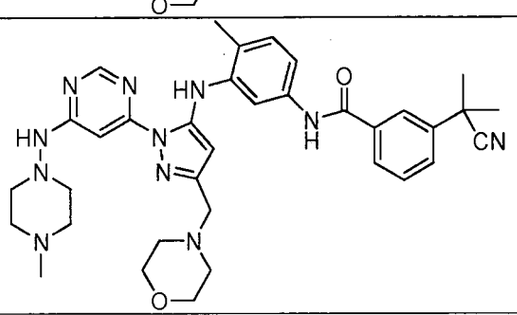
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
118		MS *m/z* 570.3 (M + 1)
119		MS *m/z* 556.3 (M + 1)

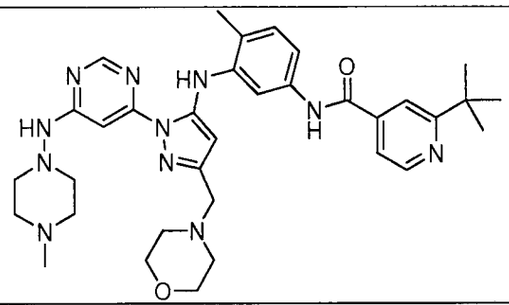
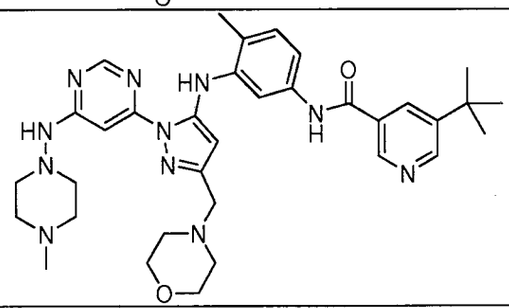
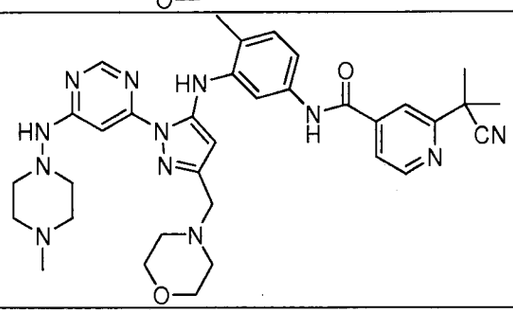
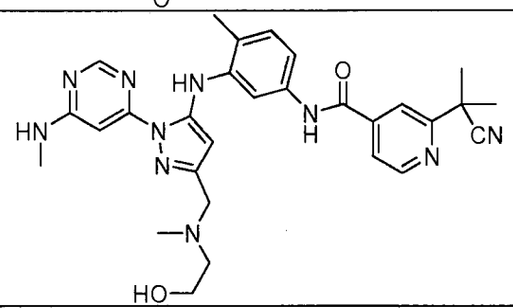
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
120		MS *m/z* 555.3 (M + 1)
121		MS *m/z* 475.2 (M + 1)
122		MS *m/z* 487.3 (M + 1)
123		MS *m/z* 559.3 (M + 1)

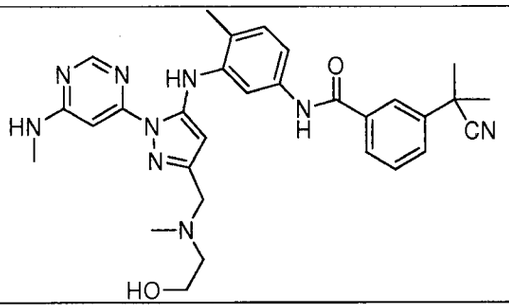
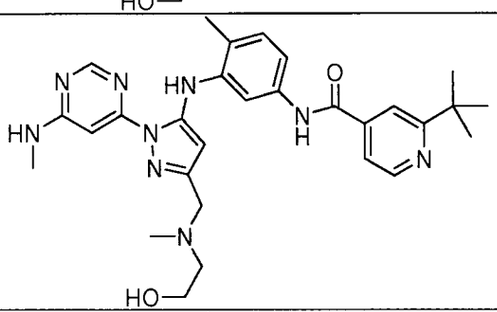
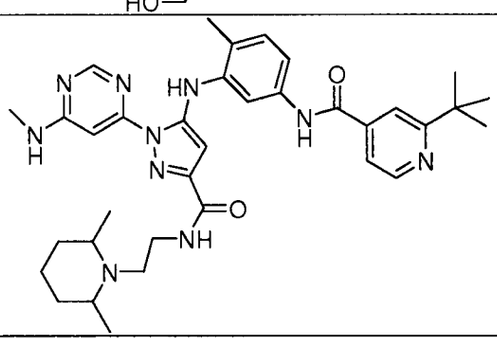
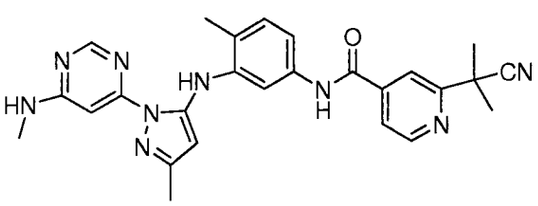
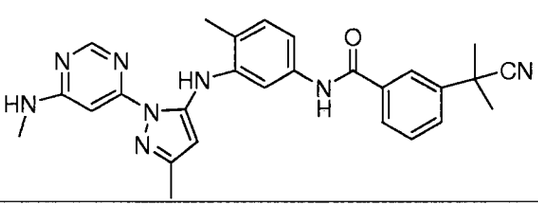
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
124		MS *m/z* 571.3 (M + 1)
125		MS *m/z* 567.3 (M + 1)
126		MS *m/z* 554.3 (M + 1)
127		MS *m/z* 471.3 (M + 1)
128		MS *m/z* 470.3 (M + 1)
129		MS *m/z* 481.3 (M + 1)

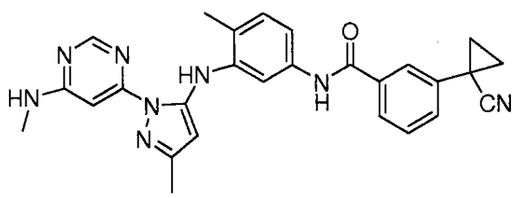
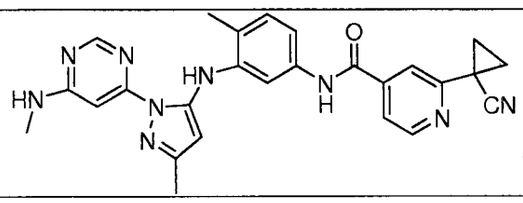
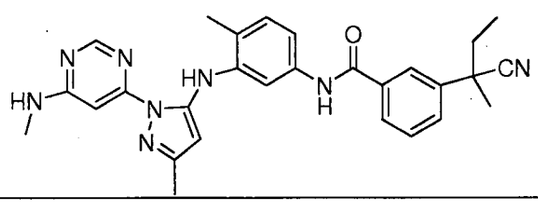
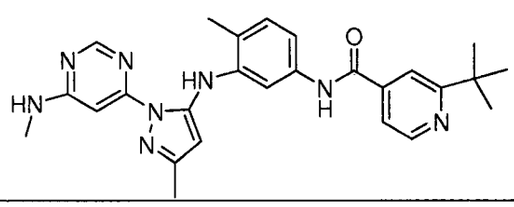
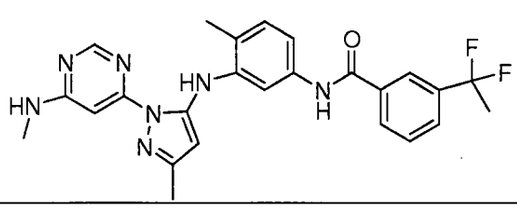
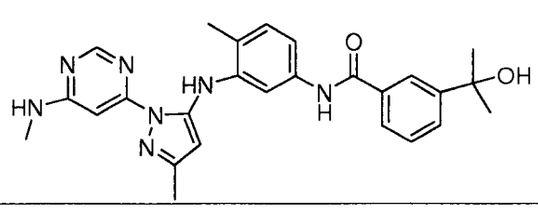
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
130		MS *m/z* 483.3 (M + 1)
131		MS *m/z* 551.3 (M + 1)
132		MS *m/z* 563.3 (M + 1)
133		MS *m/z* 562.3 (M + 1)
134		MS *m/z* 566.3 (M + 1)
135		MS *m/z* 585.3 (M + 1)

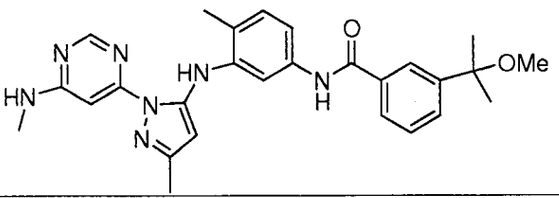
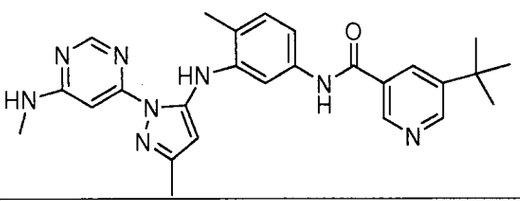
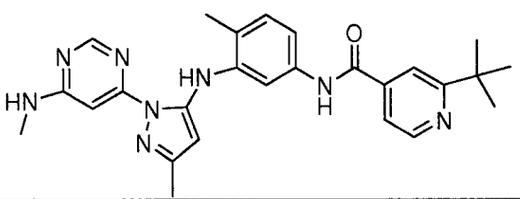
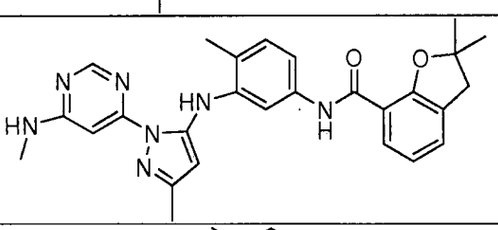
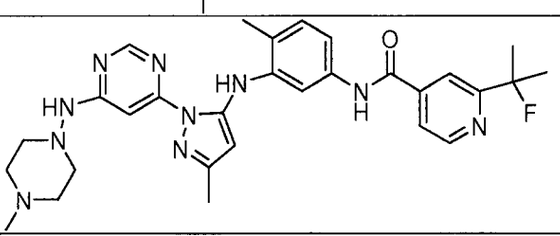
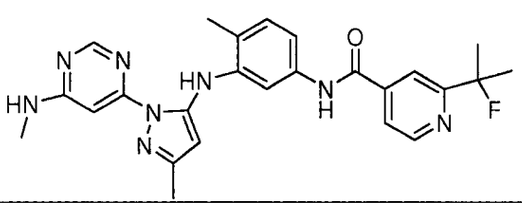
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
136		MS *m/z* 684.3 (M + 1)
137		MS *m/z* 642.3 (M + 1)
138		MS *m/z* 627.3 (M + 1)
139		MS *m/z* 642.3 (M + 1)
140		MS *m/z* 598.3 (M + 1)

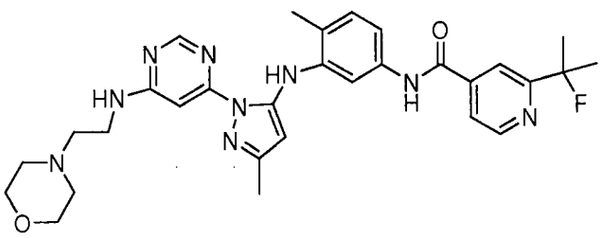
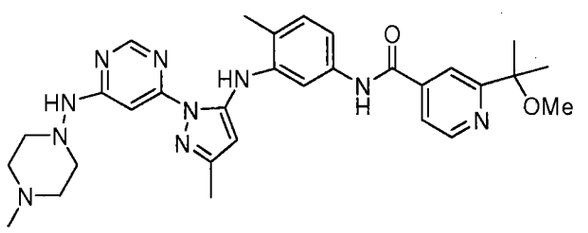
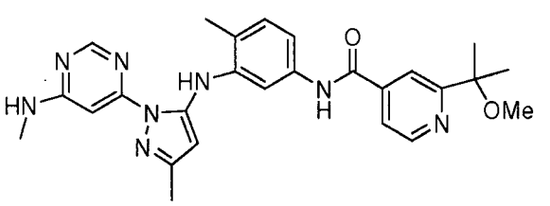
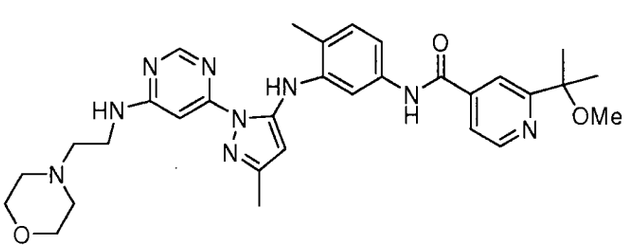
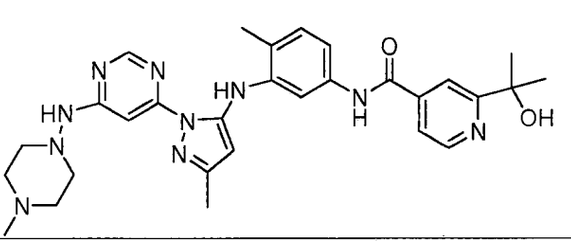
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
141		MS *m/z* 704.3 (M + 1)
142		MS *m/z* 651.3 (M + 1)
143		MS *m/z* 647.3 (M + 1)
144		MS *m/z* 650.3 (M + 1)

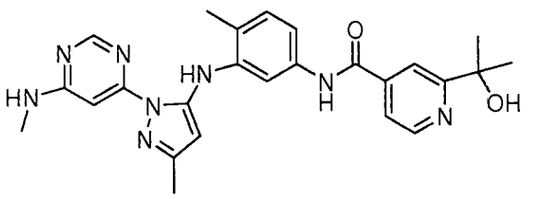
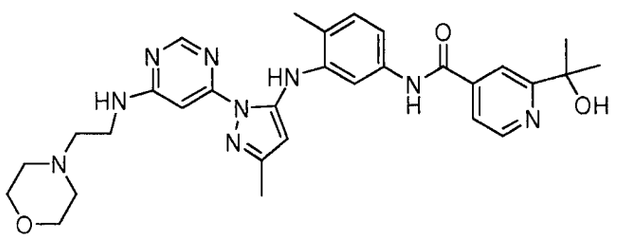
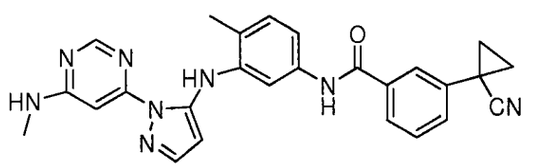
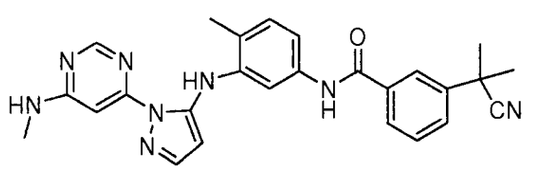
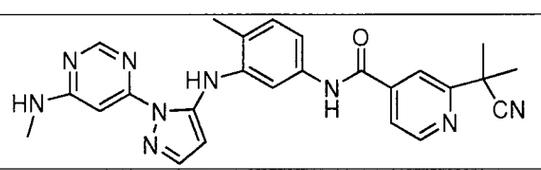
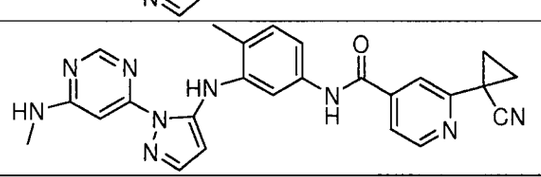
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
145		MS *m/z* 640.3 (M + 1)
146		MS *m/z* 640.3 (M + 1)
147		MS *m/z* 651.3 (M + 1)
148		MS *m/z* 555.3 (M + 1)

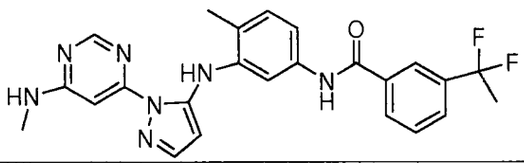
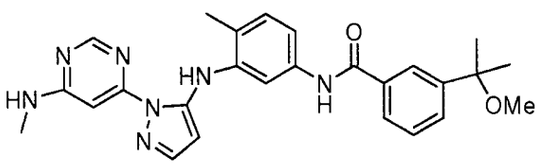
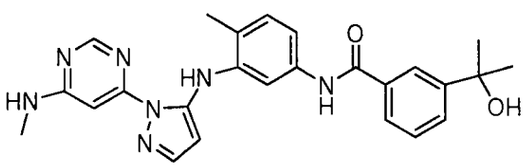
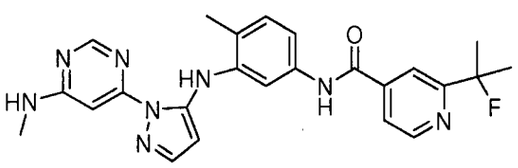
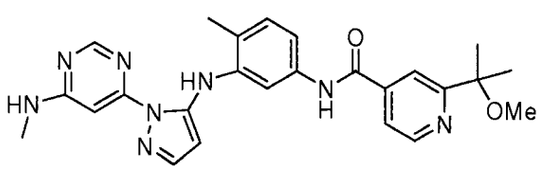
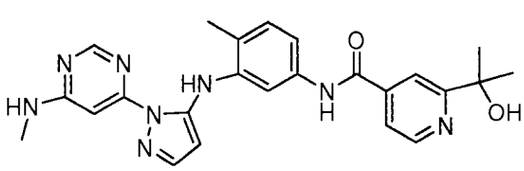
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
149		MS *m/z* 554.3 (M + 1)
150		MS *m/z* 544.3 (M + 1)
151		MS *m/z* 639.3 (M + 1)
152		MS *m/z* 482.2 (M + 1)
153		MS *m/z* 481.2 (M + 1)

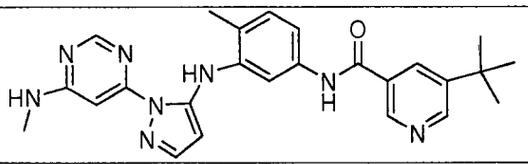
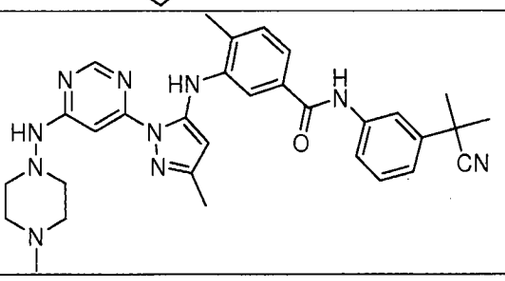
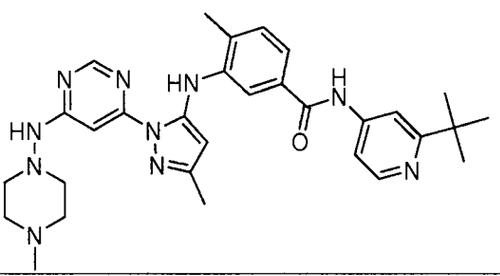
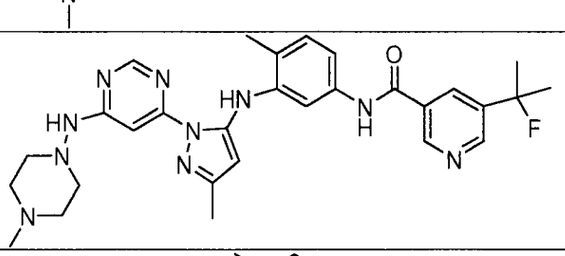
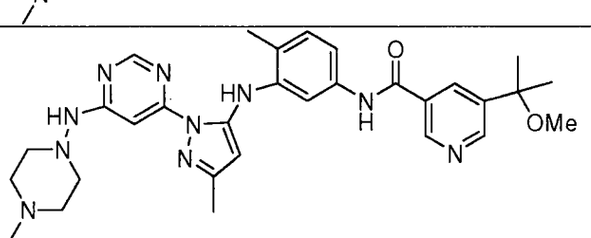
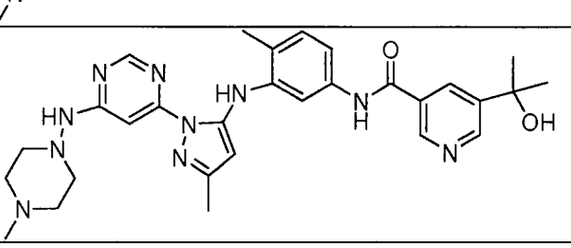
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
154		MS *m/z* 479.2(M + 1)
155		MS *m/z* 480.2 (M + 1)
156		MS *m/z* 495.3 (M + 1)
157		MS *m/z* 471.3 (M + 1)
158		MS *m/z* 478.2 (M + 1)
159		MS *m/z* 472.2 (M + 1)

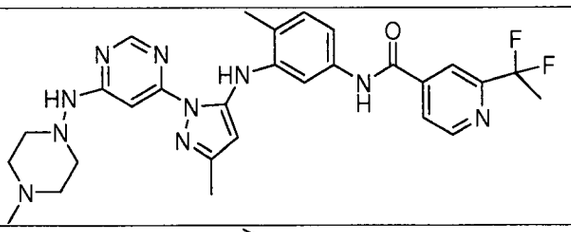
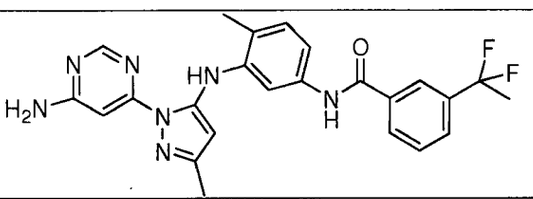
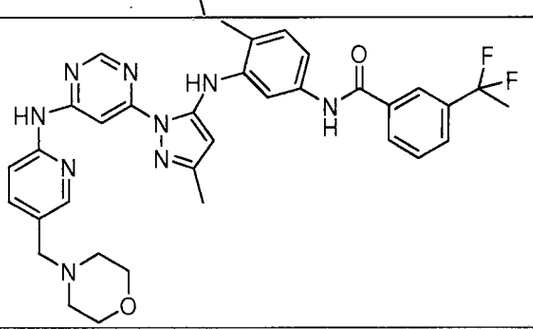
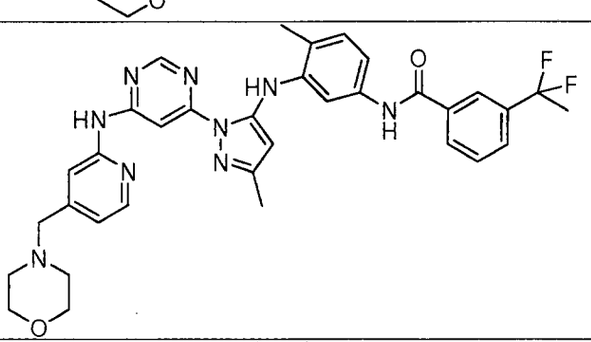
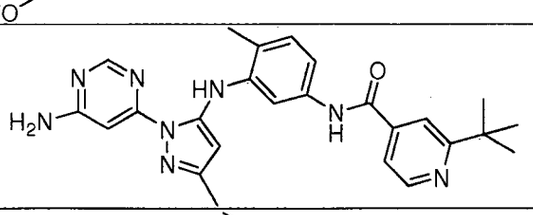
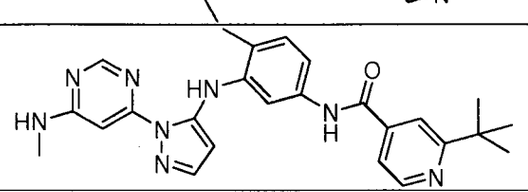
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
160		MS *m/z* 486.3 (M + 1)
161		MS *m/z* 471.3 (M + 1)
162		MS *m/z* 471.3 (M + 1)
163		MS *m/z* 484.2 (M + 1)
164		MS *m/z* 559.3 (M + 1)
165		MS *m/z* 475.2 (M + 1)

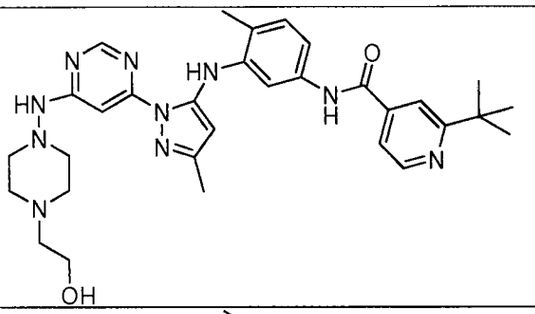
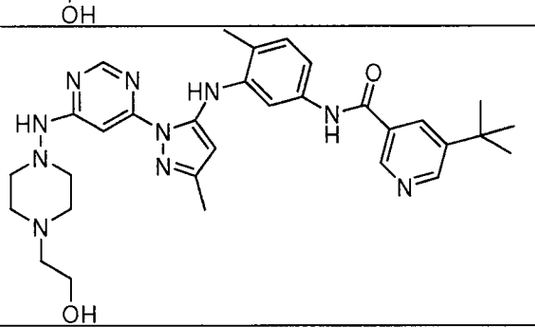
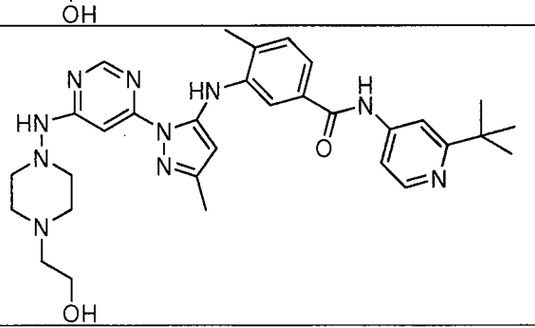
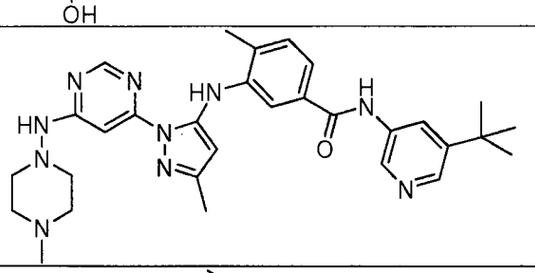
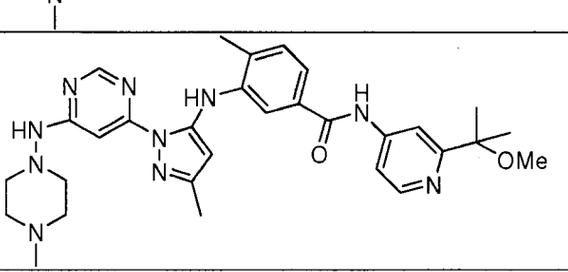
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
166		MS *m/z* 574.3 (M + 1)
167		MS *m/z* 571.3 (M + 1)
168		MS *m/z* 487.3 (M + 1)
169		MS *m/z* 586.3 (M + 1)
170		MS *m/z* 557.3 (M + 1)

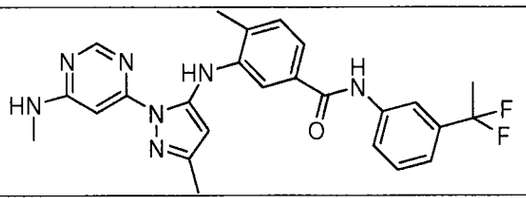
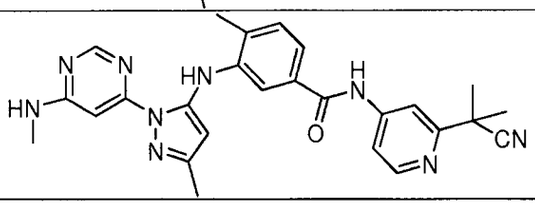
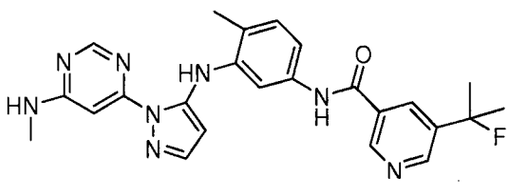
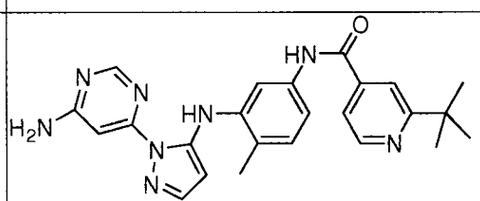
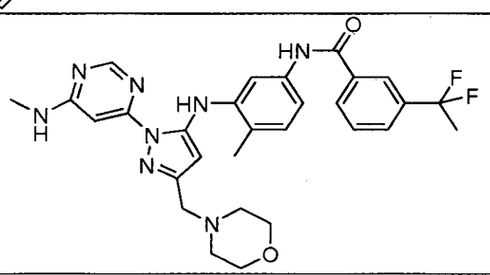
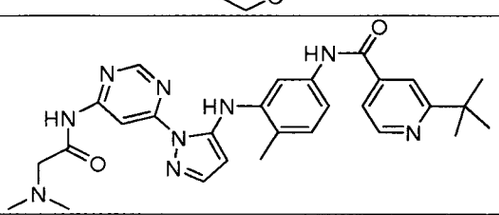
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
171		MS *m/z* 473.2 (M + 1)
172		MS *m/z* 572.3 (M + 1)
173		MS *m/z* 465.2 (M + 1)
174		MS *m/z* 467.2 (M + 1)
175		MS *m/z* 468.2 (M + 1)
176		MS *m/z* 466.2 (M + 1)

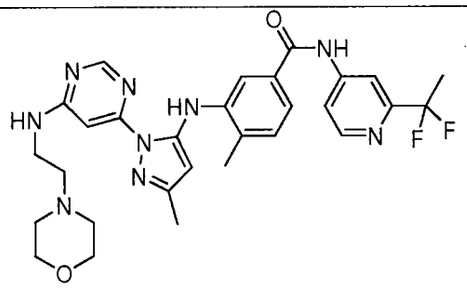
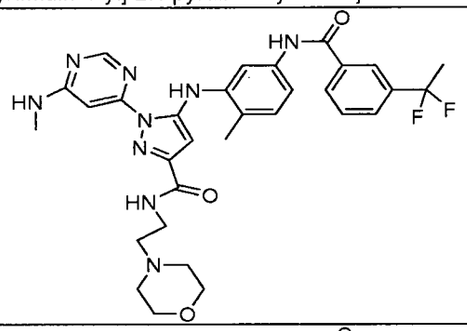
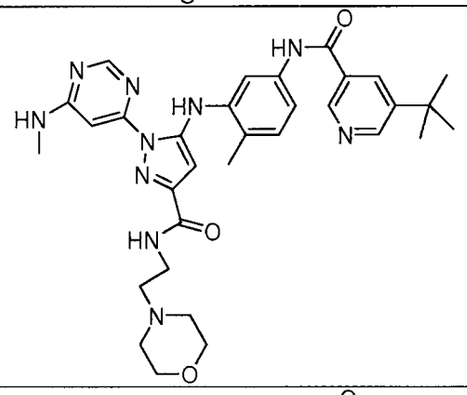
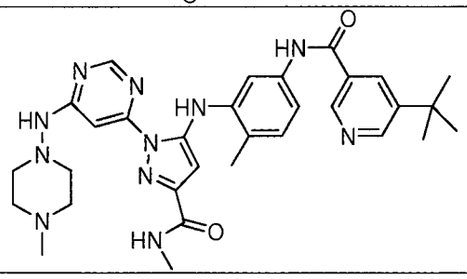
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
177		MS *m/z* 464.2 (M + 1)
178		MS *m/z* 472.2 (M + 1)
179		MS *m/z* 458.2 (M + 1)
180		MS *m/z* 461.2 (M + 1)
181		MS *m/z* 473.2 (M + 1)
182		MS *m/z* 459.2 (M + 1)

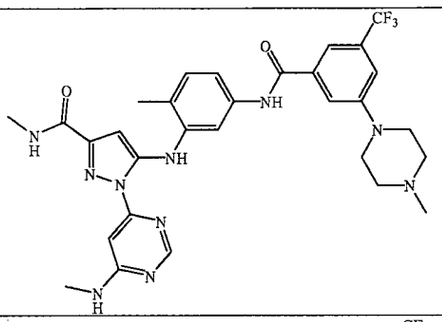
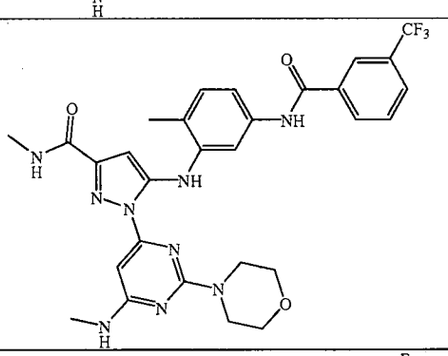
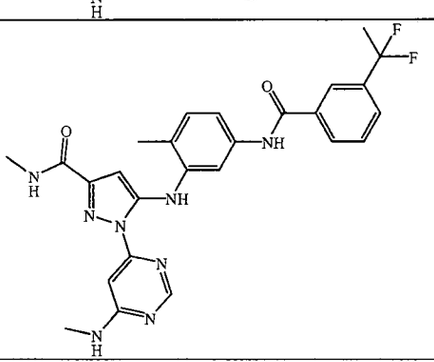
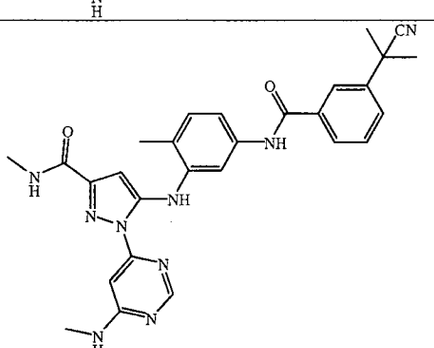
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
183		MS *m/z* 457.2 (M + 1)
184		MS *m/z* 565.3 (M + 1)
185		MS *m/z* 555.3 (M + 1)
186		MS *m/z* 559.3 (M + 1)
187		MS *m/z* 571.3 (M + 1)
188		MS *m/z* 557.3 (M + 1)

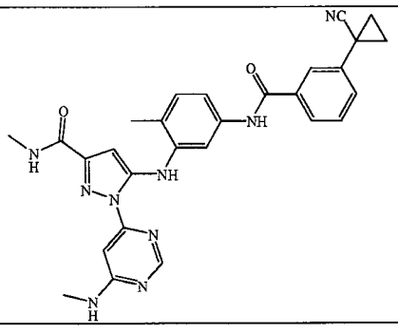
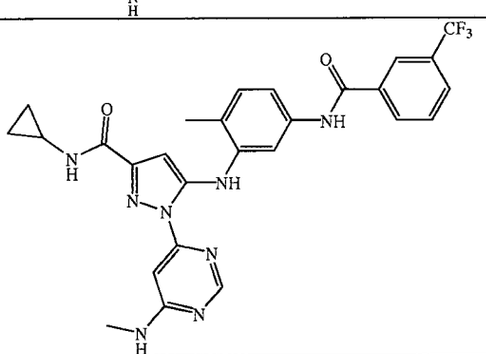
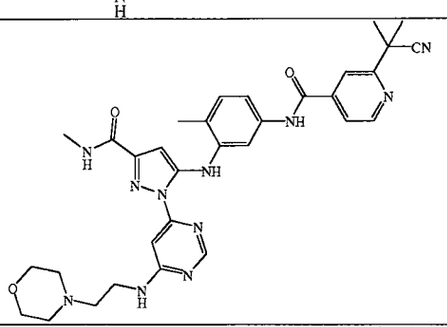
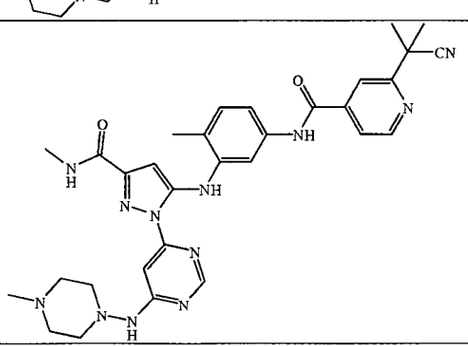
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
189		MS *m/z* 563.3 (M + 1)
190		MS *m/z* 464.2 (M + 1)
191		MS *m/z* 640.3 (M + 1)
192		MS *m/z* 640.3 (M + 1)
193		MS *m/z* 457.2 (M + 1)
194		MS *m/z* 457.2 (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
195		MS *m/z* 585.3 (M + 1)
196		MS *m/z* 585.3 (M + 1)
197		MS *m/z* 585.3 (M + 1)
198		MS *m/z* 555.3 (M + 1)
199		MS *m/z* 571.3 (M + 1)

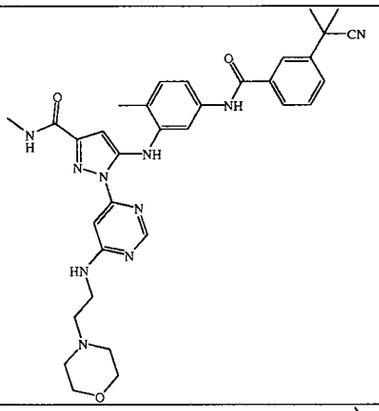
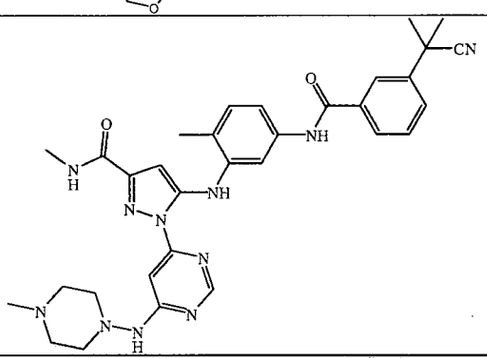
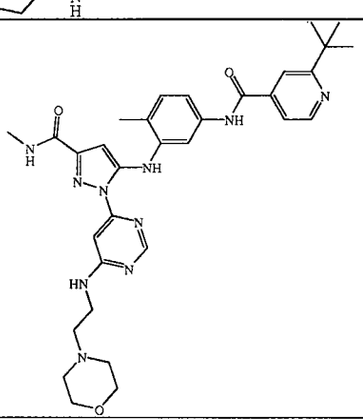
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
200		MS *m/z* 478.2 (M + 1)
201		MS *m/z* 482.2 (M + 1)
202		MS *m/z* 461.2 (M + 1)
203		MS 443.2 *m/z* (M + 1)
204		MS 563.3 *m/z* (M + 1)
205		Ms 528.3 *m/z* (M + 1)

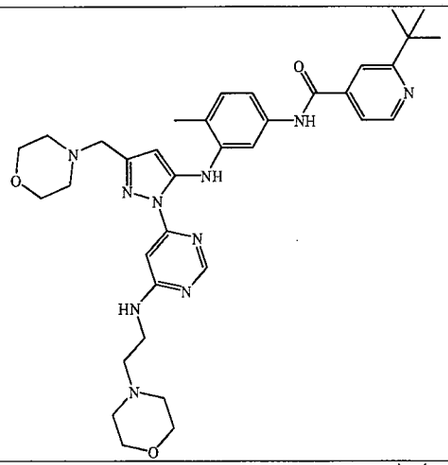
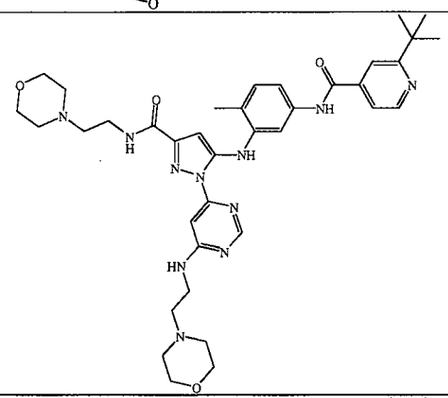
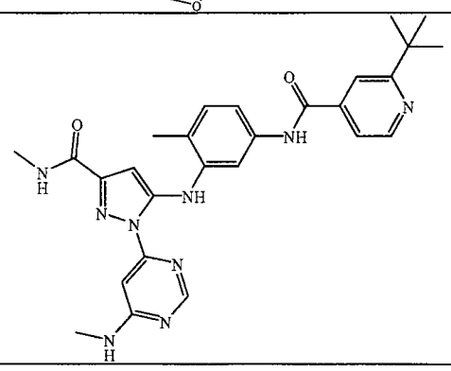
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
206	 *N*-[2-(1,1-Difluoro-ethyl)-pyridin-4-yl]-4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2*H*-pyrazol-3-ylamino}-benzamide	Ms 577.3 *m/z* (M + 1)
207		Ms 620.3 *m/z* (M + 1)
208		Ms 613.3 *m/z* (M + 1)
209		Ms 598.3 *m/z* (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
210		MS *m/z* 623.3 (M + 1)
211		MS *m/z* 610.3 (M + 1)
212		MS *m/z* 521.3 (M + 1)
213		MS *m/z* 524.3 (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
214		MS *m/z* 522.3 (M + 1)
215		MS *m/z* 551.3 (M + 1)
216		MS *m/z* 624.3 (M + 1)
217		MS *m/z* 609.3 (M + 1)

150

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
218		MS *m/z* 623.3 (M + 1)
219		MS *m/z* 608.3 (M + 1)
220		MS *m/z* 613.3 (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
221		MS *m/z* 655.4 (M + 1)
222		MS *m/z* 712.4 (M + 1)
223		MS *m/z* 514.3 (M + 1)

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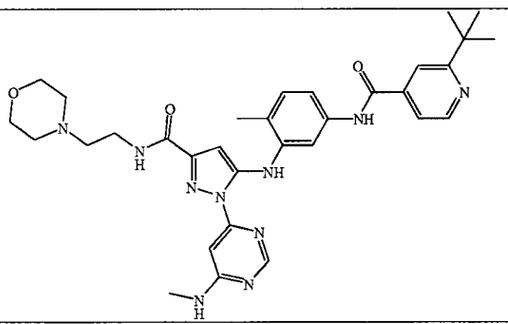
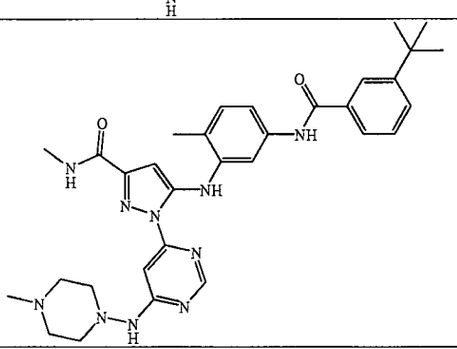
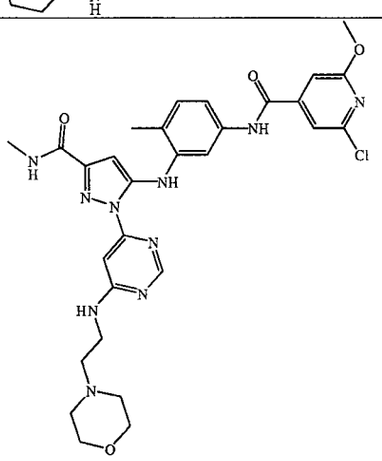
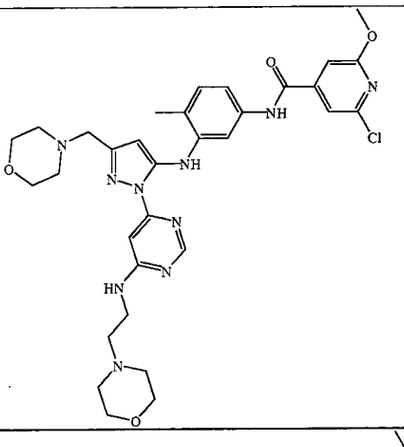
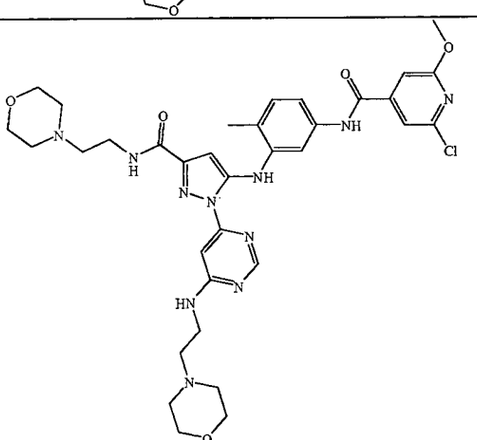
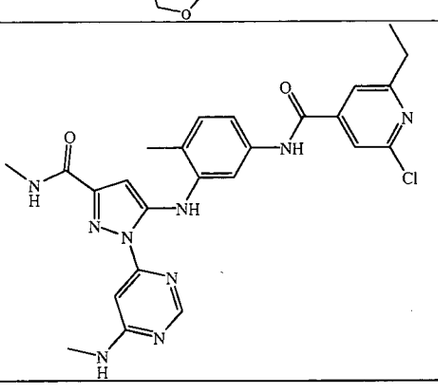
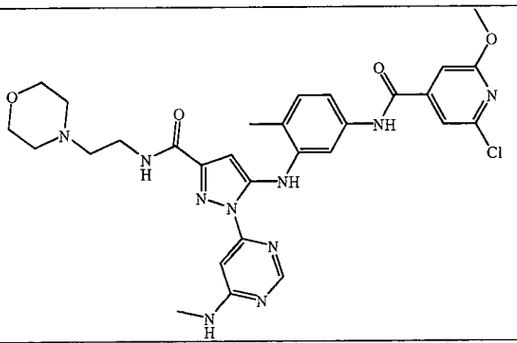
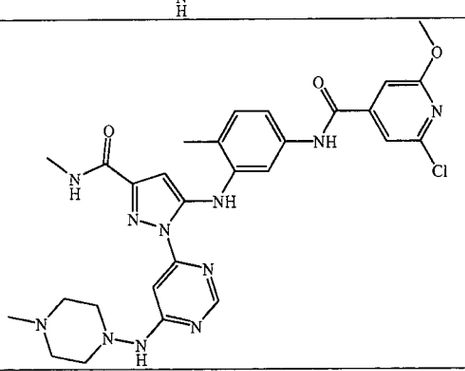
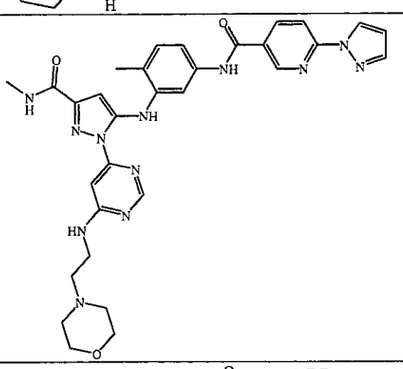
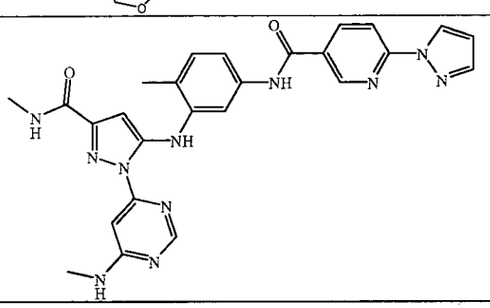
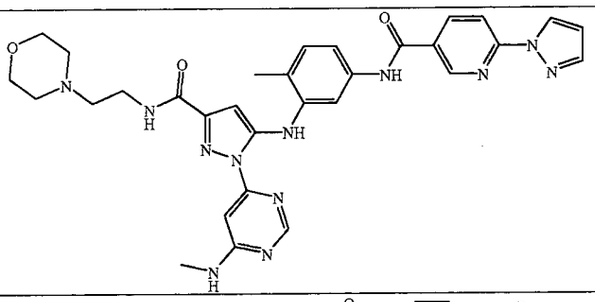
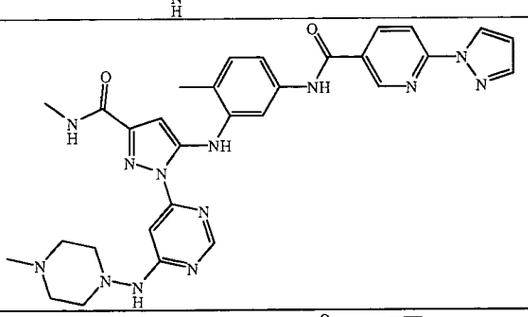
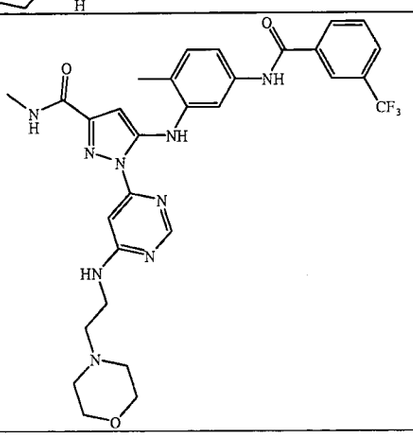
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
224		MS *m/z* 613.3 (M + 1)
225		MS *m/z* 597.3 (M + 1)
226	 2-Chloro-6-methoxy-*N*-(4-methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2*H*-pyrazol-3-ylamino}-phenyl)-isonicotinamide	MS *m/z* 620.3 (M + 1)

153

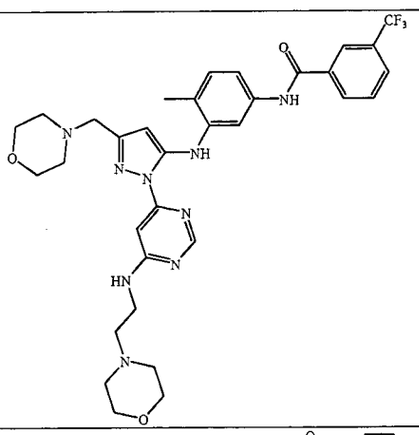
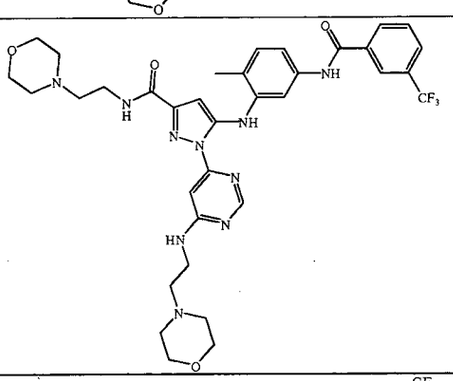
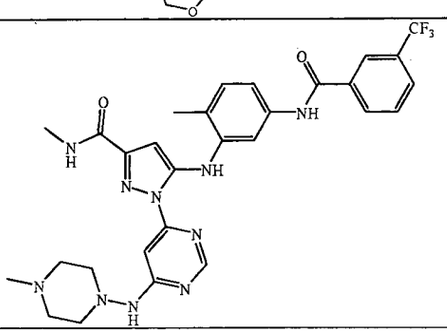
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
227		MS *m/z* 663.3 (M + 1)
228		MS *m/z* 720.3 (M + 1)
229		MS *m/z* 520.2 (M + 1)

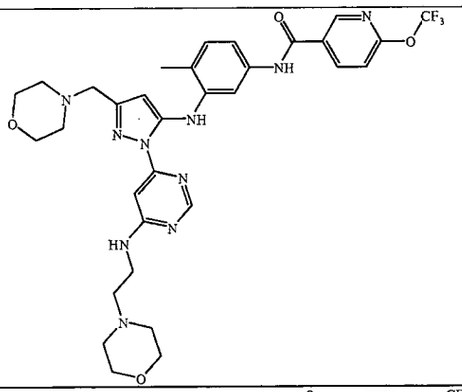
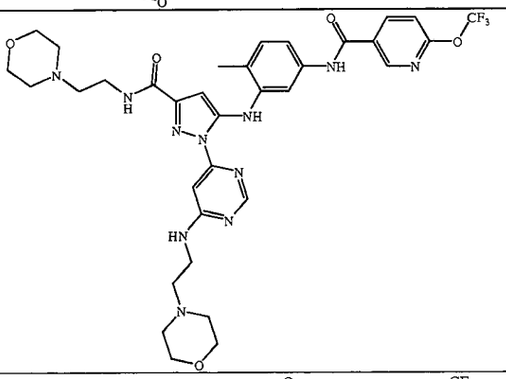
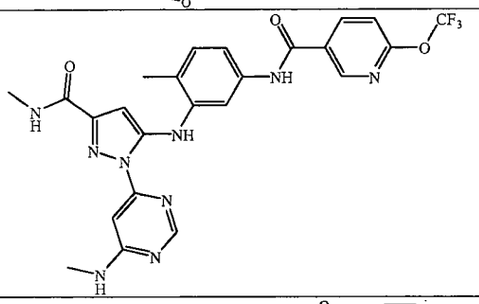
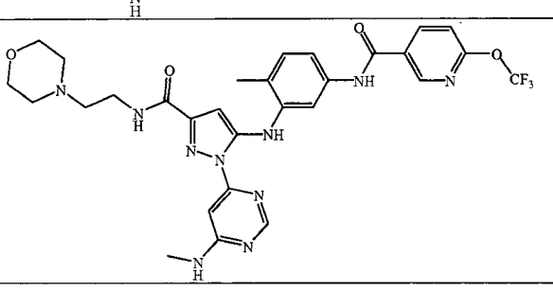
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
230		MS *m/z* 620.2 (M + 1)
231		MS *m/z* 606.2 (M + 1)
232		MS *m/z* 623.3 (M + 1)
233		MS *m/z* 524.2 (M + 1)

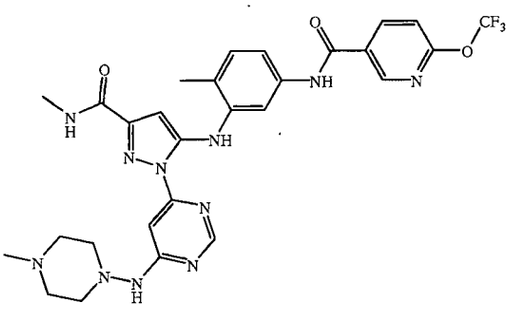
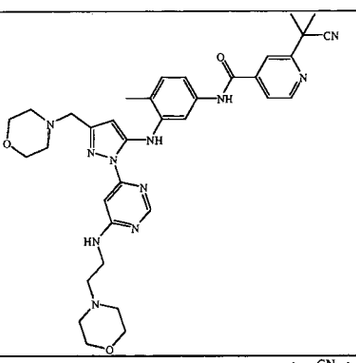
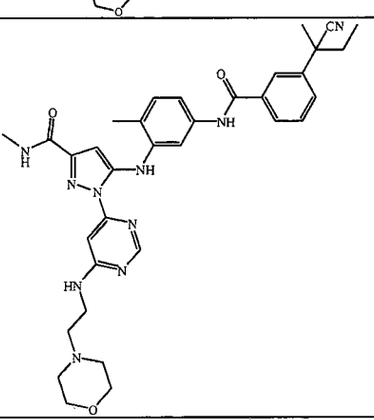
155

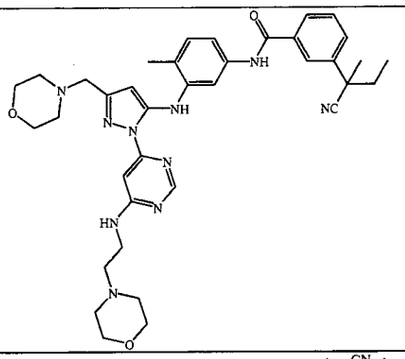
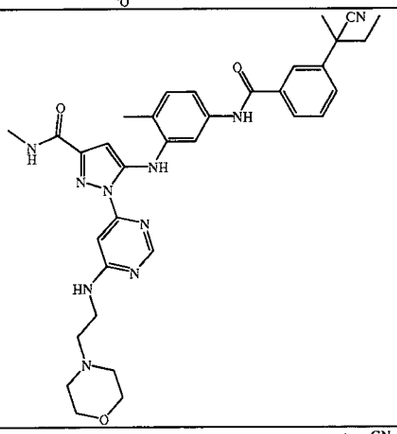
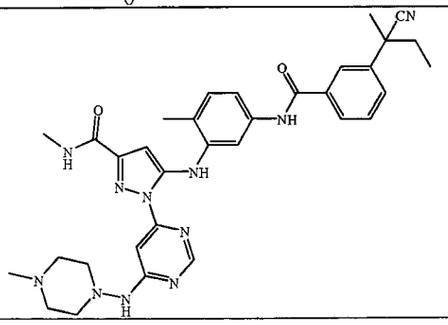
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
234		MS *m/z* 623.3 (M + 1)
235		MS *m/z* 608.3 (M + 1)
236		MS *m/z* 624.3 (M + 1)

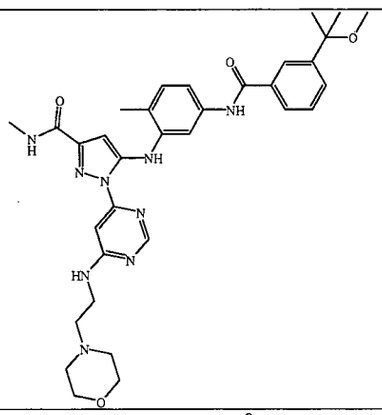
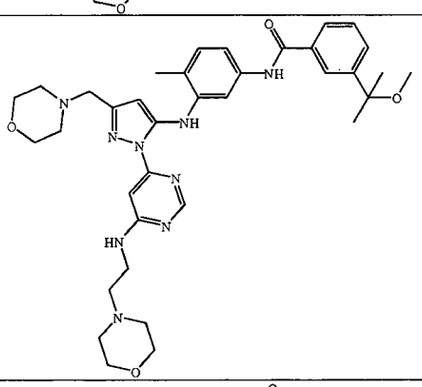
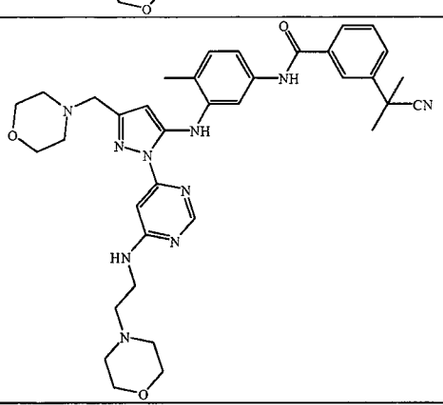
156

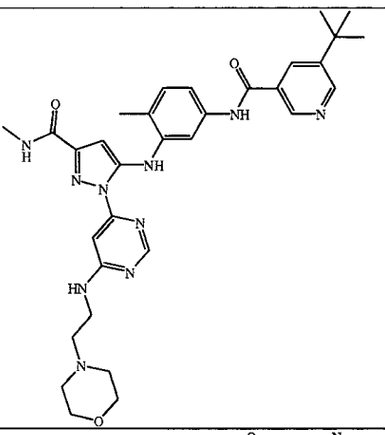
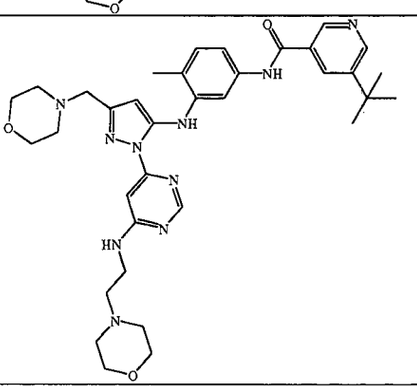
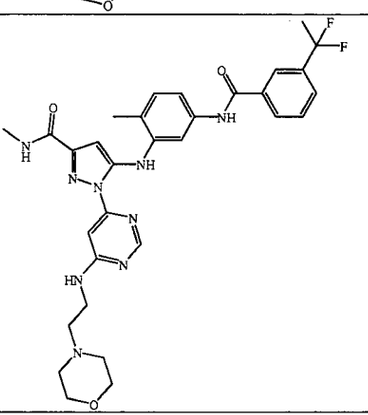
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
237		MS *m/z* 666.3 (M + 1)
238		MS *m/z* 723.3 (M + 1)
239		MS *m/z* 609.3 (M + 1)

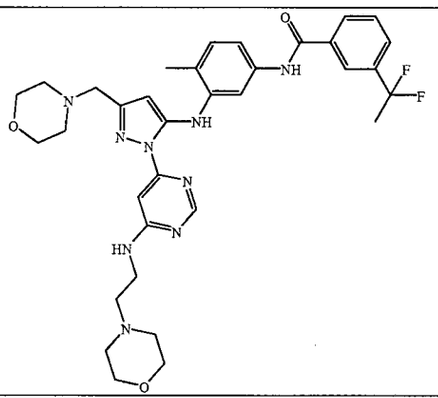
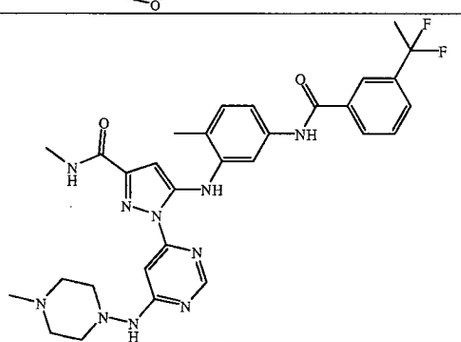
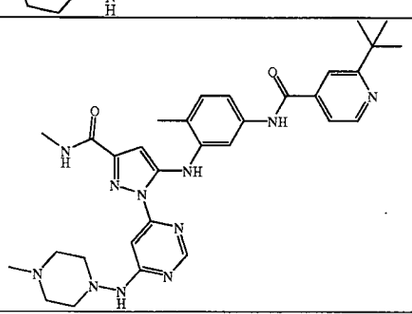
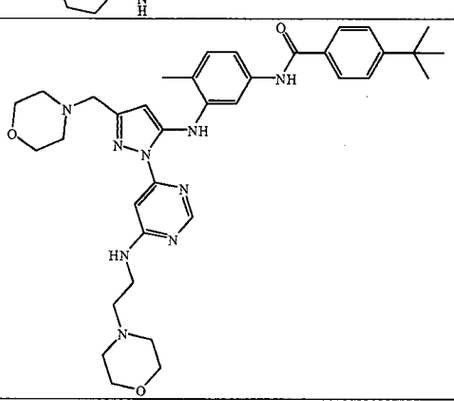
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
240		MS *m/z* 683.3 (M + 1)
241		MS *m/z* 740.3 (M + 1)
242		MS *m/z* 542.2 (M + 1)
243		MS *m/z* 640.3 (M + 1)

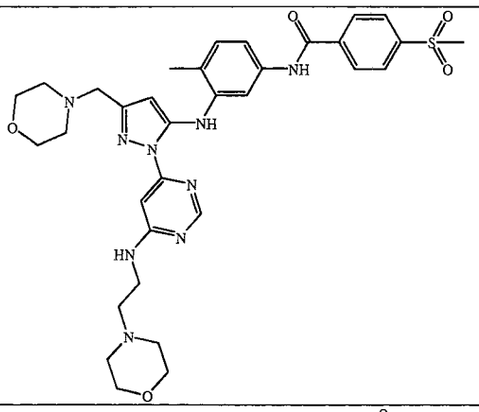
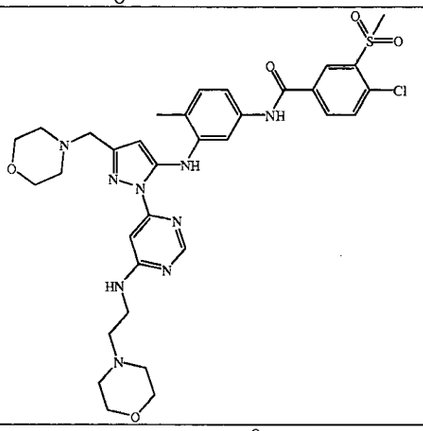
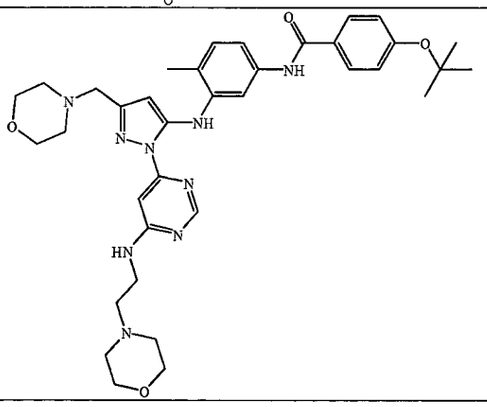
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
244		MS *m/z* 626.3 (M + 1)
245		MS *m/z* 666.4 (M + 1)
246		MS *m/z* 637.3 (M + 1)

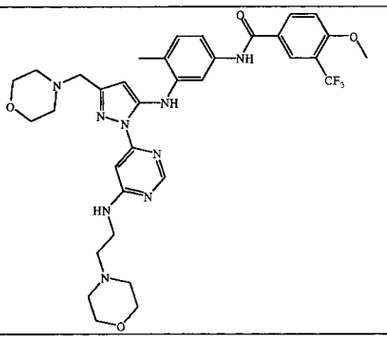
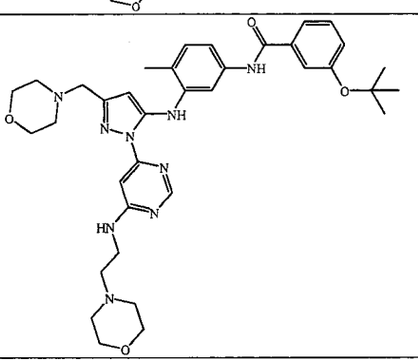
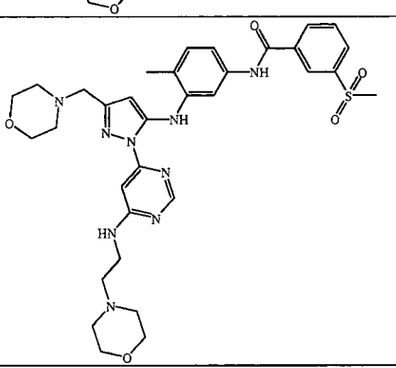
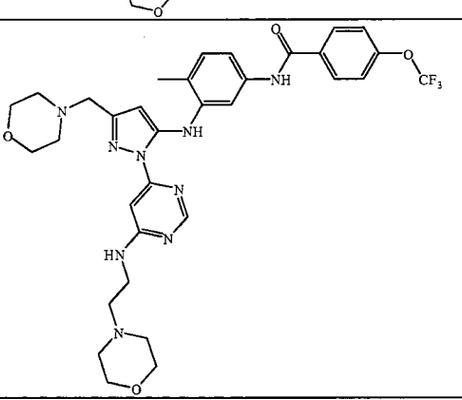
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
247		MS *m/z* 679.4 (M + 1)
248		MS *m/z* 637.3 (M + 1)
249		MS *m/z* 622.3 (M + 1)

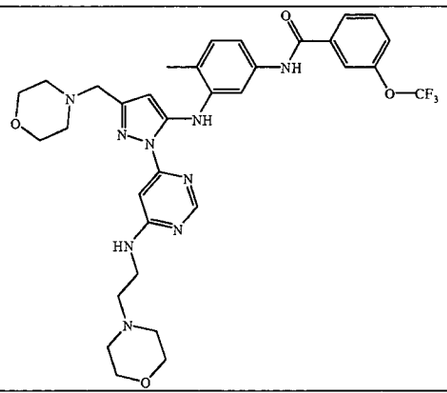
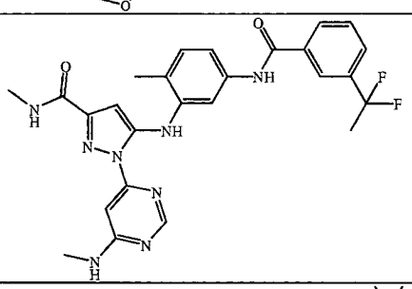
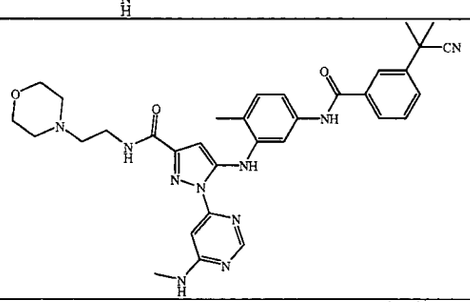
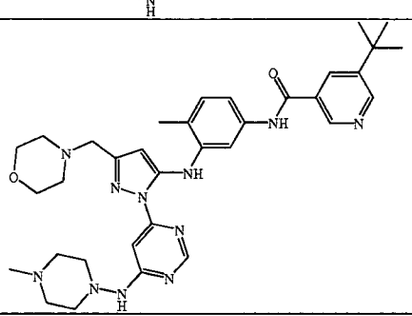
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
250		MS *m/z* 628.3 (M + 1)
251		MS *m/z* 670.4 (M + 1)
252		MS *m/z* 665.4 (M + 1)

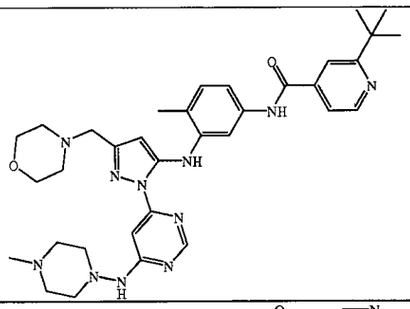
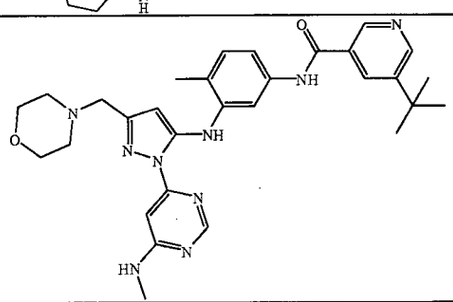
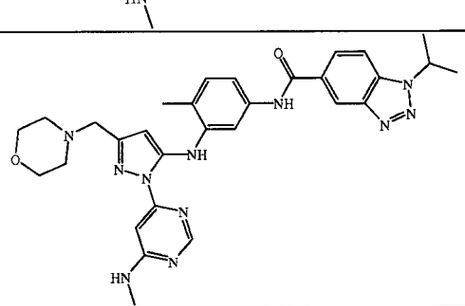
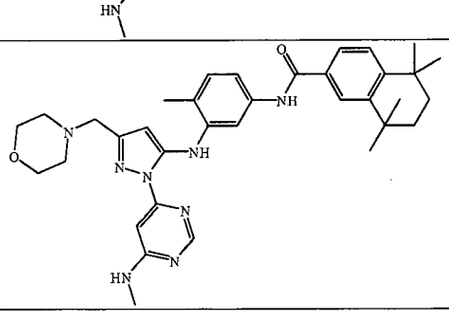
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
253		MS *m/z* 613.3 (M + 1)
254		MS *m/z* 655.4(M + 1)
255		MS *m/z* 620.3 (M + 1)

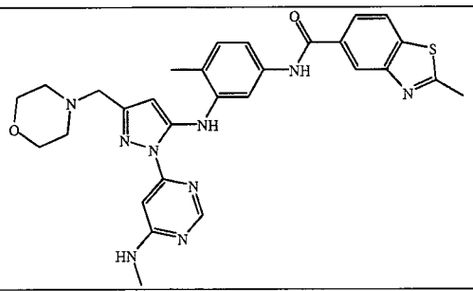
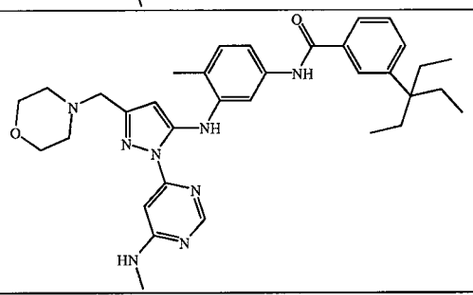
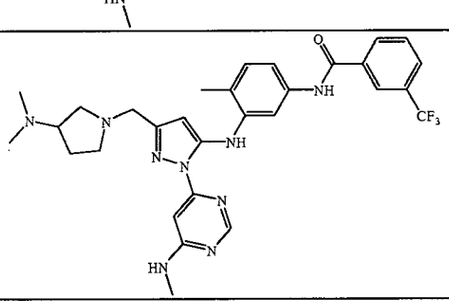
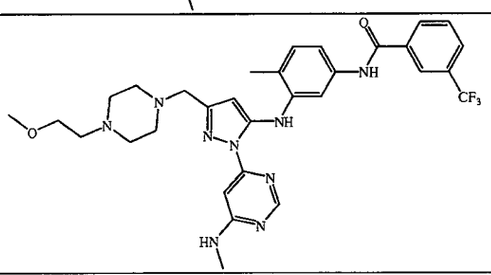
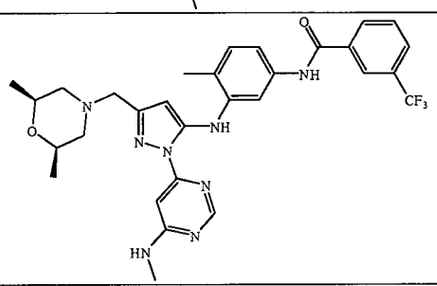
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
256		MS *m/z* 662.3 (M + 1)
257		MS *m/z* 605.3 (M + 1)
258		MS *m/z* 598.3 (M + 1)
259		MS *m/z* 654.4 (M + 1)

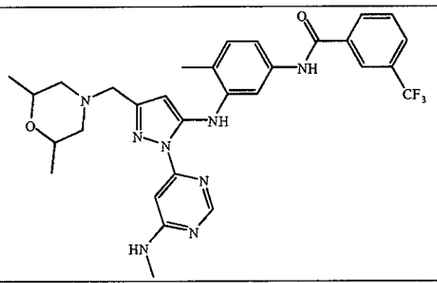
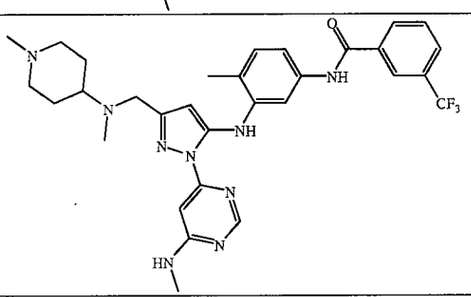
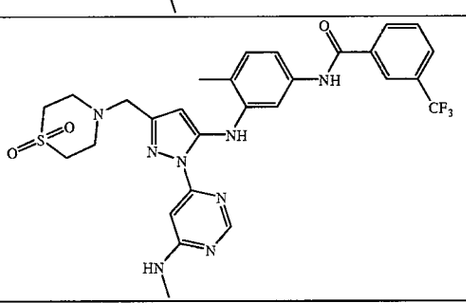
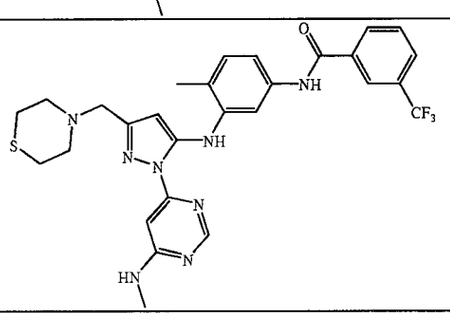
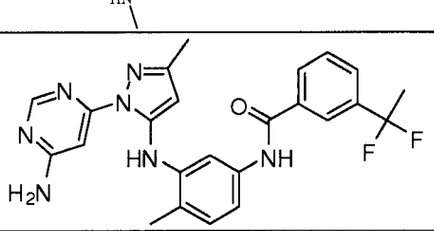
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
260		MS *m/z* 676.3 (M + 1)
261		MS *m/z* 710.3 (M + 1)
262		MS *m/z* 670.4 (M + 1)

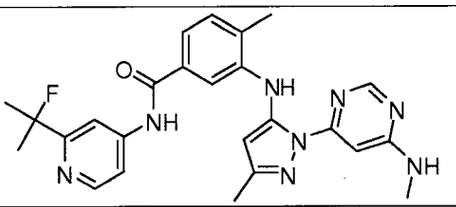
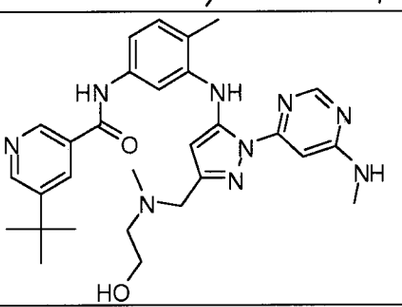
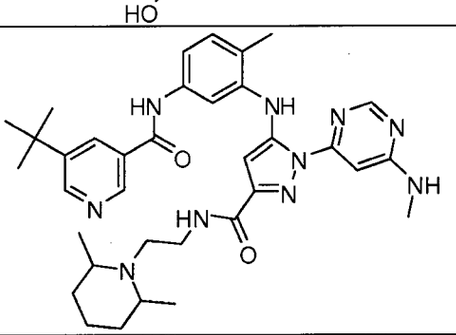
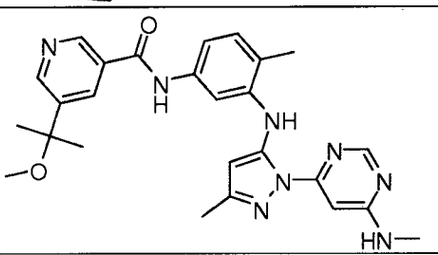
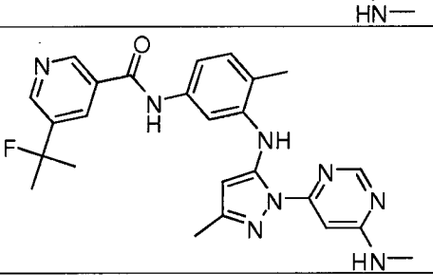
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
263		MS *m/z* 696.3 (M + 1)
264		MS *m/z* 670.4 (M + 1)
265		MS *m/z* 676.3 (M + 1)
266		MS *m/z* 682.3 (M + 1)

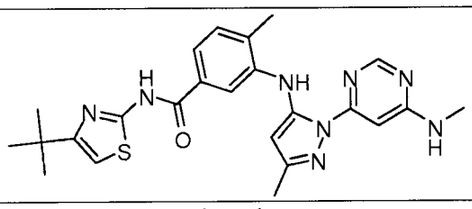
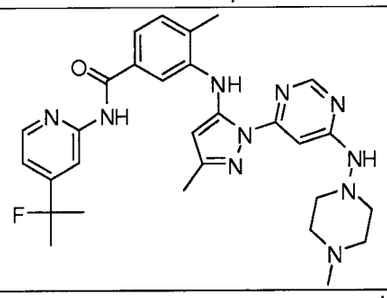
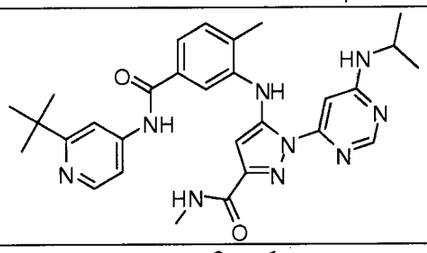
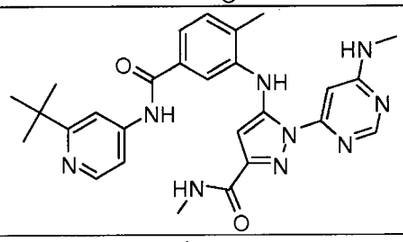
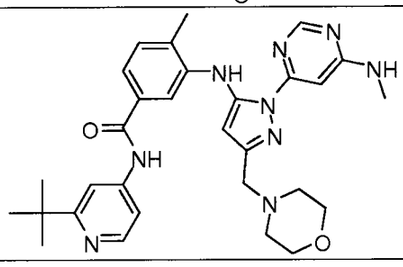
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
267		MS *m/z* 682.3 (M + 1)
268		MS *m/z* 521.2 (M + 1)
269		MS *m/z* 623.3 (M + 1)
270		MS *m/z* 640.4 (M + 1)

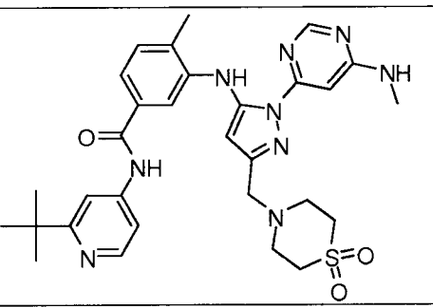
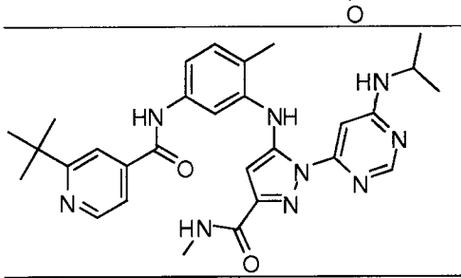
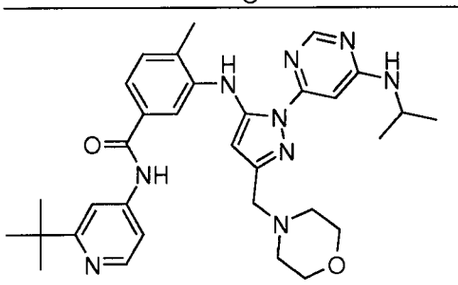
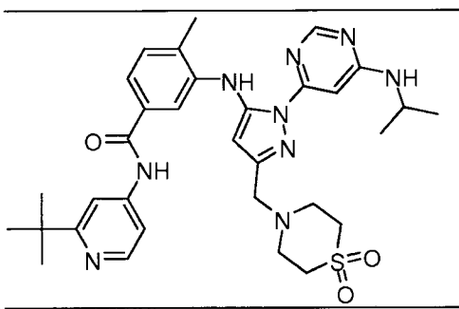
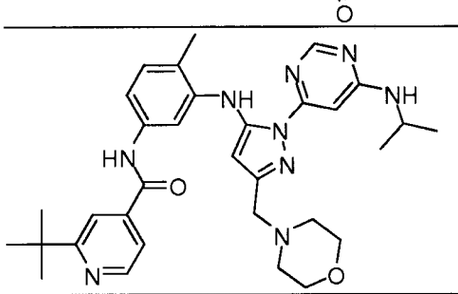
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
271		MS *m/z* 682.3 (M + 1)
272		MS *m/z* 556.3 (M + 1)
273		MS *m/z* 582.3 (M + 1)
274		MS *m/z* 609.4 (M + 1)

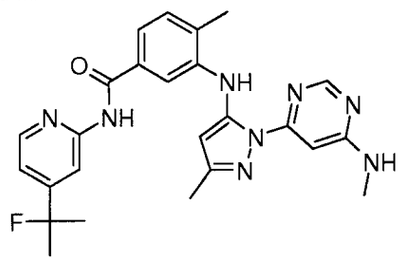
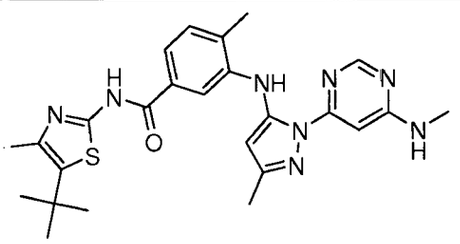
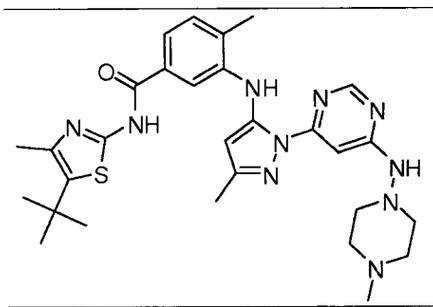
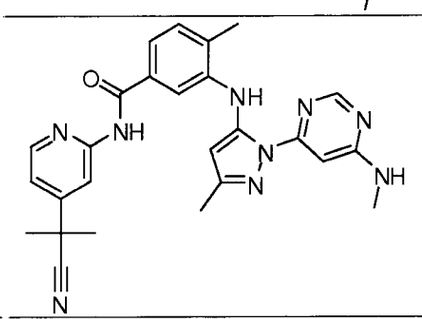
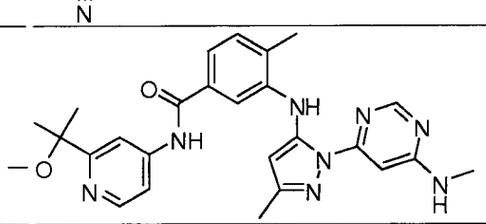
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
275		MS *m/z* 570.2 (M + 1)
276		MS *m/z* 597.4 (M + 1)
277		MS *m/z* 594.3 (M + 1)
278		MS *m/z* 624.3 (M + 1)
279		MS *m/z* 595.3 (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
280		MS *m/z* 595.3 (M + 1)
281		MS *m/z* 608.3 (M + 1)
282		MS *m/z* 615.2 (M + 1)
283		MS *m/z* 583.2 (M + 1)
284		MS m/z 464.2 (M + 1)

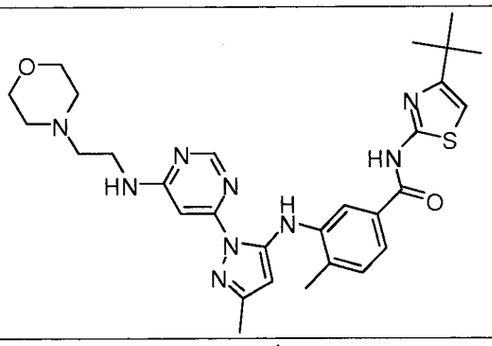
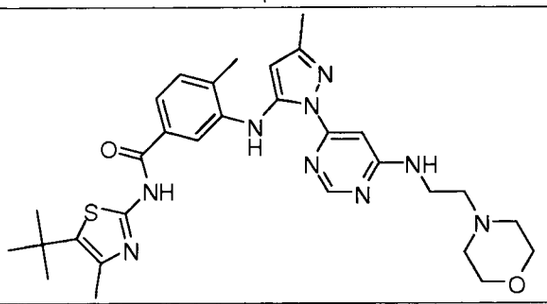
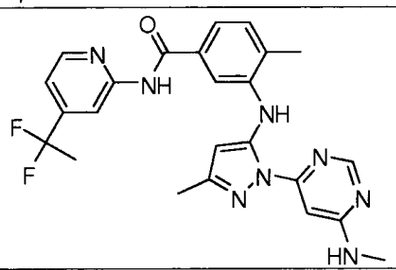
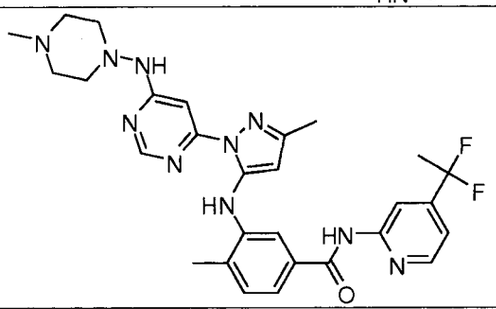
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
285		MS 474.2 m/z (M + 1)
286		MS m/z 544.3 (M + 1)
287		MS m/z 639.4 (M + 1)
288		MS m/z 487.3 (M + 1)
289		MS m/z 475.2 (M + 1)

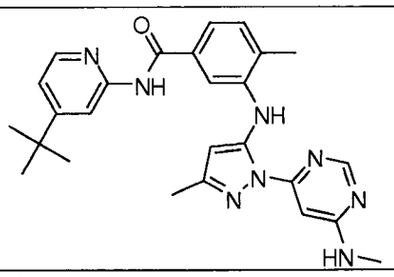
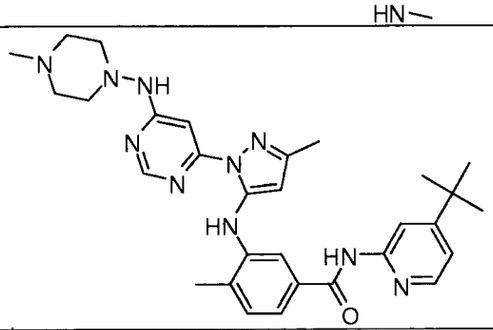
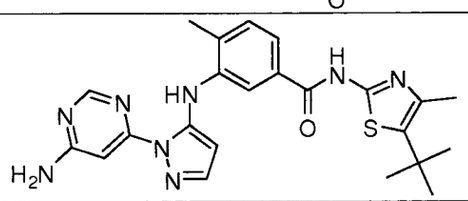
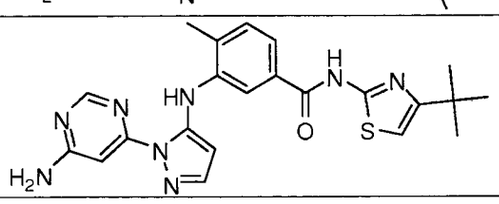
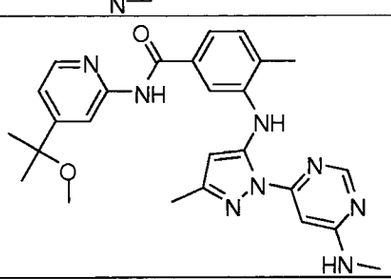
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
290		MS m/z 477.2 (M + 1)
291		MS m/z 559.3 (M + 1)
292		MS m/z 542.3 (M + 1)
293		MS m/z 514.3 (M + 1)
294		MS m/z 556.3 (M + 1)

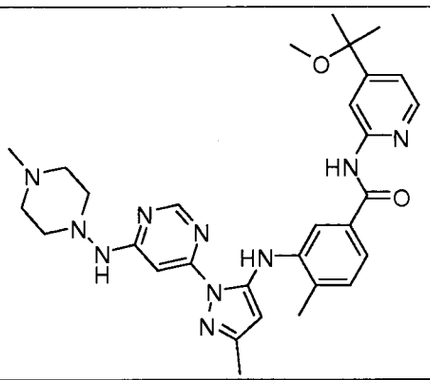
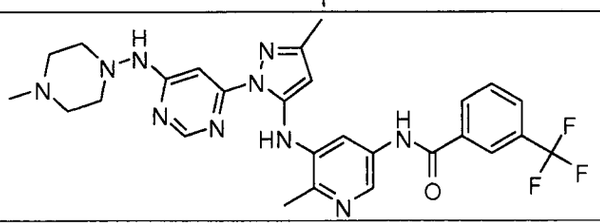
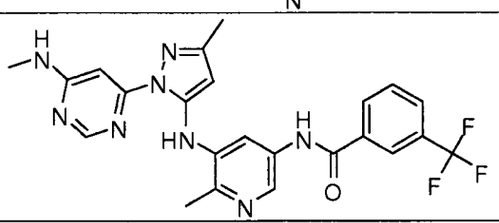
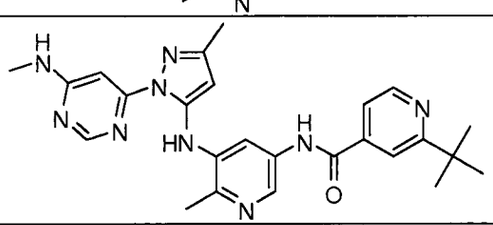
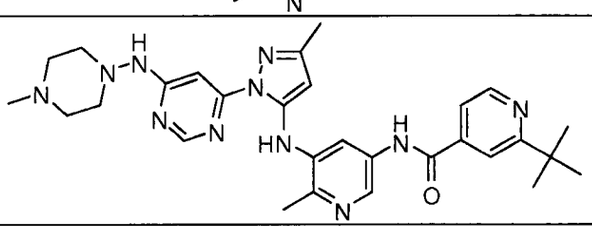
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
295		MS m/z 604.3(M + 1)
296		MS m/z 542.3 (M + 1)
297		MS m/z 584.3 (M + 1)
298		MS m/z 632.3 (M + 1)
299		MS m/z 584.3 (M + 1)

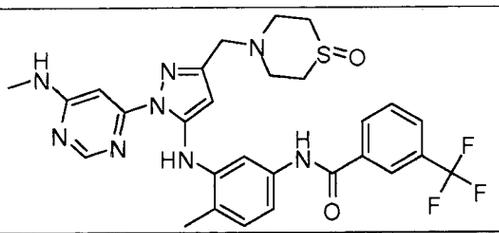
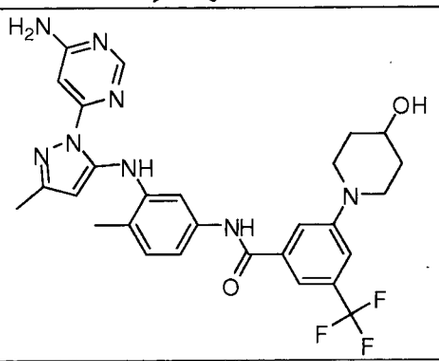
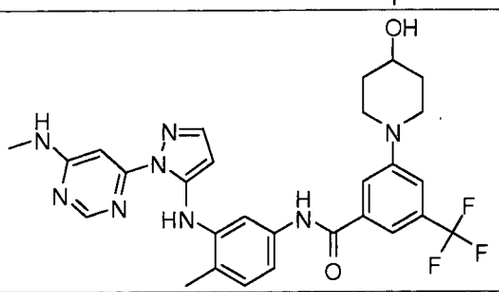
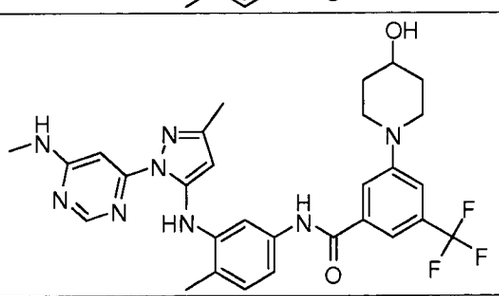
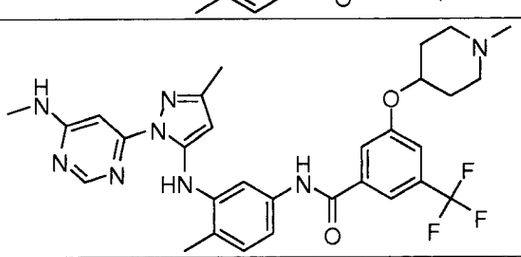
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
300		MS m/z 475.3 (M + 1)
301		MS m/z 491.2 (M + 1)
302		MS m/z 575.3 (M + 1)
303		MS m/z 482.2 (M + 1)
304		MS m/z 487.3 (M + 1)

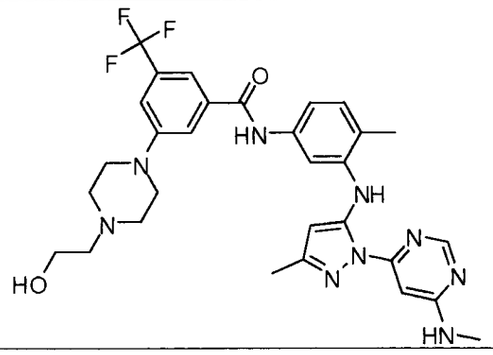
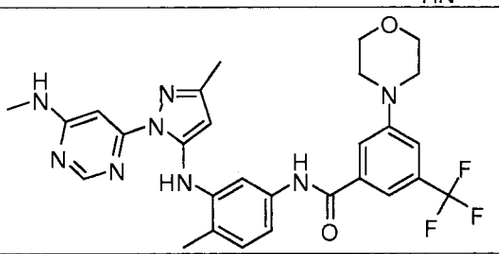
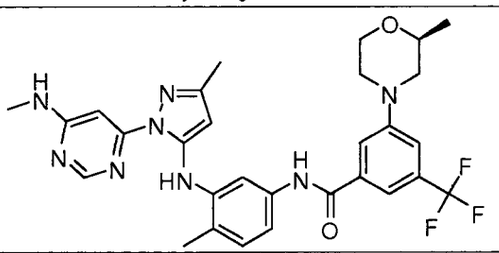
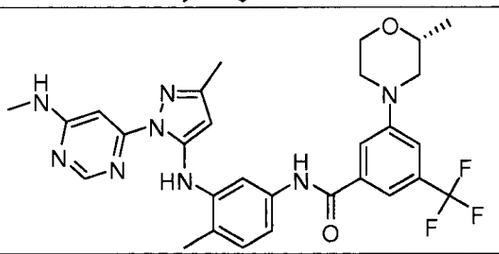
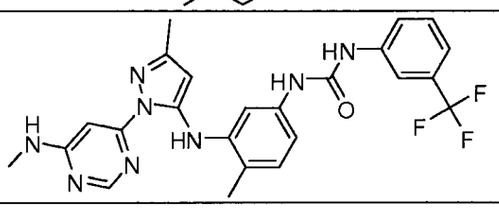
123

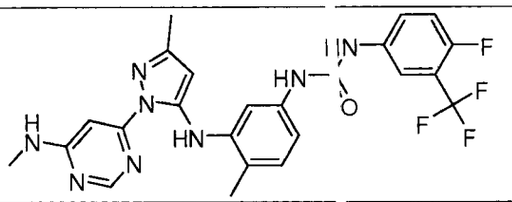
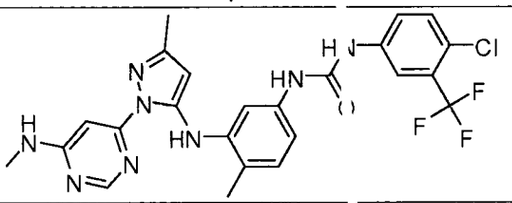
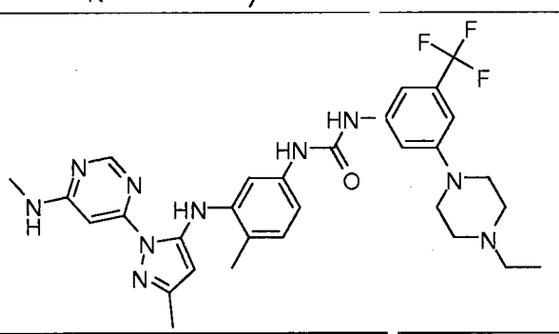
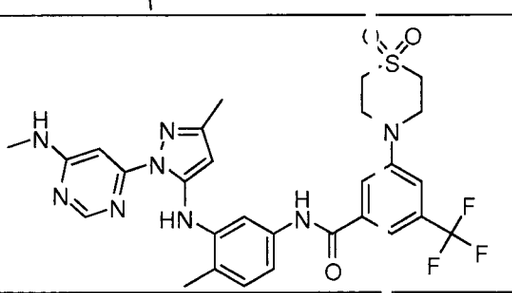
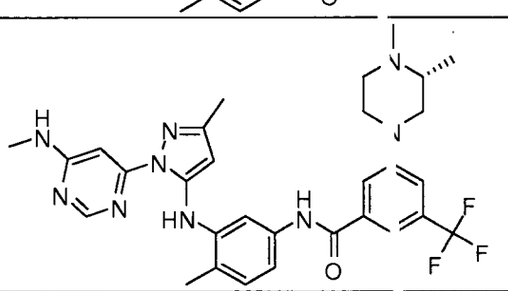
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
305		MS m/z 576.3 (M + 1)
306		MS m/z 590.3 (M + 1)
307		MS m/z 479.2 (M + 1)
308		MS m/z 563.3 (M + 1)

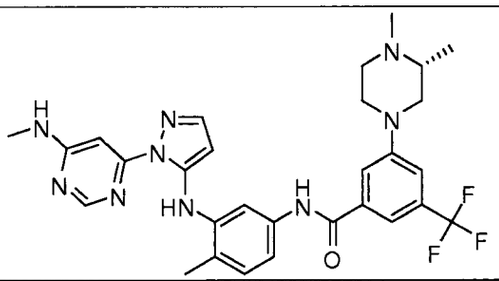
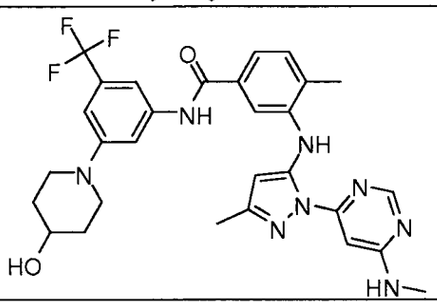
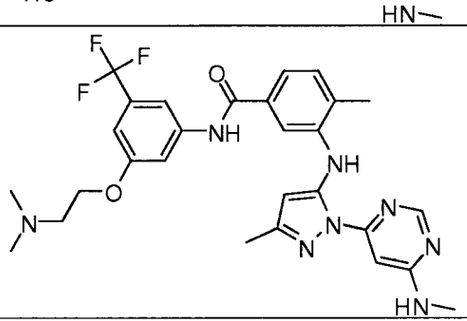
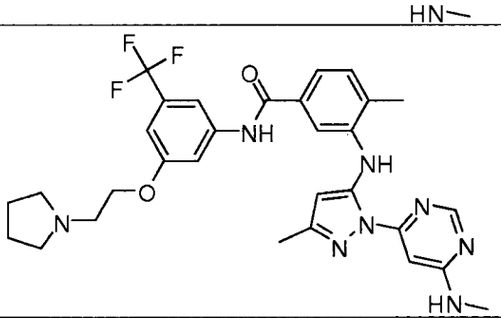
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
309		MS m/z 471.3 (M + 1)
310		MS m/z 555.3 (M + 1)
311		MS m/z 463.2 (M + 1)
312		MS m/z 449.2 (M + 1)
313		MS m/z 487.3 (M + 1)

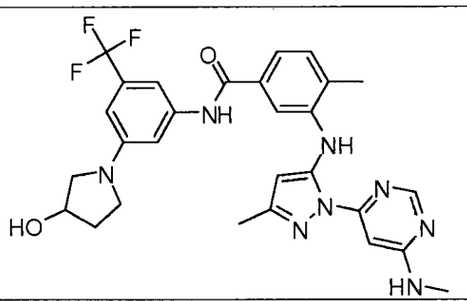
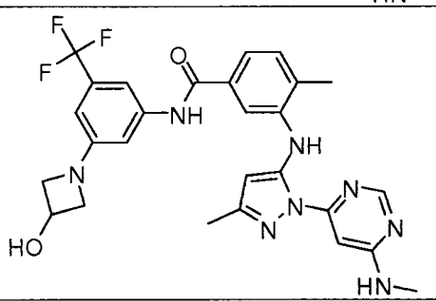
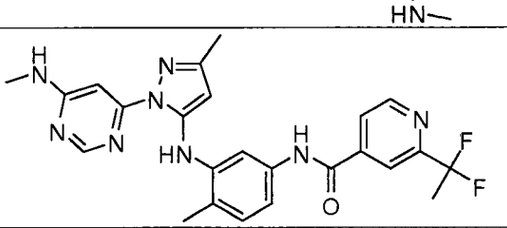
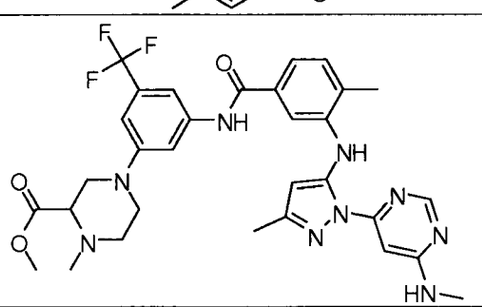
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
314		MS m/z 571.3 (M + 1)
315		MS m/z 567.3 (M + 1)
316		MS m/z 483.2 (M + 1)
317		MS m/z 472.3 (M + 1)
318		MS m/z 556.3 (M + 1)

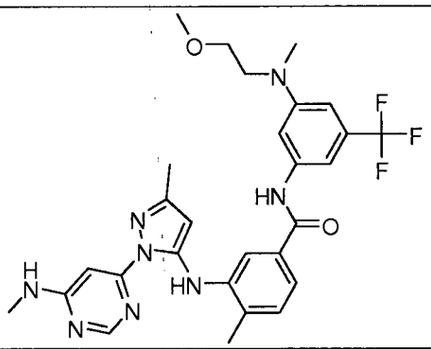
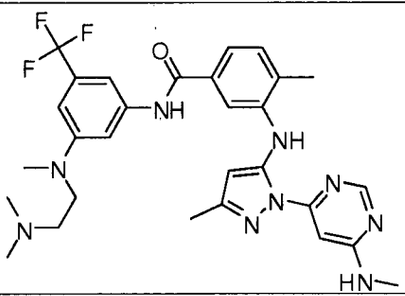
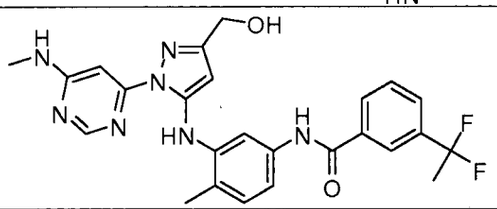
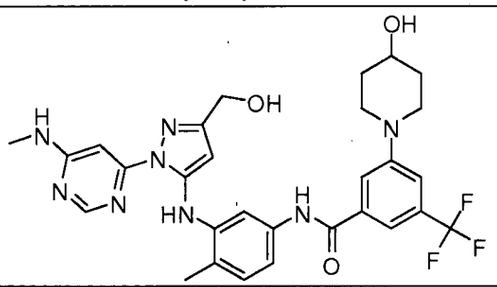
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
319		MS m/z 599.6 (M + 1)
320		MS m/z 567.2 (M + 1)
321		MS m/z 567.2 (M + 1)
322		MS m/z 581.3 (M + 1)
323		MS m/z 595.3 (M + 1)

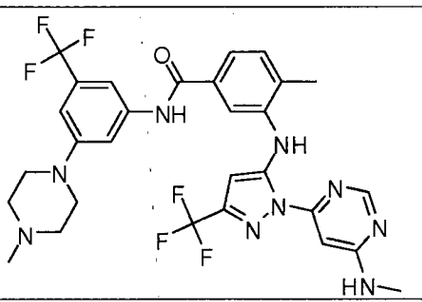
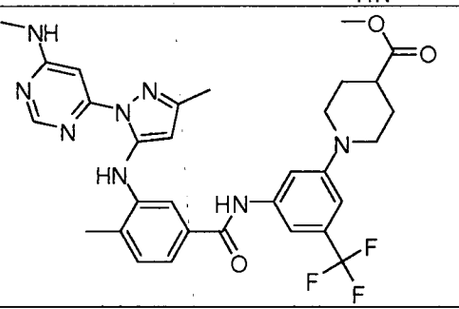
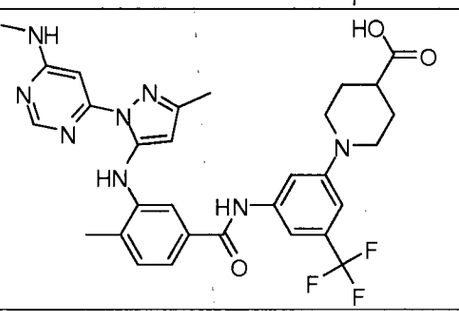
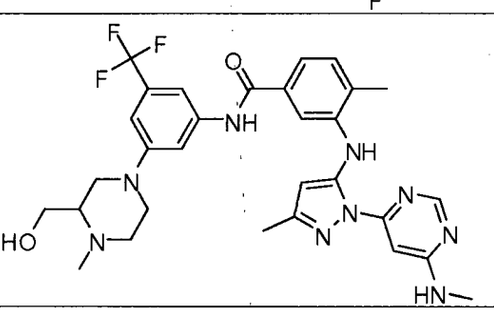
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
324		MS m/z 610.3 (M + 1)
325		MS m/z 567.2 (M + 1)
326		MS m/z 581.3 (M + 1)
327		MS m/z 581.3 (M + 1)
328		MS m/z 497.2 (M + 1)

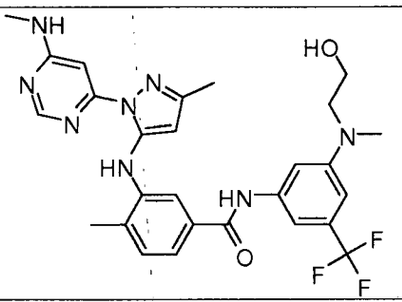
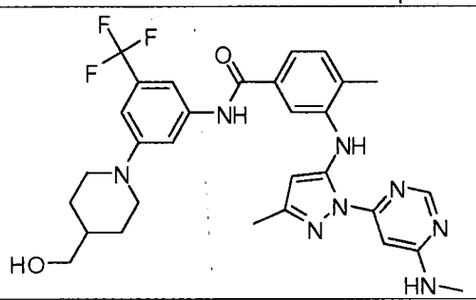
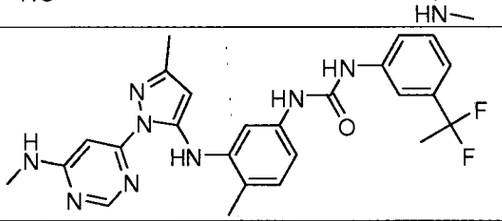
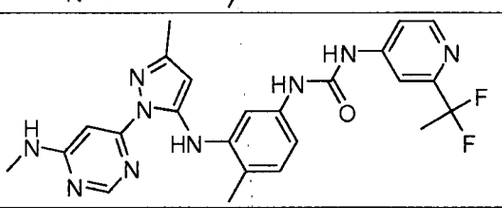
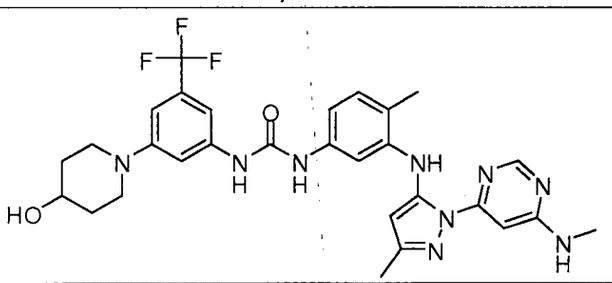
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
329		MS m/z 515.2 (M + 1)
330		MS m/z 531.2 (M + 1)
331		MS m/z 609.3 (M + 1)
332		MS m/z 615.2 (M + 1)
333		MS m/z 594.3 (M + 1)

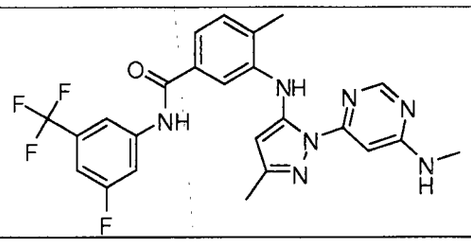
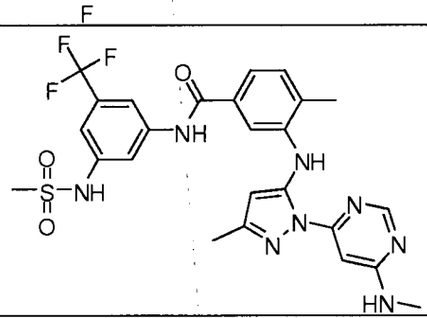
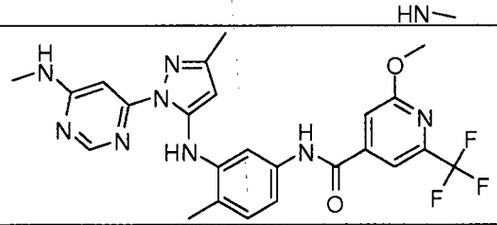
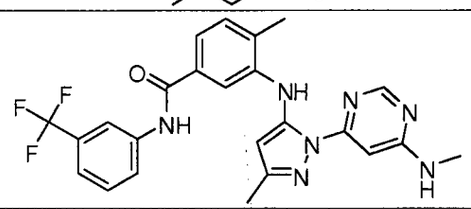
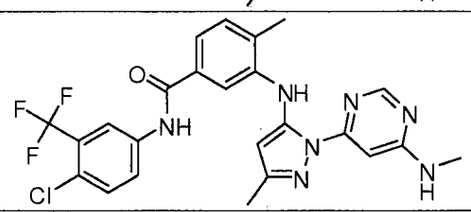
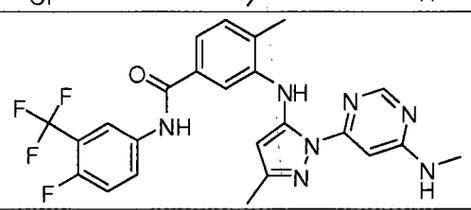
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
334		MS m/z 580.3 (M + 1)
335		MS m/z 581.3 (M + 1)
336		MS m/z 569.3 (M + 1)
337		MS m/z 595.3 (M + 1)

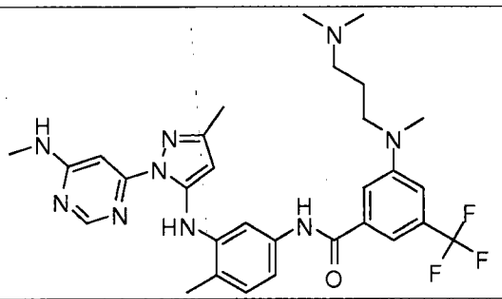
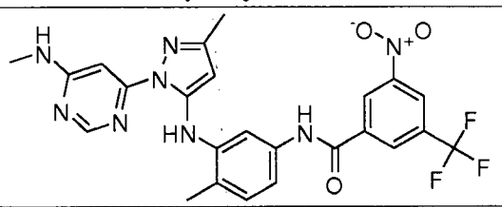
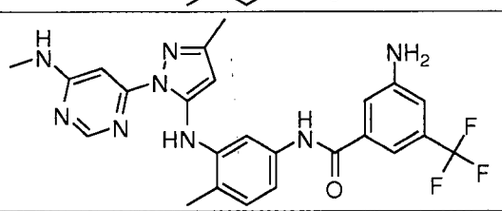
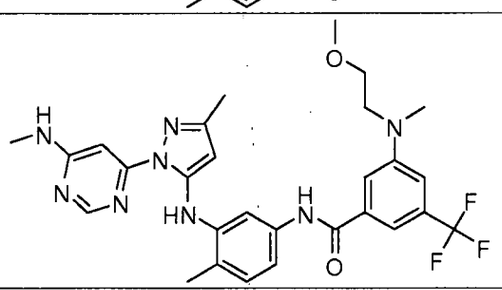
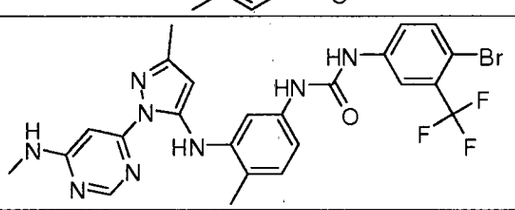
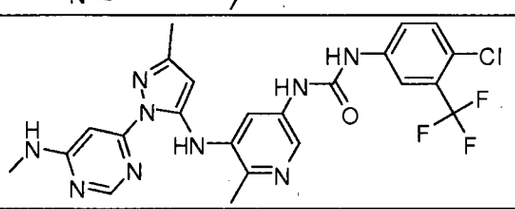
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
338		MS m/z 567.2 (M + 1)
339		MS m/z 553.2 (M + 1)
340		MS m/z 479.2 (M + 1)
341		MS m/z 638.3 (M + 1)

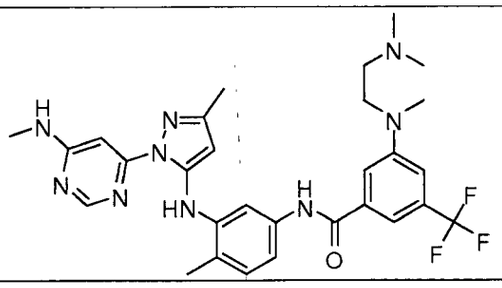
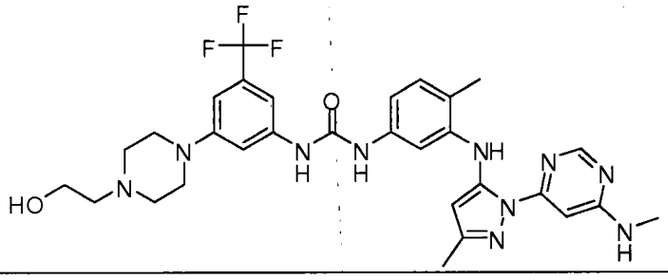
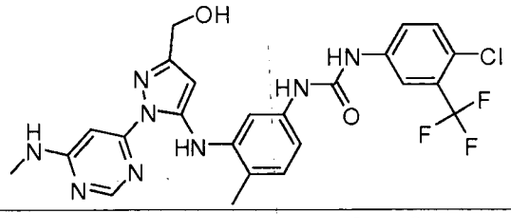
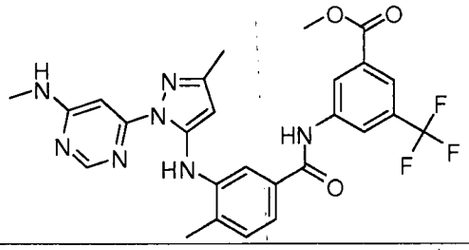
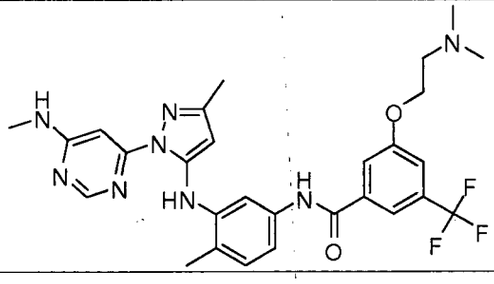
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
342		MS m/z 569.3 (M + 1)
343		MS m/z 582.3 (M + 1)
344		MS m/z 494.2 (M + 1)
345		MS m/z 597.3 (M + 1)

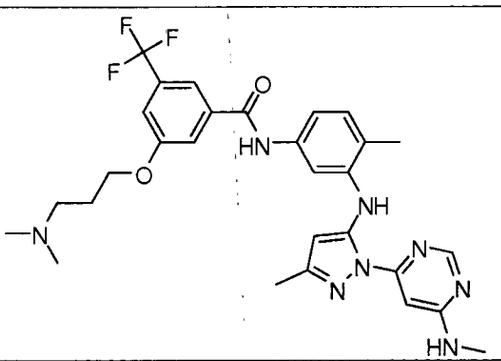
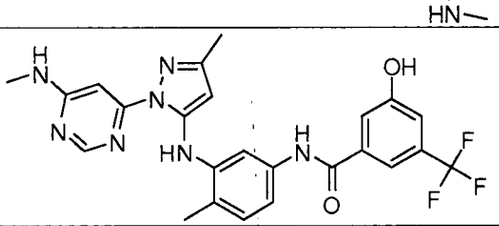
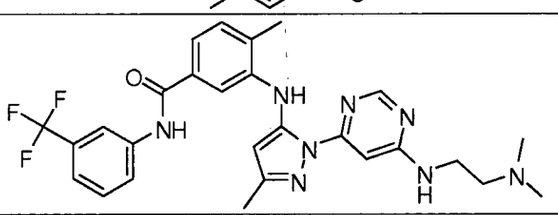
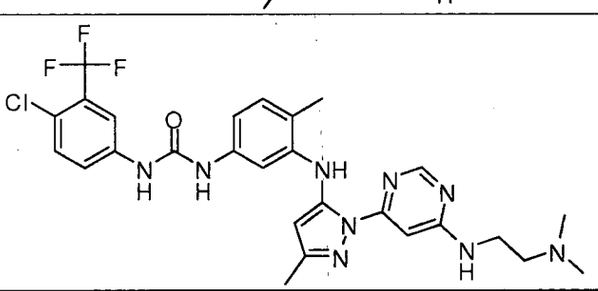
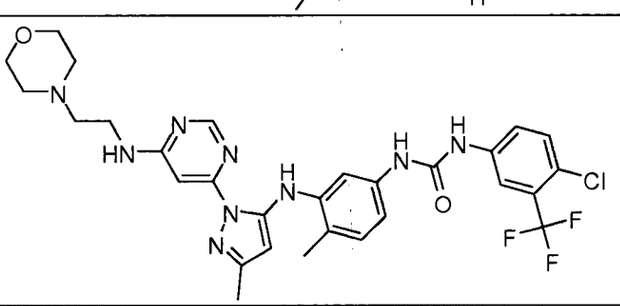
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
346		MS m/z 634.2 (M + 1)
347		MS m/z 623.3 (M + 1)
348		MS m/z 609.3 (M + 1)
349		MS m/z 610.3 (M + 1)

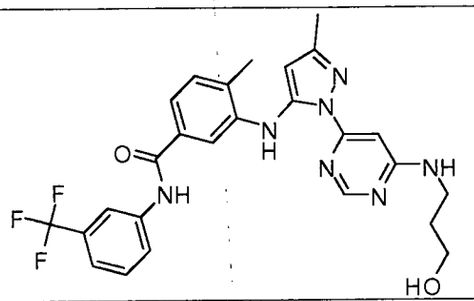
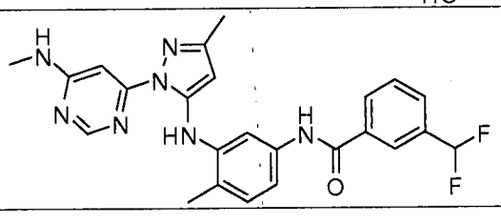
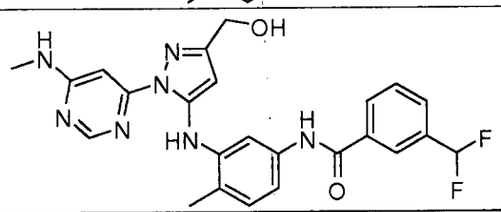
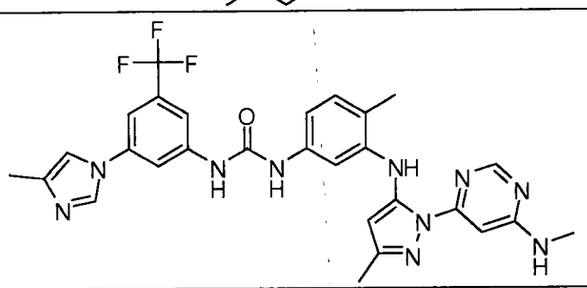
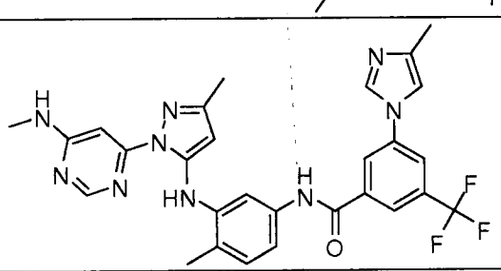
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
350		MS m/z 555.2 (M + 1)
351		MS m/z 595.3 (M + 1)
352		MS m/z 493.2 (M + 1)
353		MS m/z 494.2 (M + 1)
354		MS m/z 596.3 (M + 1)

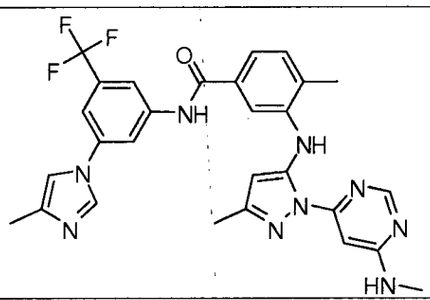
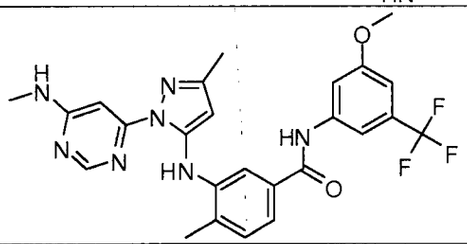
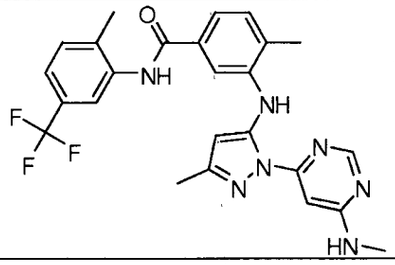
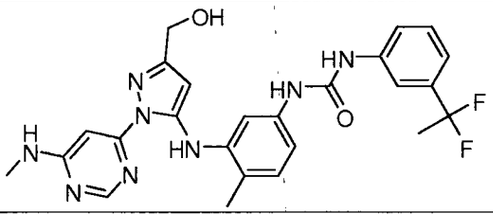
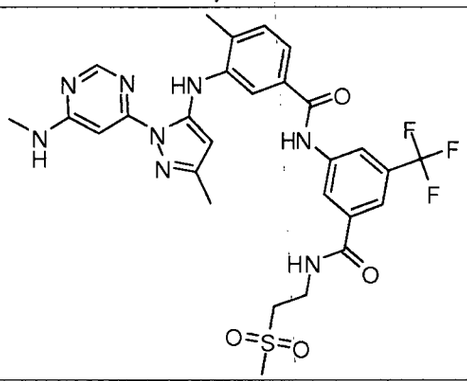
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
355		MS m/z 500.2 (M + 1)
356		MS m/z 575.2 (M + 1)
357		MS m/z 513.2 (M + 1)
358		MS m/z 482.2 (M + 1)
359		MS m/z 516.1 (M + 1)
360		MS m/z 500.2 (M + 1)

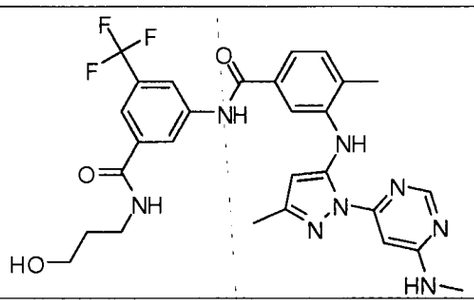
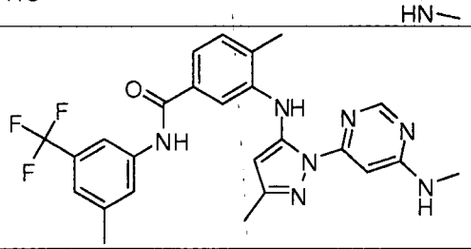
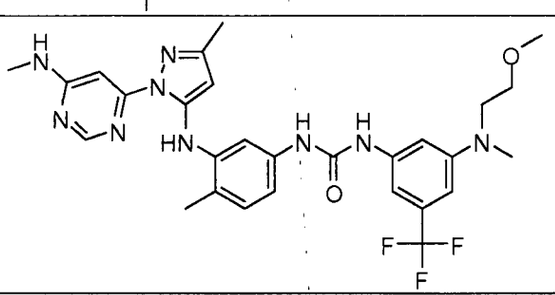
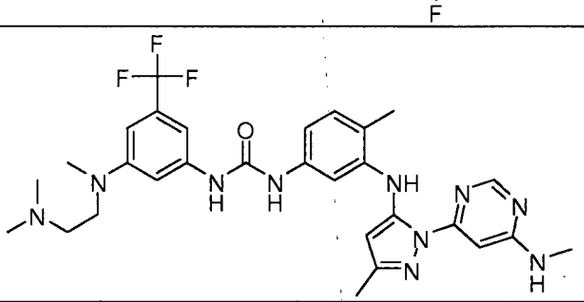
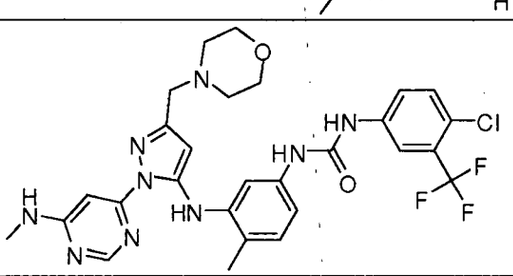
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
361		MS m/z 596.3 (M + 1)
362		MS m/z 527.2 (M + 1)
363		MS m/z 497.2 (M + 1)
364		MS m/z 569.3 (M + 1)
365		MS m/z 575.1 (M + 1)
366		MS m/z 532.2 (M + 1)

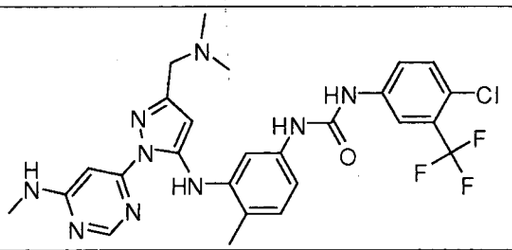
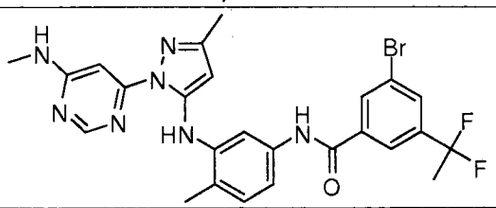
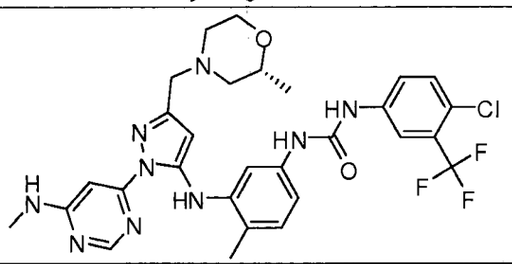
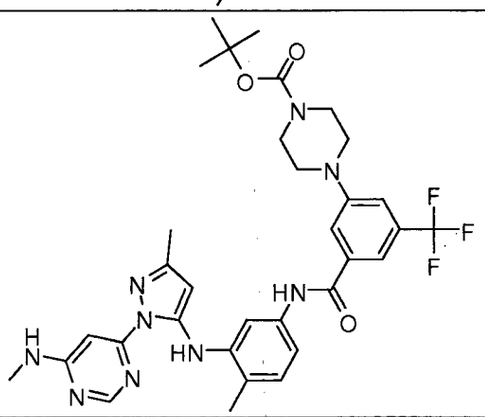
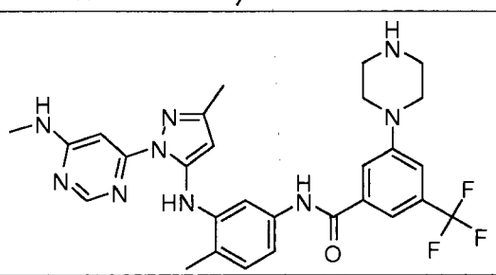
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
367		MS m/z 582.3 (M + 1)
368		MS m/z 625.3 (M + 1)
369		MS m/z 547.2 (M + 1)
370		MS m/z 540.2 (M + 1)
371		MS m/z 569.3 (M + 1)

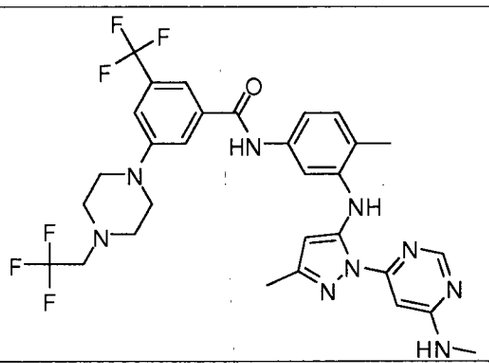
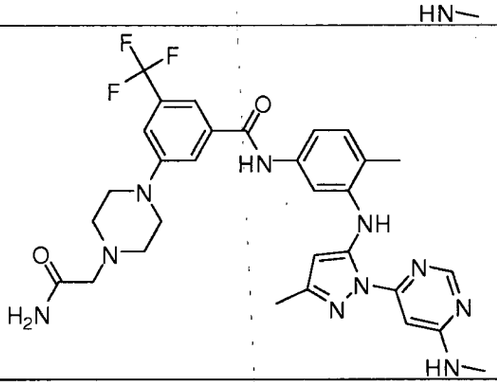
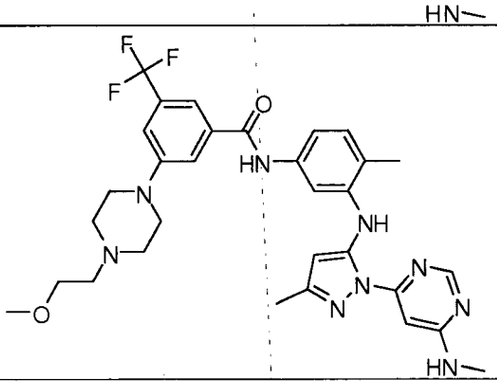
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
372		MS m/z 583.3 (M + 1)
373		MS m/z 498.2 (M + 1)
374		MS m/z 539.2 (M + 1)
375		MS m/z 588.2 (M + 1)
376		MS m/z 630.22 (M + 1)

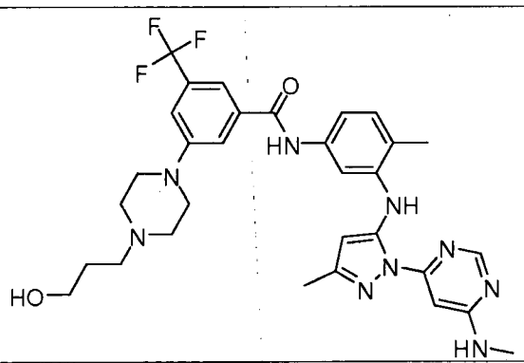
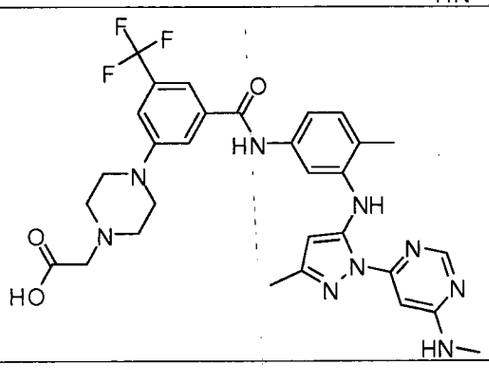
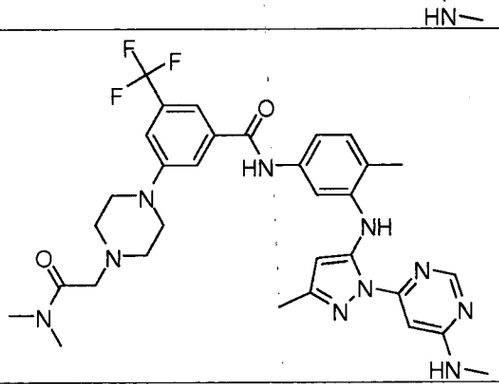
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
377		MS m/z 526.2 (M + 1)
378		MS m/z 464.2 (M + 1)
379		MS m/z 480.2 (M + 1)
380		MS m/z 577.2 (M + 1)
.381		MS m/z 562.2 (M + 1)

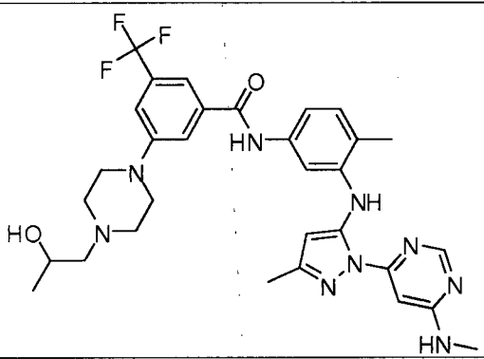
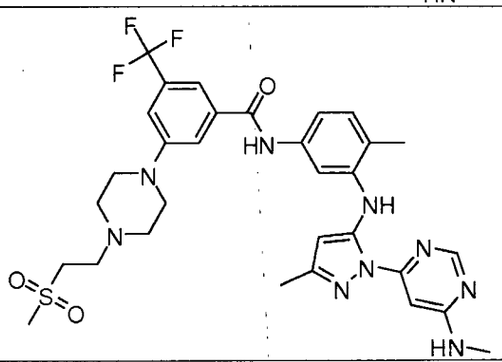
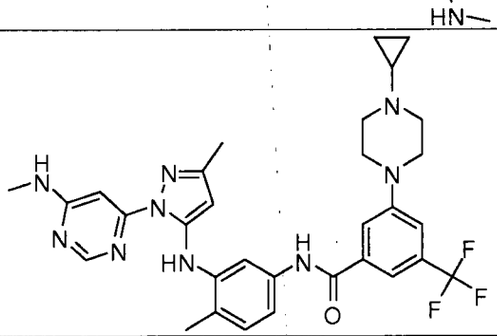
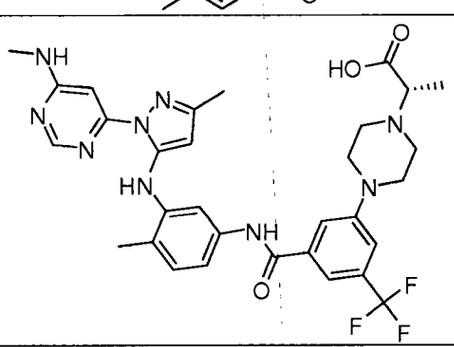
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
382		MS m/z 562.2 (M + 1)
383		MS m/z 512.2 (M + 1)
384		MS m/z 496.2 (M + 1)
385		MS m/z 509.2 (M + 1)
386		MS m/z 631.2 (M + 1)

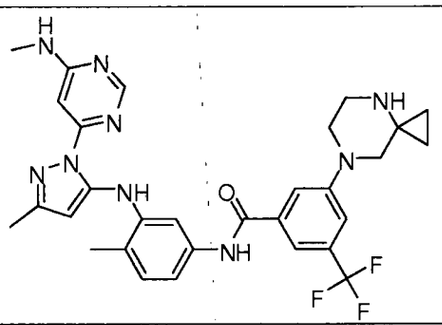
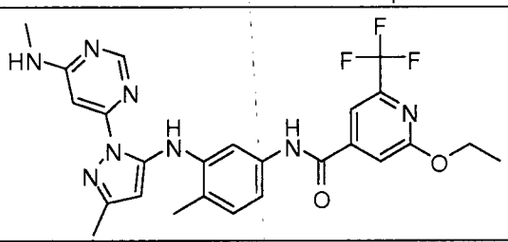
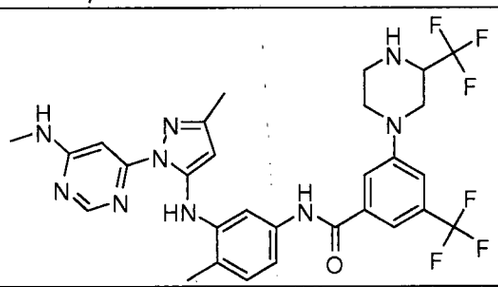
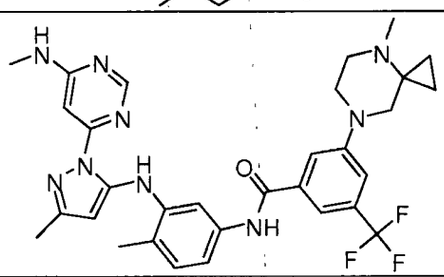
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
387		MS m/z 583.2 (M + 1)
388		MS m/z 496.2 (M + 1)
389		MS m/z 584.3 (M + 1)
390		MS m/z 597.3 (M + 1)
391		MS m/z 616.2 (M + 1)

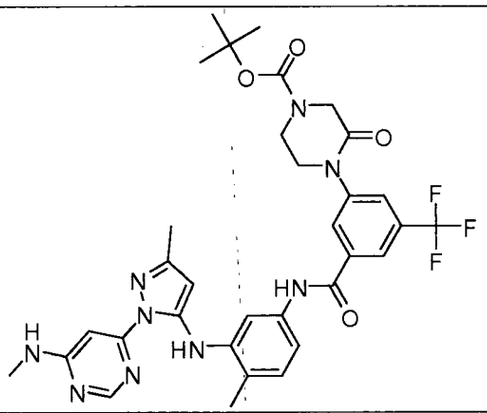
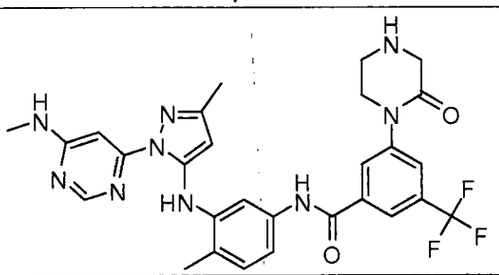
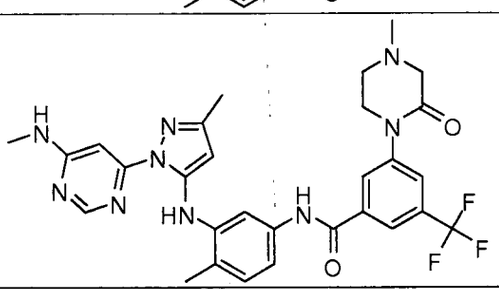
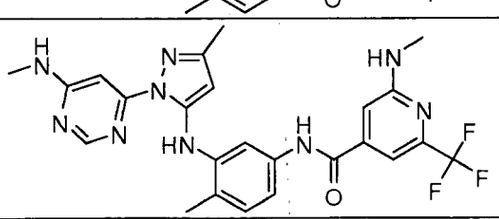
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
392		MS m/z 574.2 (M + 1)
393		MS m/z 556.1 (M + 1)
394		MS m/z 630.2 (M + 1)
395		MS m/z 666.3 (M + 1)
396		MS m/z 566.3 (M + 1)

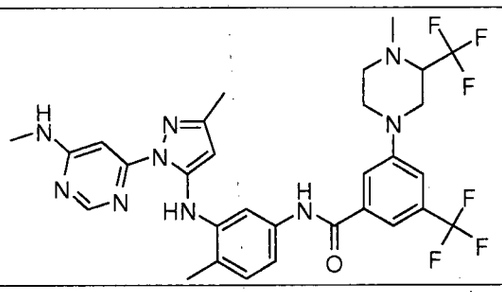
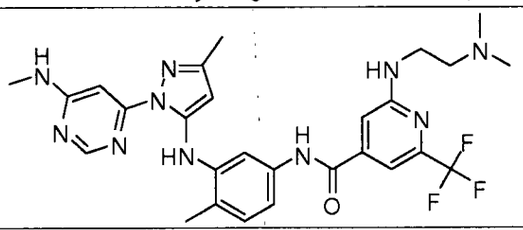
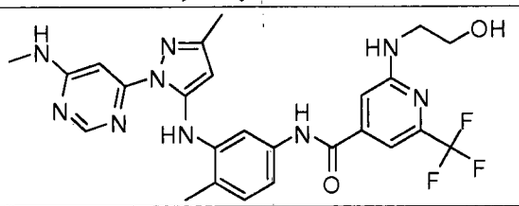
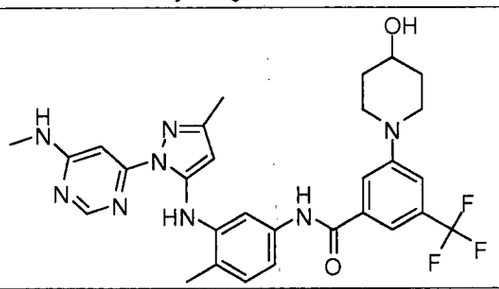
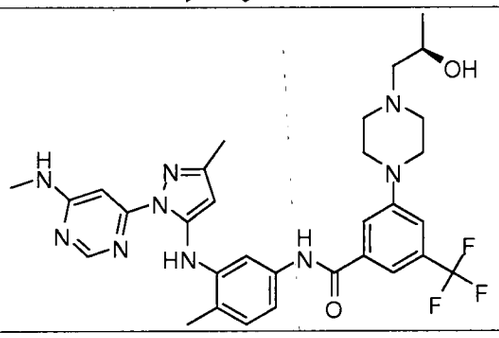
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
397		MS m/z 648.3 (M + 1)
398		MS m/z 623.3 (M + 1)
399		MS m/z 624.3 (M + 1)

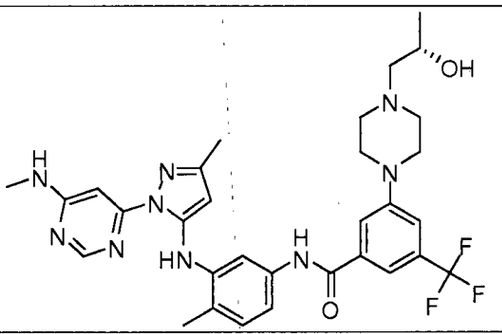
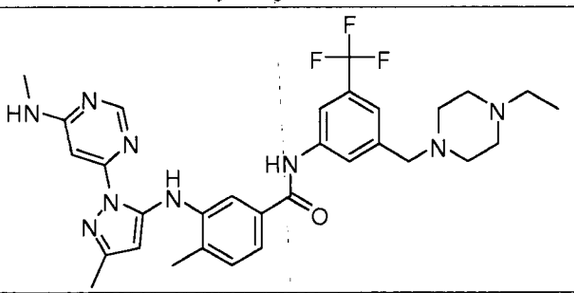
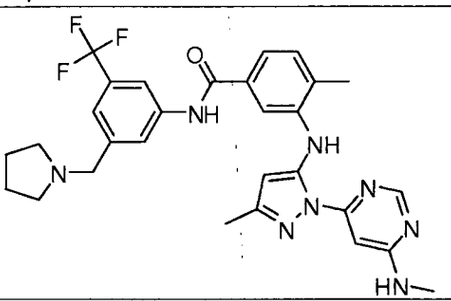
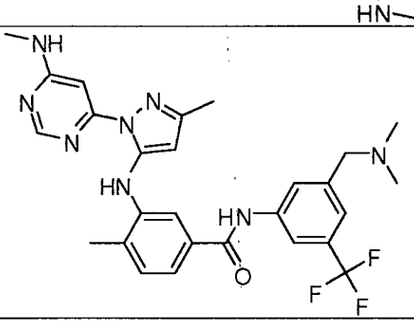
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
400		MS m/z 624.3 (M + 1)
401		MS m/z 624.3 (M + 1)
402		MS m/z 651.3 (M + 1)

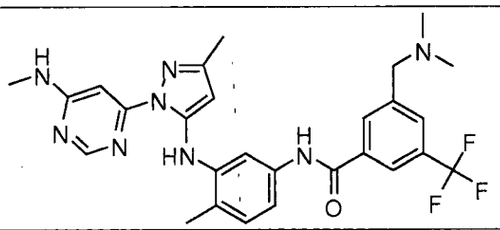
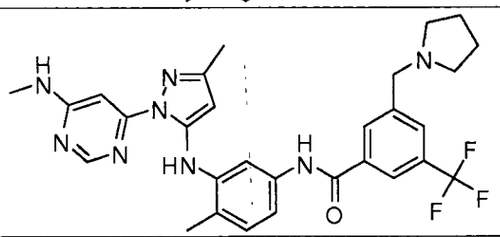
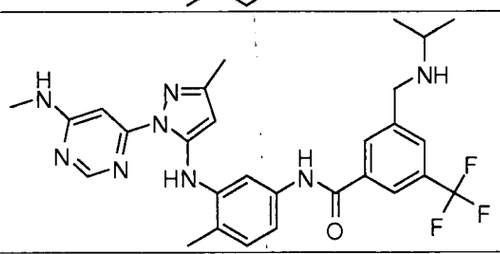
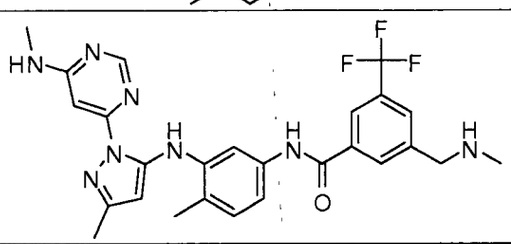
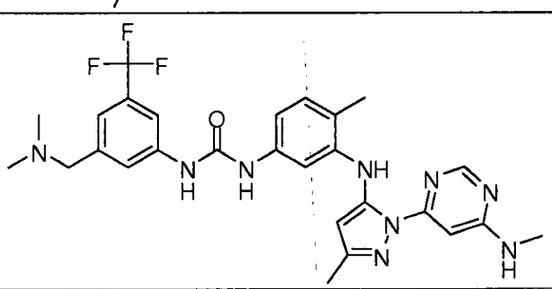
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
403		MS m/z 624.3 (M + 1)
404		MS m/z 672.3 (M + 1)
405		MS m/z 606.3 (M + 1)
406		MS m/z 638.3 (M + 1)

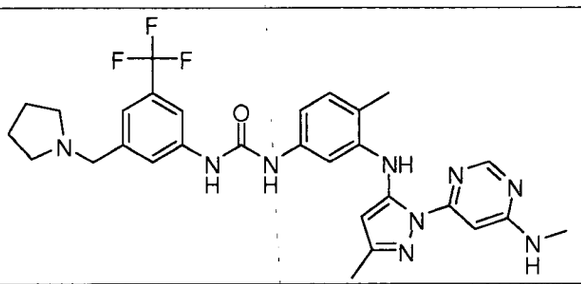
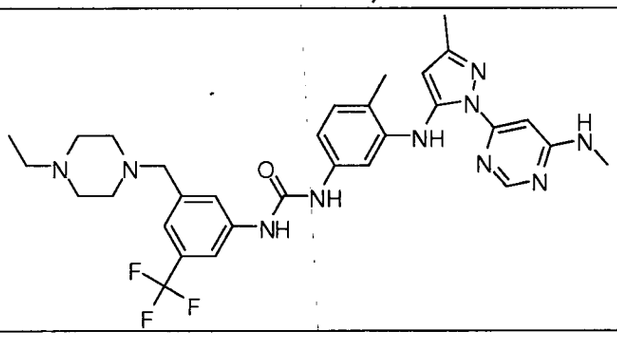
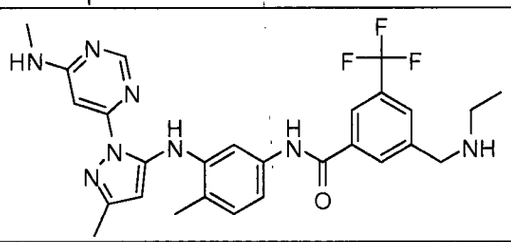
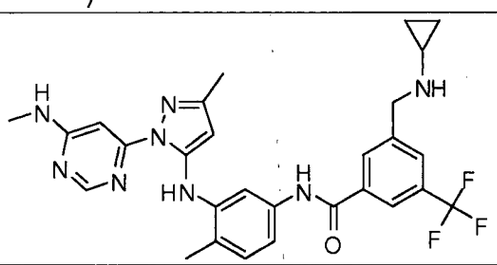
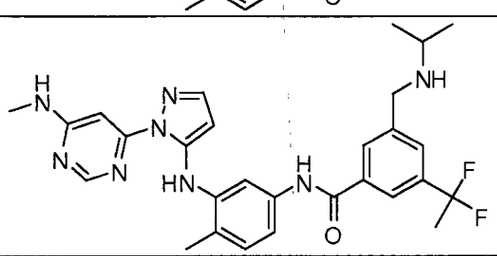
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
407		MS m/z 592.3 (M + 1)
408		MS m/z 527.2 (M + 1)
409		MS m/z 634.2 (M + 1)
410		MS m/z 606.3 (M + 1)

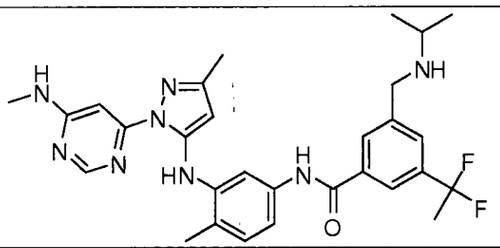
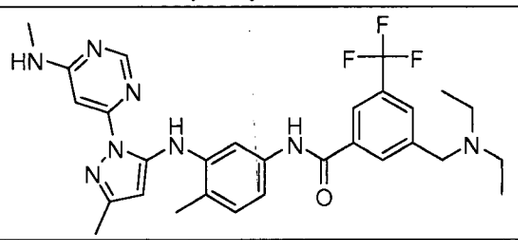
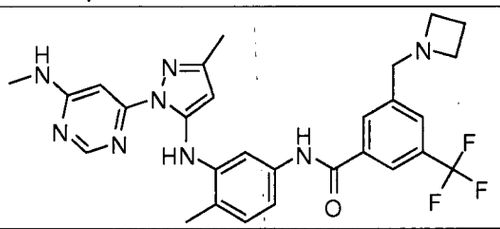
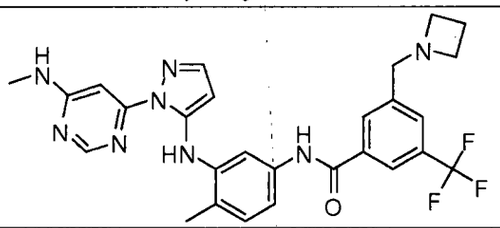
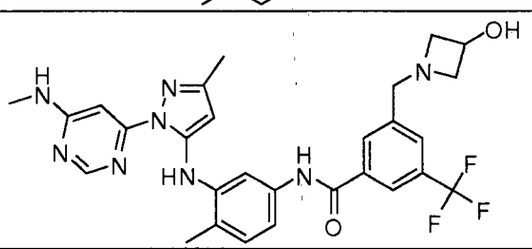
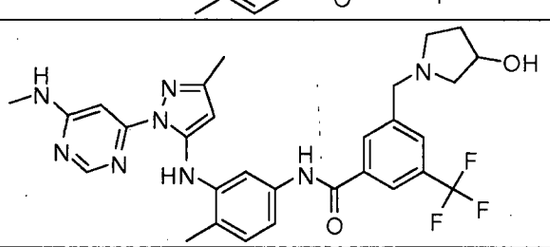
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
411		MS m/z 680.3 (M + 1)
412		MS m/z 580.2 (M + 1)
413		MS m/z 594.3 (M + 1)
414		MS m/z 512.2 (M + 1)

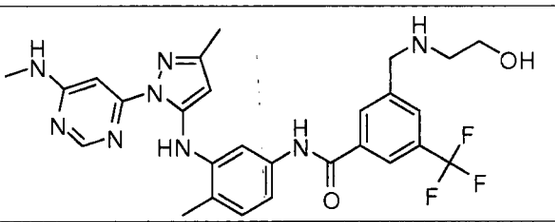
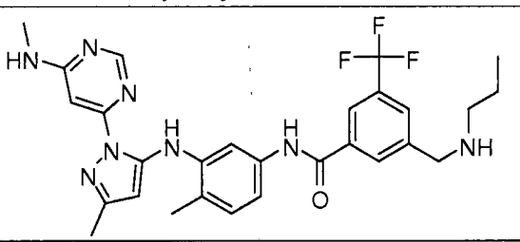
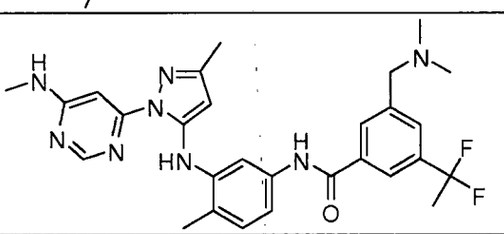
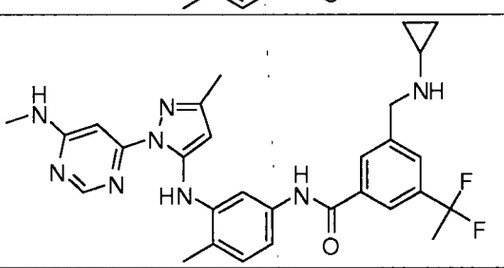
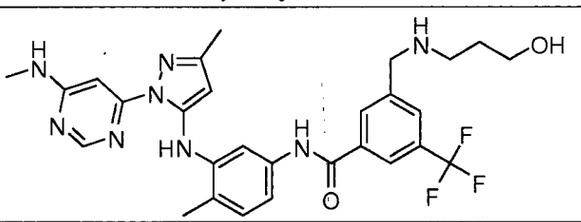
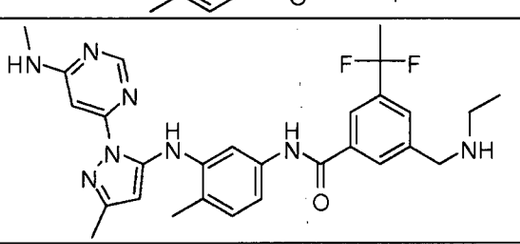
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
415		MS m/z 648.3 (M + 1)
416		MS m/z 569.3 (M + 1)
417		MS m/z 542.2 (M + 1)
418		MS m/z 581.3 (M + 1)
419		MS m/z 624.3 (M + 1)

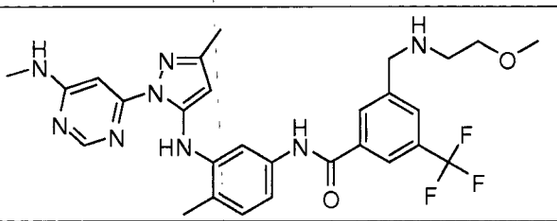
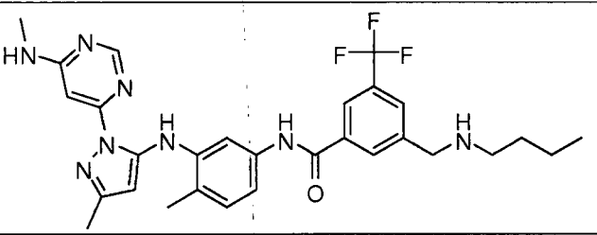
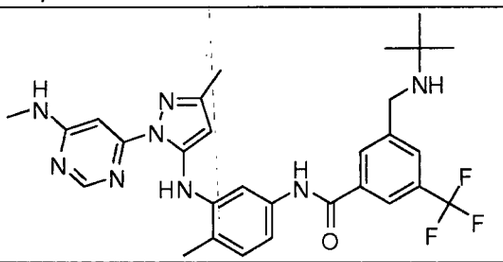
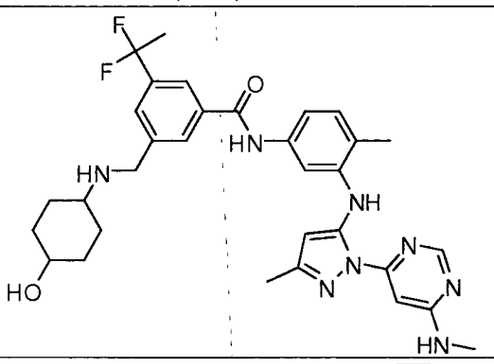
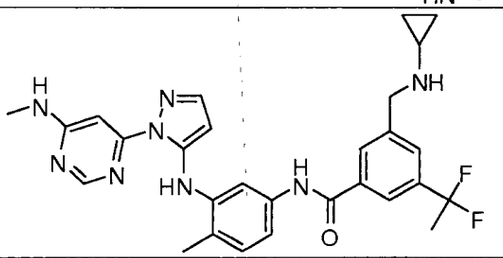
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
420		MS m/z 624.3 (M + 1)
421		MS m/z 608.3 (M + 1)
422		MS m/z 565.3 (M + 1)
423		MS m/z 539.2 (M + 1)

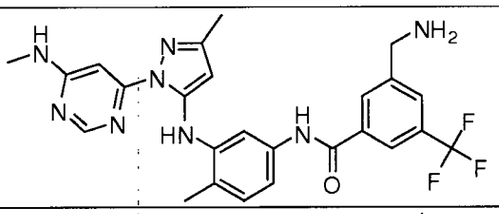
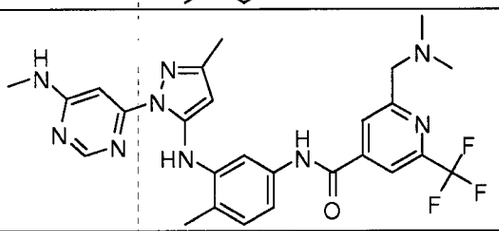
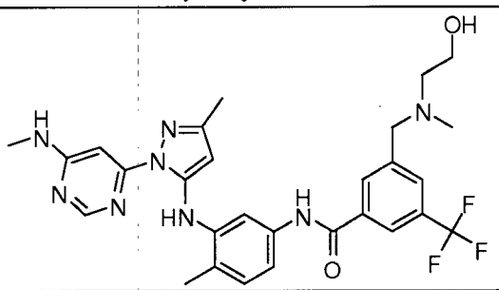
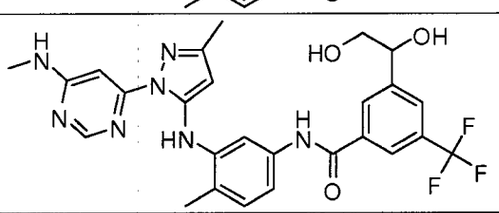
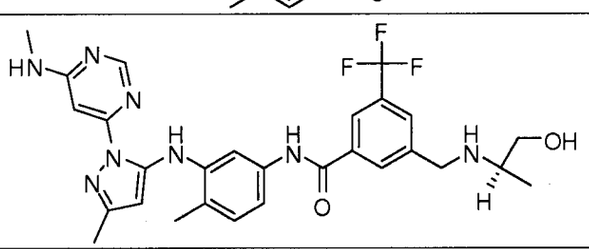
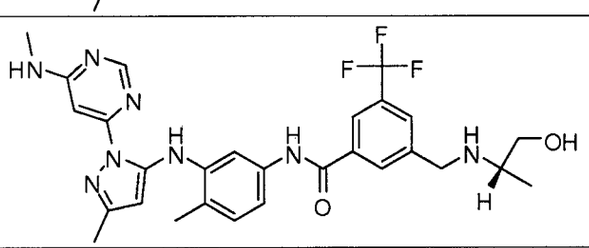
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
424		MS m/z 539.2 (M + 1)
425		MS m/z 565.3 (M + 1)
426		MS m/z 553.3 (M + 1)
427		MS m/z 525.2 (M + 1)
428		MS m/z 554.3 (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
429		MS m/z 580.3 (M + 1)
430		MS m/z 623.3 (M + 1)
431		MS m/z 539.2 (M + 1)
432		MS m/z 551.2 (M + 1)
433		MS m/z 535.3 (M + 1)

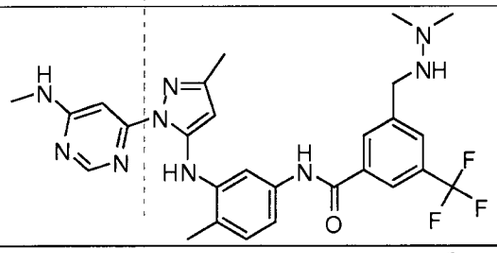
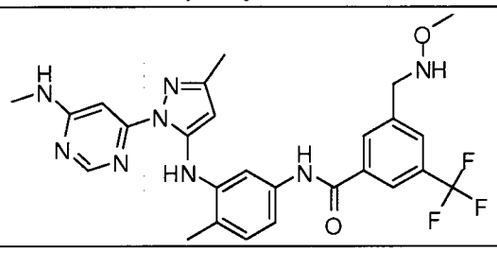
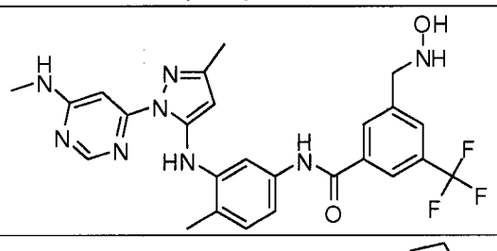
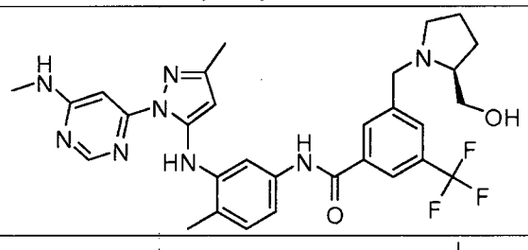
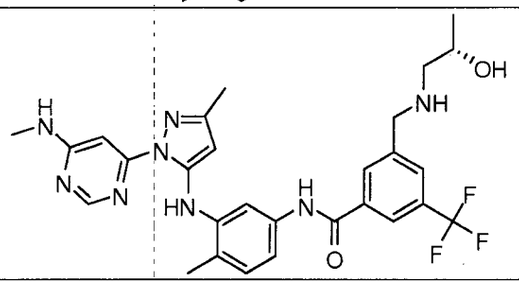
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
434		MS m/z 549.3 (M + 1)
435		MS m/z 567.3 (M + 1)
436		MS m/z 551.2 (M + 1)
437		MS m/z 537.2 (M + 1)
438		MS m/z 567.2 (M + 1)
439		MS m/z 581.3 (M + 1)

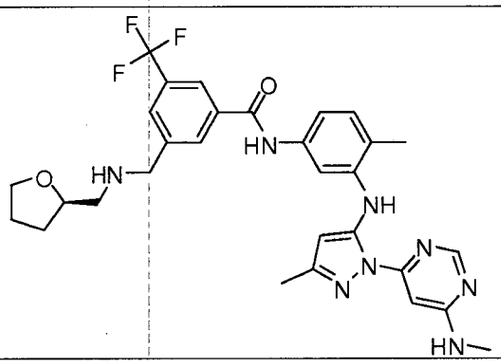
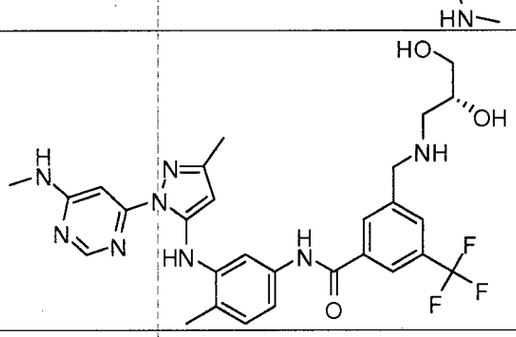
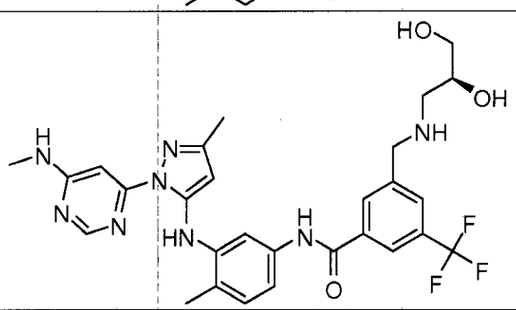
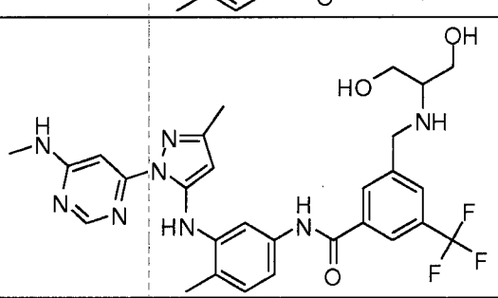
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
440		MS m/z 555.2 (M + 1)
441		MS m/z 553.3 (M + 1)
442		MS m/z 535.3 (M + 1)
443		MS m/z 547.3 (M + 1)
444		MS m/z 569.3 (M + 1)
445		MS m/z 535.3 (M + 1)

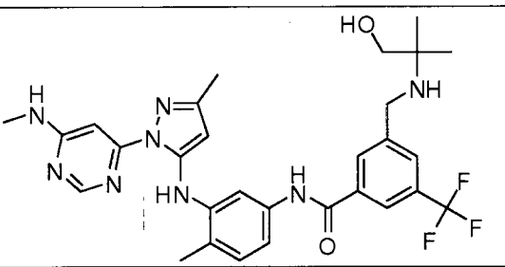
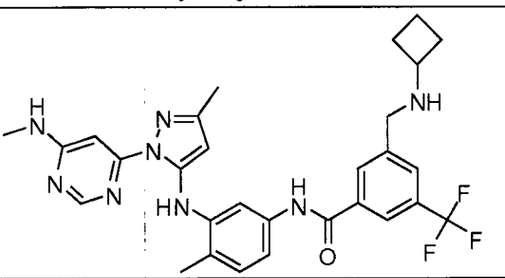
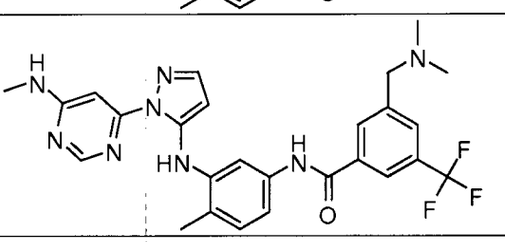
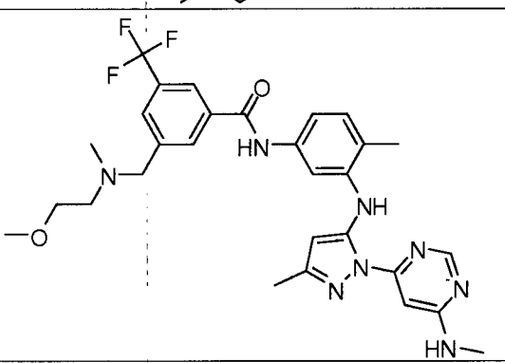
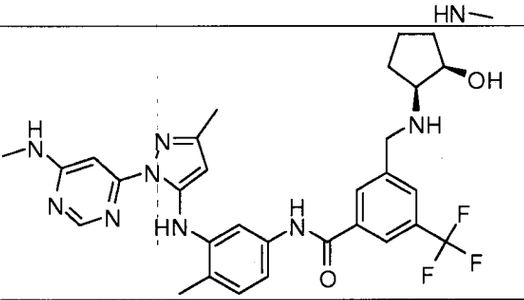
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
446		MS m/z 569.3 (M + 1)
447		MS m/z 567.3 (M + 1)
448		MS m/z 567.3 (M + 1)
449		MS m/z 605.3 (M + 1)
450		MS m/z 533.3 (M + 1)

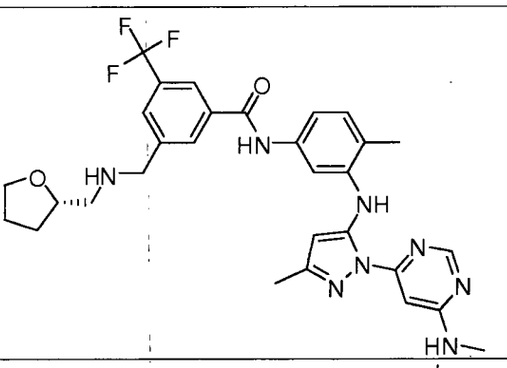
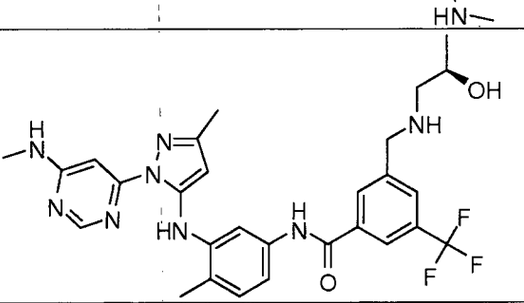
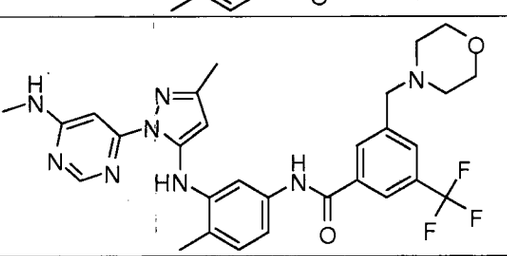
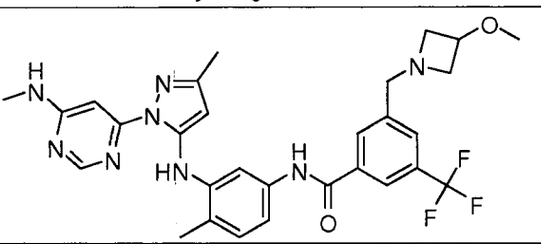
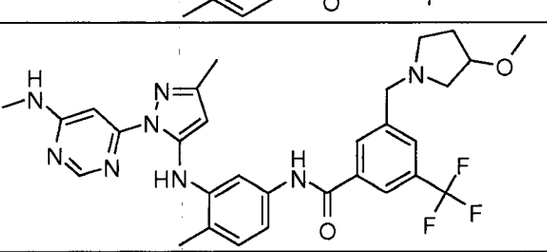
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
451		MS m/z 511.2 (M + 1)
452		MS m/z 540.2 (M + 1)
453		MS m/z 569.3 (M + 1)
454		MS m/z 542.2 (M + 1)
455		MS m/z 569.3 (M + 1)
456		MS m/z 569.3 (M + 1)

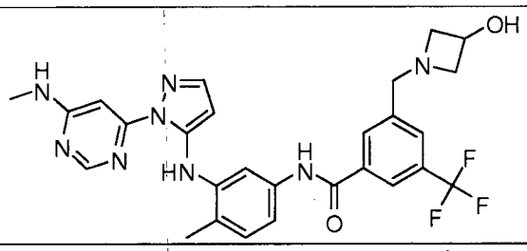
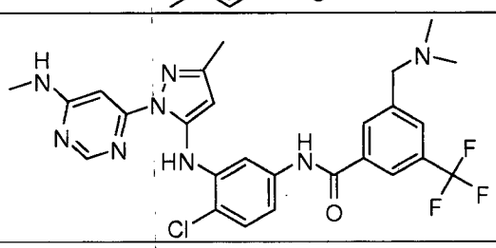
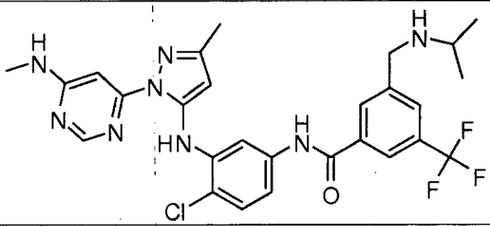
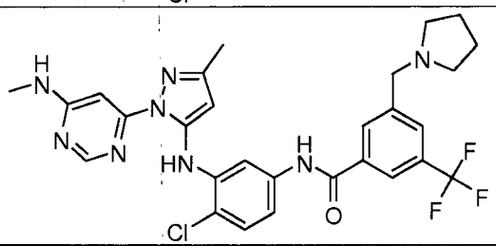
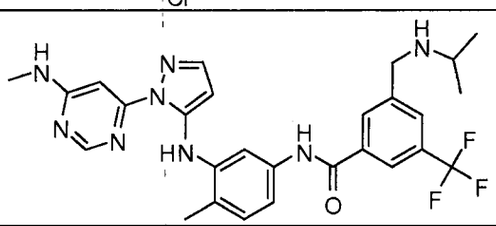
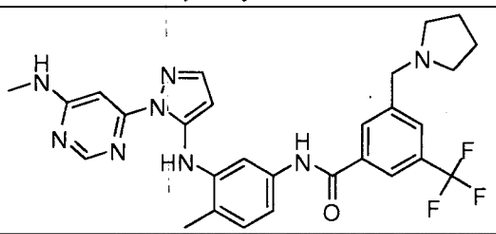
205

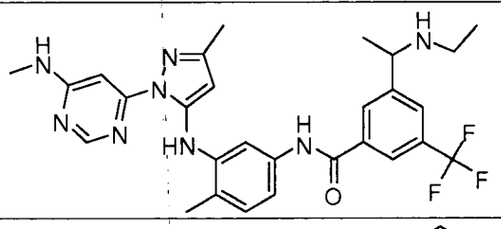
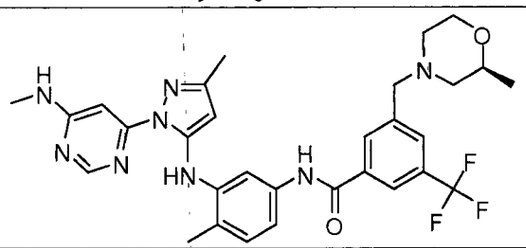
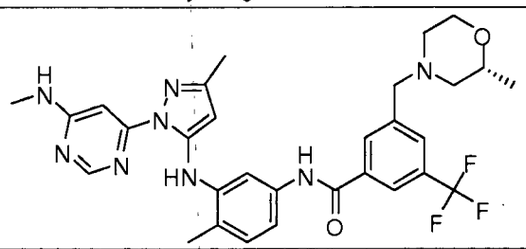
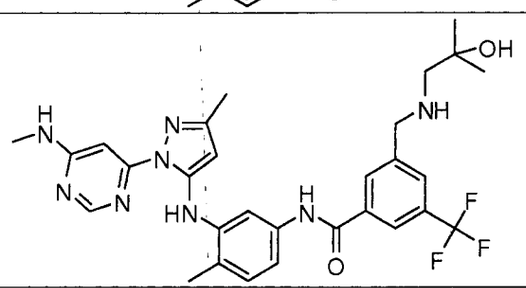
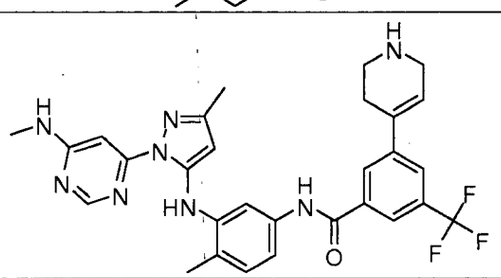
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
457		MS m/z 554.3 (M + 1)
458		MS m/z 541.2 (M + 1)
459		MS m/z 527.2 (M + 1)
460		MS m/z 595.3 (M + 1)
461		MS m/z 569.3 (M + 1)

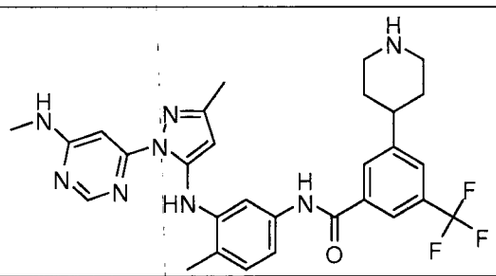
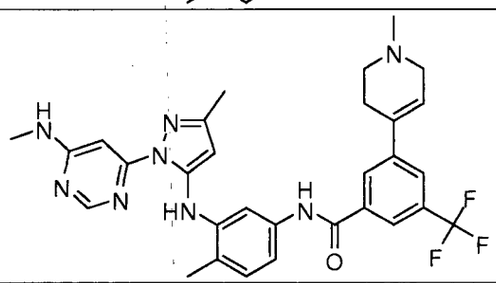
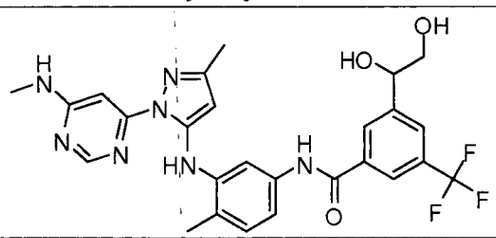
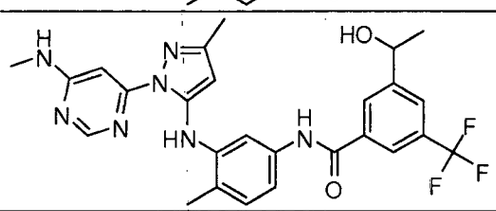
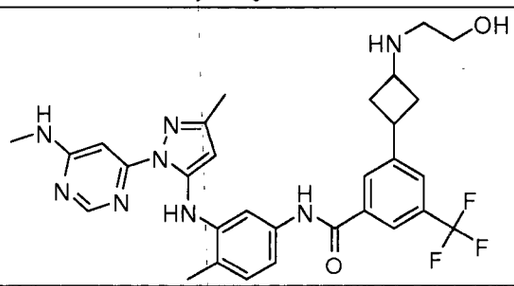
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
462		MS m/z 595.3 (M + 1)
463		MS m/z 585.3 (M + 1)
464		MS m/z 585.3 (M + 1)
465		MS m/z 585.3 (M + 1)

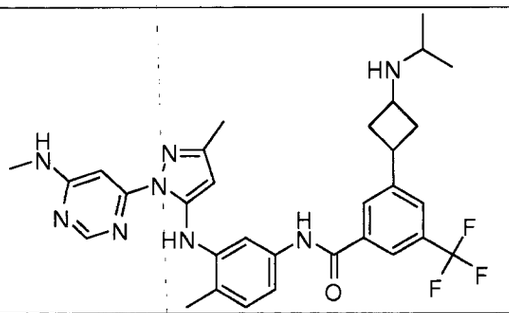
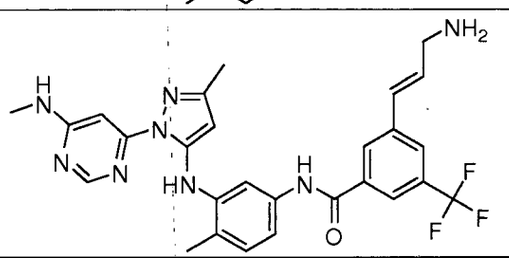
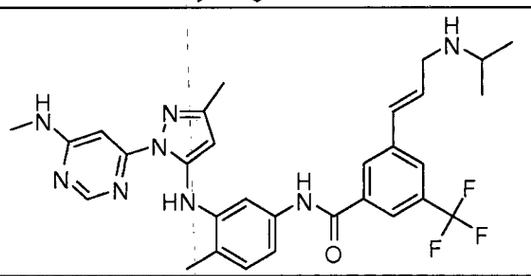
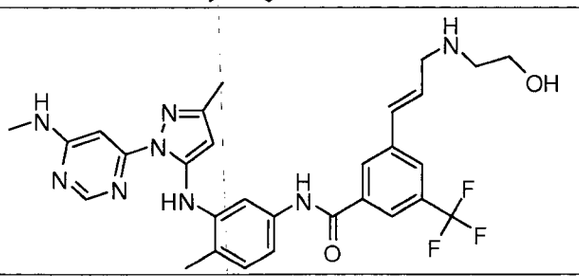
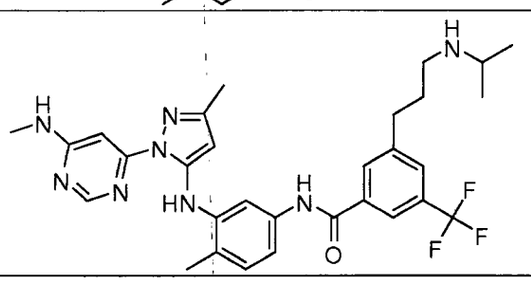
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
466		MS m/z 583.3(M + 1)
467		MS m/z 565.3 (M + 1)
468		MS m/z 525.2 (M + 1)
469		MS m/z 583.3 (M + 1)
470		MS m/z 595.3 (M + 1)

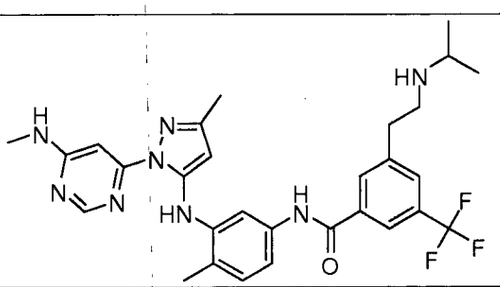
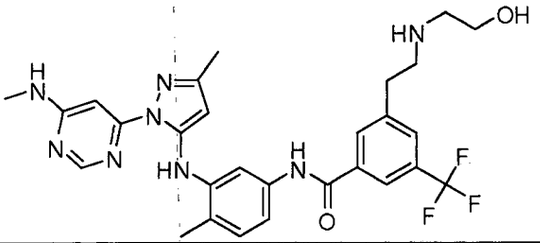
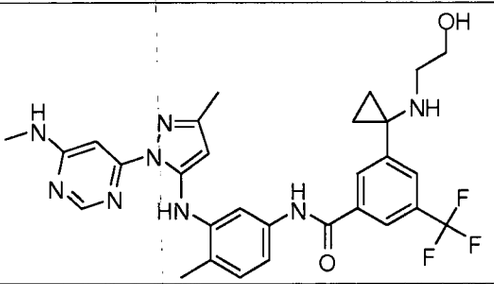
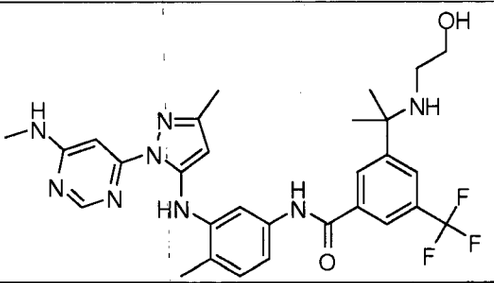
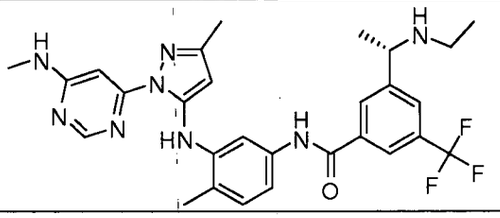
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
471		MS m/z 595.3 (M + 1)
472		MS m/z 569.3 (M + 1)
473		MS m/z 581.3 (M + 1)
474		MS m/z 581.3 (M + 1)
475		MS m/z 595.3 (M + 1)

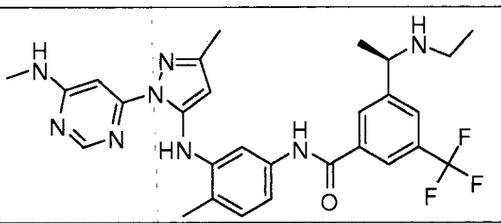
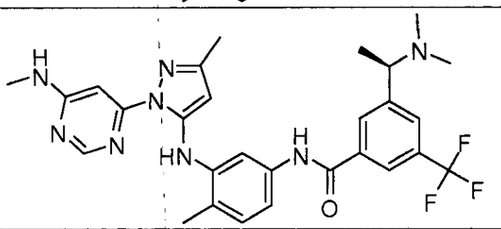
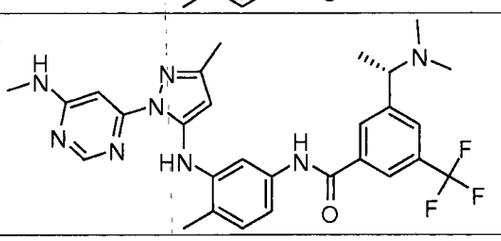
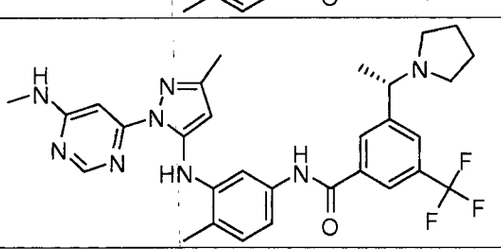
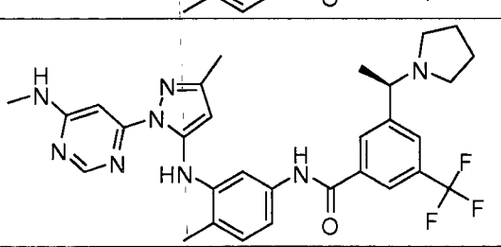
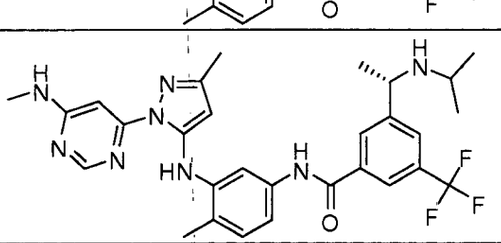
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
476		MS m/z 553.3 (M + 1)
477		MS m/z 559.2 (M + 1)
478		MS m/z 573.2 (M + 1)
479		MS m/z 585.2 (M + 1)
480		MS m/z 539.2 (M + 1)
481		MS m/z 551.2 (M + 1)

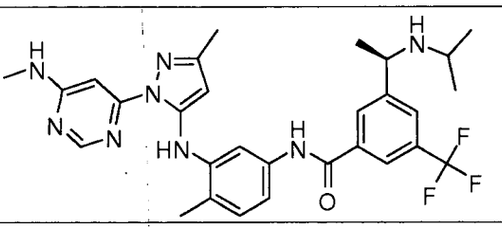
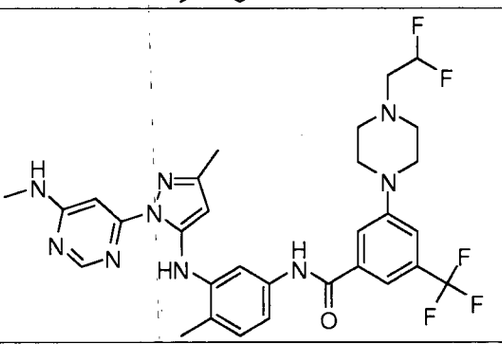
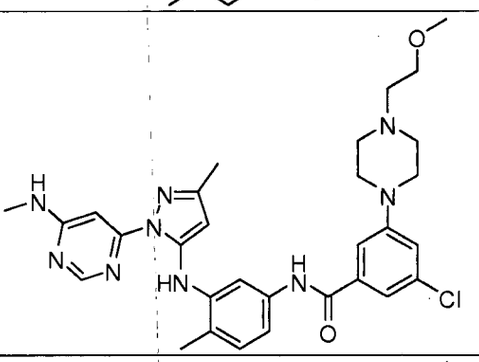
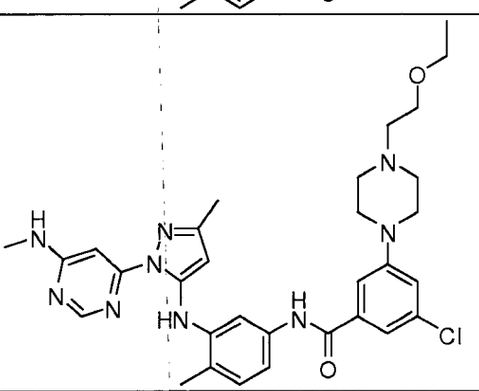
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
482		MS m/z 553.3 (M + 1)
483		MS m/z 595.3 (M + 1)
484		MS m/z 595.3 (M + 1)
485		MS m/z 583.3 (M + 1)
486		MS m/z 563.2 (M + 1)

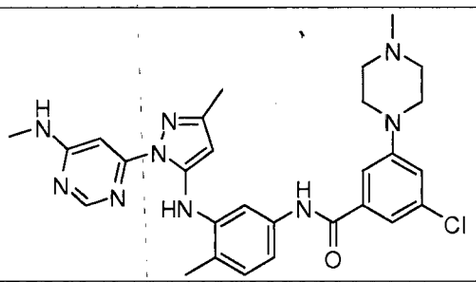
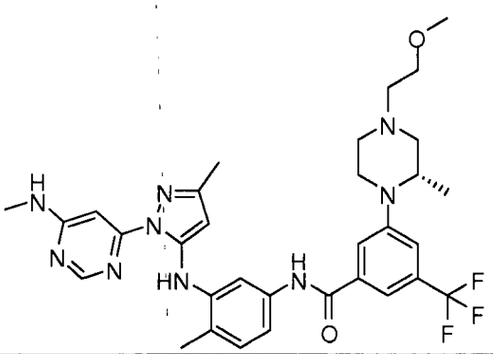
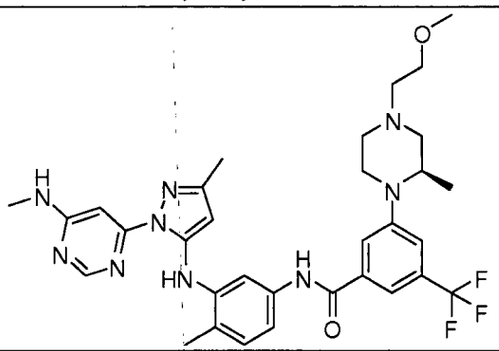
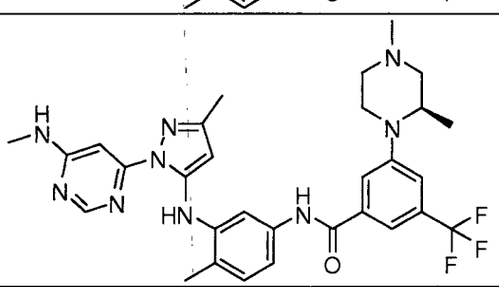
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
487		MS m/z 565.3 (M + 1)
488		MS m/z 577.3 (M + 1)
489		MS m/z 542.2 (M + 1)
490		MS m/z 526.2 (M + 1)
491		

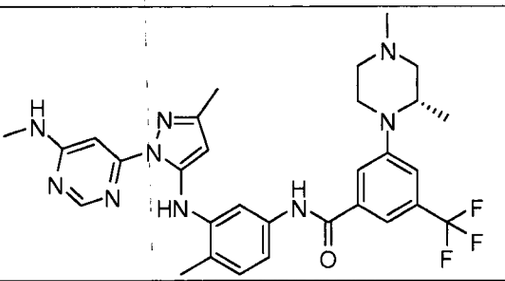
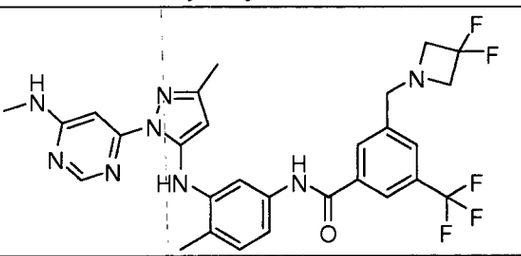
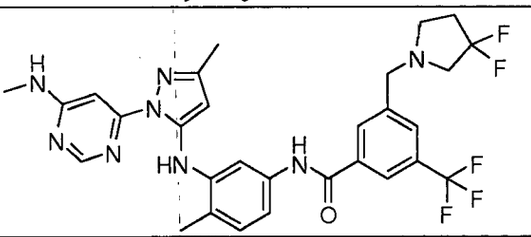
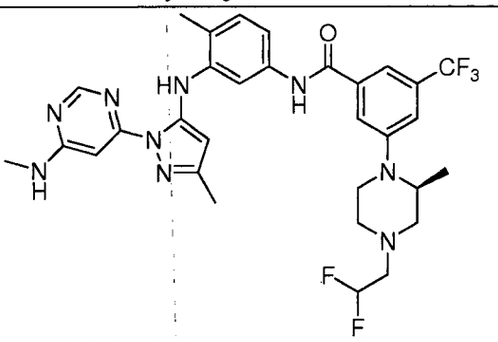
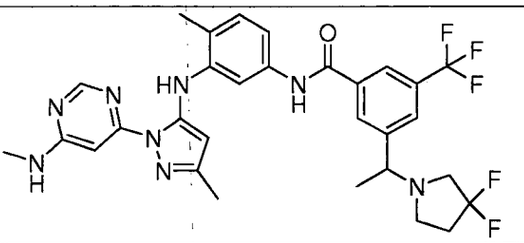
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
492		
493		
494		
495		
496		

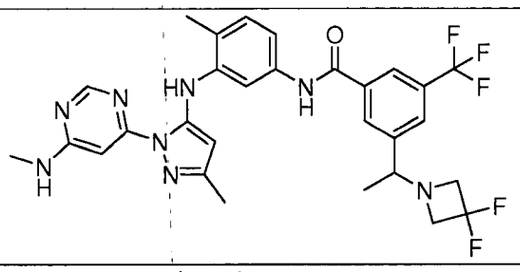
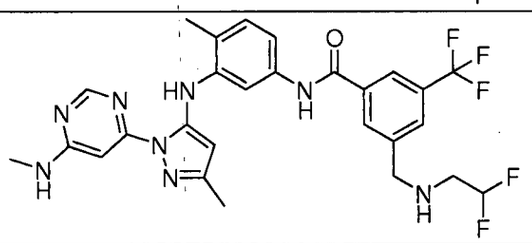
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
497		
498		
499		
500		
501		

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
502		
503		
504		
505		
506		
507		

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
508		
509		MS m/z 630.3 (M + 1)
510		MS m/z 590.3 (M + 1)
511		MS m/z 604.3 (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
512		MS m/z 546.3 (M + 1)
513		MS m/z 638.3 (M + 1)
514		MS m/z 638.3 (M + 1)
515		MS m/z 594.3 (M + 1)

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
516		MS m/z 594.3 (M + 1)
517		
518		
519		
520		

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) and/or MS (m/z)
521		
522		

Assays

[00163] Compounds of the present invention are assayed to measure their capacity to selectively inhibit cell proliferation of 32D cells expressing BCR-Abl (32D-p210) compared with parental 32D cells. Compounds selectively inhibiting the proliferation of these BCR-Abl transformed cells are tested for anti-proliferative activity on Ba/F3 cells expressing either wild type or the mutant forms of Bcr-abl. In addition, 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.

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

[00164] 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.

[00165] 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

[00166] 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 570nm is quantified spectrophotometrically and IC_{50} values, the concentration of compound required for 50% inhibition, determined from a dose response curve.

Effect on cell cycle distribution

[00167] 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 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

[00168] 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

[00169] 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 were 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 were determined from the dose response curves obtained as describe above.

FGFR3 (Enzymatic Assay)

[00170] 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 pH7.5, 15 mM $MgCl_2$, 4.5 mM $MnCl_2$, 15 µM Na_3VO_4 and 50 µg/mL BSA), and substrates (5 µg/mL biotin-poly-EY(Glu, Tyr) (CIS-US, Inc.) and 3µM ATP). Two solutions are made: the first solution of 5 µl contains the FGFR3 enzyme in kinase buffer was first dispensed into 384- format ProxiPlate® (Perkin-Elmer) followed by adding 50 nL of compounds dissolved in DMSO, then 5 µl of second solution contains the substrate (poly-EY) and ATP in kinase buffer was 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)

[00171] 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 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.

FLT3 and PDGFRβ (Cellular Assay)

[00172] The effects of compounds of the invention on the cellular activity of FLT3 and PDGFRβ are conducted using identical methods as described above for FGFR3 cellular activity, except that instead of using Ba/F3-TEL-FGFR3, Ba/F3-FLT3-ITD and Ba/F3-Tel-PDGFRβ are used, respectively.

b-Raf – enzymatic assay

[00173] 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

[00174] 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

[00175] 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. Note that the kinase buffer composition and the substrates vary for the different kinases included in the "Upstate KinaseProfiler™" panel. 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.

Antimalarial Assay using SYBR Green I

[00176] Compounds of the present invention can be assayed to measure their capacity to inhibit the proliferation of parasitemia in infected red blood cells. The proliferation is quantified by addition of SYBR Green I (Invitrogen)® dye which has a high affinity for double stranded DNA.

[00177] For drug screening, 20μl of screening media, containing no human serum, is dispensed into 3 assay plates. 50nl of each of the compounds of the invention, including antimalarial controls (chloroquine and artimesinin), are then transferred into the assay plates. 50nl of DMSO is transferred into the baseline and background control plates. Then 30μl of a suspension of P. *falciparum* infected human red blood cells in screening media is dispensed into the assay plates and the baseline control plate such that the final hematocrit is 2.5% with a final parasitemia of 3%. Non-infected red blood cells are dispensed into the background control plate such that the final hematocrit is 2.5%. The plates are placed in a

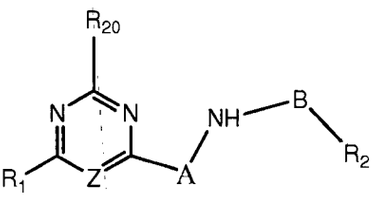
37°C incubator for 72 hours with a 93% N_2, 4% CO_2, and 3% O_2 gas mixture. 10µl of a 10X solution of SYBR Green I® is dispensed into the plates. The plates are sealed and placed in a -80°C freezer overnight for the lysis of the red blood cells. The plates are thawed and left at room temperature overnight for optimal staining. The fluorescence intensity is measured (excitation 497nm, emission 520nm) using the Acquest system (Molecular Devices). The percentage inhibition is calculated for each compound.

[00178] Compounds of Formula I, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the *in vitro* tests described in this application.

[00179] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A compound of Formula I:



I

in which :

A is a 5 member, unsaturated or partially unsaturated, ring containing 1 to 3 heteroatoms selected from –N=, –NR_3–, –O– and –S–; wherein R_3 is selected from hydrogen, halo, substituted or unsubstituted-C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6} alkynyl, -XOR_{4a}, -XCN, -$XC(O)OR_{4a}$, -$XC(O)R_{4b}$, -$XNR_{4a}R_{4a}$, -$XNR_{4a}XNR_{4a}R_{4a}$, -$XC(O)NR_{4a}XNR_{4a}R_{4a}$, -$XC(O)NR_{4a}XR_{4b}$, -$XC(O)NR_{4a}XNR_{4a}R_{4b}$, -$XC(O)NR_{4a}XOR_{4a}$, -$XNR_{4a}XNR_{4a}R_{4b}$, -$XNR_{4a}XOR_{4a}$, -$XNR_{4a}XCF_3$, -$XC(O)NR_{4a}R_{4a}$, and -$XR_{4b}$; wherein each X is independently selected from a bond and C_{1-4}alkylene; R_{4a} is selected from hydrogen and substituted or unsubstituted C_{1-6}alkyl, and two R_{4a} on the same or adjacent atoms can optionally be joined to form a 5-6 membered ring containing up to two heteroatoms selected from N, O and S as ring members; and R_{4b} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein any cycloalkyl, heterocycloalkyl, aryl or heteroaryl of R_{4b} is optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl and -$NR_{4c}R_{4d}$; wherein each R_{4c} and R_{4d} is independently selected from hydrogen and substituted or unsubstituted C_{1-6}alkyl, and R_{4c} and R_{4d} can optionally be joined together to form a 5-6 membered ring containing N and optionally containing an additional heteroatom selected from N, O and S; with the proviso that ring A is not imidazole;

wherein any ring A can be optionally substituted with one or two R_3 radicals, with the proviso that R_3 is not halo when attached directly to a nitrogen atom;

B is 5 or 6 member, unsaturated or partially unsaturated, ring containing 0 to 3 heteroatoms selected from –N=, $–NR_{21}–$, –O– and –S–; wherein R_{21} is selected from hydrogen, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo; wherein B can be optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo;

Z is selected from CH and N;

R_1 is selected from $–XNR_5R_6$, $–XNR_5XNR_5R_6$, $–XNR_5XR_5$, $–XNR_5XOR_6$, $–XNR_6XC(O)OR_5$, $–XNR_6XC(O)NR_6R_6$, $–XOR_5$, $–XC(O)R_5$, $–XR_5$ and $–XS(O)_{0-2}R_5$; wherein X is selected from a bond and C_{1-4}alkylene optionally substituted by 1 to 2 C_{1-6}alkyl radicals; R_5 is selected from hydrogen, substituted or unsubstituted C_{1-6}alkyl, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; and each R_6 is independently selected from hydrogen and substituted or unsubstituted C_{1-6}alkyl; or R_5 and R_6 together with the nitrogen to which R_5 and R_6 are both attached form heteroaryl or heterocycloalkyl that can contain an additional heteroatom selected from N, O and S as a ring member; or R_1 together with the N1 of the pyrimidine ring to which R_1 is attached forms 2,3-dihydroimidazo[1,2-f]pyrimidine;

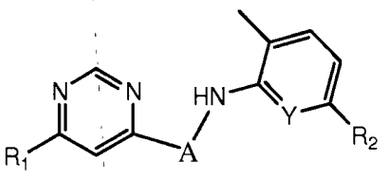
wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_5 or the combination of R_5 and R_6 can be optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-alkyl, halo-substituted-alkoxy, $–XNR_7R_8$, $–XOR_7$, $–XNR_7S(O)_2R_8$, $–XNR_7S(O)R_8$, $–XNR_7SR_8$, $–XC(O)NR_7R_8$, $–XC(O)NR_7XNR_7R_8$, $–XNR_7C(O)NR_7R_8$, $–XNR_7XNR_7R_8$, $–XNR_7XOR_7$, $–XNR_7C(=NR_7)NR_7R_8$, $–XS(O)_2R_9$, $–XNR_7C(O)R_8$, $–XNR_7C(O)R_9$, $–XR_9$, $–XC(O)OR_8$, $–XS(O)_2NR_7R_8$, $–XS(O)NR_7R_8$ and $–XSNR_7R_8$; wherein X is a bond or C_{1-4}alkylene; R_7 and R_8 are independently selected from the group consisting of hydrogen and substituted or unsubstituted C_{1-4}alkyl, and wherein R_7 and R_8 on one nitrogen can optionally cyclize to form a 5-6 membered ring that can contain an additional heteroatom selected from N, O and S as a ring member; and R_9 is selected from C_{3-10}heterocycloalkyl and C_{1-10}heteroaryl; wherein said heterocycloalkyl or heteroaryl of R_9 is optionally substituted with a radical selected from the group consisting of C_{1-4}alkyl, $–XNR_7XNR_7R_7$, XNR_7XOR_7 and $–XOR_7$;

R_2 is selected from $–R_{11}$, $–CONR_{10}R_{11}$, $SO_2NR_{10}R_{11}$, $-NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}S(O)_{0-2}R_{11}$ and $-NR_{10}C(O)NR_{10}R_{11}$; wherein R_{10} is selected from

hydrogen and substituted or unsubstituted C_{1-6}alkyl; R_{11} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein R_{10} and R_{11} on the same nitrogen can optionally cyclize to form a 5-6 membered ring that can contain an additional heteroatom selected from N, O and S as a ring member, and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{11} is optionally substituted by 1 to 3 radicals selected from halo, nitro, cyano, hydroxy, substituted or unsubstituted C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-X_2R_{13}$, $-X_2NR_{12}C(O)R_{13}$, $-X_2NR_{12}C(O)NR_{12}R_{13}$, $-X_2NR_{12}R_{12}$, $-X_2NR_{12}R_{13}$, $-X_2NR_{12}X_2R_{13}$, $-X_2NR_{12}NR_{12}R_{12}$, $-X_2NR_{12}X_2OR_{12}$, $-X_2C(O)NR_{12}R_{13}$, $-X_2NR_{12}S(O)_{0-2}R_{13}$ and $-X_2S(O)_{0-2}NR_{12}R_{13}$; wherein X_2 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{12} is selected from hydrogen, C_{1-6}alkyl and hydroxy-substituted-C_{1-6}alkyl; R_{13} is selected from substituted or unsubstituted C_{1-6} alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein two R_{12} groups or R_{12} and R_{13} on the same nitrogen can optionally cyclize to form a 5-6 membered ring that can contain an additional heteroatom selected from N, O and S as a ring member, any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{13} is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, hydroxy, nitro, amino, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-X_3NR_7R_8$, $-X_3NR_7X_3OR_7$, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl, C_{3-10}heterocycloalkyl-C_{0-4}alkoxy and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; wherein X_3 is selected from a bond and C_{1-4}alkylene; R_7 and R_8 are as described above and wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituents of R_{13} is further optionally substituted by 1 to 3 radicals independently selected from halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-10}heterocycloalkyl and halo-substituted-C_{1-6}alkoxy;

R_{20} is selected from hydrogen, substituted or unsubstituted C_{1-6}alkyl, and $N(R_{21})_2$, wherein each R_{21} is independently H or substituted or unsubstituted C_{1-6} alkyl, and wherein two R_{21} on the same nitrogen can cyclize to form a 5-6 membered ring that can contain an additional heteroatom selected from N, O and S; and the pharmaceutically acceptable salts thereof.

2. The compound of claim 1 of Formula Ia:



Ia

in which:

A is a 5 member, unsaturated or partially unsaturated, ring containing 1 to 3 heteroatoms selected from –N=, –NR_3–, –O– and –S–; wherein R_3 is selected from hydrogen, halo, halo-substituted-C_{1-6}alkyl, C_{1-6}alkyl, -XOR_{4a}, -XCN, -$XC(O)OR_{4a}$, -$XC(O)R_{4b}$, -$XNR_{4a}R_{4a}$, -$XNR_{4a}R_{4b}$, -$XNR_{4a}XNR_{4a}R_{4a}$, -$XC(O)NR_{4a}XNR_{4a}R_{4a}$, -$XC(O)NR_{4a}XR_{4b}$, -$XC(O)NR_{4a}XNR_{4a}R_{4b}$, -$XC(O)NR_{4a}XOR_{4a}$, -$XNR_{4a}XNR_{4a}R_{4b}$, -$XNR_{4a}XOR_{4a}$,-$XNR_{4a}XCF_3$, -$XC(O)NR_{4a}R_{4a}$, and -$XR_{4b}$; wherein X is selected from a bond and C_{1-4}alkylene; R_{4a} is selected from hydrogen and C_{1-6}alkyl; and R_{4b} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein any cycloalkyl, heterocycloalkyl, aryl or heteroaryl of R_{4b} is optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl and -$NR_{4c}R_{4d}$; wherein each R_{4c} and R_{4d} is independently selected from hydrogen and C_{1-6}alkyl; with the proviso that ring A is not imidazole; wherein any ring A can be optionally substituted with an R_3 radical;

R_1 is selected from –XNR_5R_6, –$XNR_5XNR_5R_6$, –XNR_5XR_5, –XNR_5XOR_6, –$XNR_6XC(O)OR_5$, –$XNR_6XC(O)NR_6R_6$, –XOR_5, –$XC(O)R_5$, –XR_5 and –$XS(O)_{0-2}R_5$; wherein X is selected from a bond and C_{1-4}alkylene optionally substituted by 1 to 2 C_{1-6}alkyl radicals; R_5 is selected from hydrogen, C_{1-6}alkyl, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; and each R_6 is independently selected from hydrogen and C_{1-6}alkyl; or R_5 and R_6 together with the nitrogen to which R_5 and R_6 are both attached form heteroaryl or heterocycloalkyl; or R_1 together with the N1 of the pyrimidine ring to which R_1 is attached forms 2,3-dihydroimidazo[1,2-f]pyrimidine;

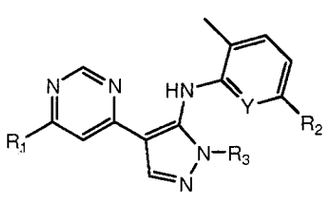
wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_5 or the combination of R_5 and R_6 can be optionally substituted with 1 to 3 radicals independently

selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-alkyl, halo-substituted-alkoxy, $-XNR_7R_8$, $-XOR_7$, $-XNR_7S(O)_2R_8$, $-XNR_7S(O)R_8$, $-XNR_7SR_8$, $-XC(O)NR_7R_8$, $-XC(O)NR_7XNR_7R_8$, $-XNR_7C(O)NR_7R_8$, $-XNR_7XNR_7R_8$, $-XNR_7XOR_7$, $-XNR_7C(=NR_7)NR_7R_8$, $-XS(O)_2R_9$, $-XNR_7C(O)R_8$, $-XNR_7C(O)R_9$, $-XR_9$, $-XC(O)OR_8$, $-XS(O)_2NR_7R_8$, $-XS(O)NR_7R_8$ and $-XSNR_7R_8$; wherein X is a bond or C_{1-4}alkylene; R_7 and R_8 are independently selected from the group consisting of hydrogen and C_{1-4}alkyl; and R_9 is selected from C_{3-10}heterocycloalkyl and C_{1-10}heteroaryl; wherein said heterocycloalkyl or heteroaryl of R_9 is optionally substituted with a radical selected from the group consisting of C_{1-4}alkyl, $-XNR_7XNR_7R_7$, XNR_7XOR_7 and $-XOR_7$;

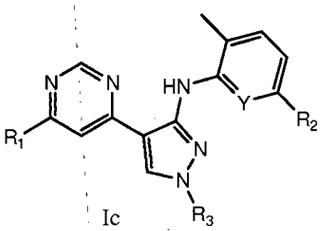
R_2 is selected from $-R_{11}$, $-CONR_{10}R_{11}$, $-SO_2NR_{10}R_{11}$, $-NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}S(O)_{0-2}R_{11}$ and $-NR_{10}C(O)NR_{10}R_{11}$; R_{10} is selected from hydrogen and C_{1-6}alkyl; R_{11} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{11} is optionally substituted by 1 to 3 radicals selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-X_2R_{13}$, $-X_2NR_{12}C(O)R_{13}$, $-X_2NR_{12}C(O)NR_{12}R_{13}$, $-X_2NR_{12}R_{12}$, $-X_2NR_{12}R_{13}$, $-X_2NR_{12}X_2R_{13}$, $-X_2NR_{12}NR_{12}R_{12}$, $-X_2NR_{12}X_2OR_{12}$, $-X_2C(O)NR_{12}R_{13}$, $-X_2NR_{12}S(O)_{0-2}R_{13}$ and $-X_2S(O)_{0-2}NR_{12}R_{13}$; wherein R_{12} is selected from hydrogen, C_{1-6}alkyl and hydroxy-substituted-C_{1-6}alkyl; wherein X_2 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{13} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{13} is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, hydroxy, nitro, amino, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-X_3NR_7R_8$, $-X_3NR_7X_3OR_7$, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl, C_{3-10}heterocycloalkyl-C_{0-4}alkoxy and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; wherein X_3 is selected from a bond and C_{1-4}alkyelene; R_7 and R_8 are as described above and wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituents of R_{13} is further optionally substituted by 1 to 3 radicals independently selected from halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-10}heterocycloalkyl and halo-substituted-C_{1-6}alkoxy; and

Y is selected from C and N.

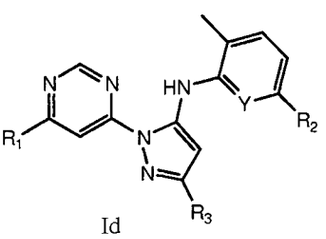
3. The compound of claim 2 selected from Formula Ib, Ic and Id:



Ib



Ic



Id

in which:

R_1 is selected from $-XNR_5R_6$, $-XNR_5XNR_5R_6$, $-XNR_5XR_5$, $-XNR_5XOR_6$, $-XNR_6XC(O)OR_5$, $-XNR_6XC(O)NR_6R_6$, $-XOR_5$, $-XC(O)R_5$, $-XR_5$ and $-XS(O)_{0-2}R_5$; wherein X is selected from a bond and C_{1-4}alkylene optionally substituted by 1 to 2 C_{1-6}alkyl radicals; R_5 is selected from hydrogen, C_{1-6}alkyl, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; and each R_6 is independently selected from hydrogen and C_{1-6}alkyl; or R_5 and R_6 together with the nitrogen to which R_5 and R_6 are both attached form heteroaryl or heterocycloalkyl; or R_1 together with the N1 of the pyrimidine ring to which R_1 is attached forms 2,3-dihydroimidazo[1,2-f]pyrimidine;

wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_5 or the combination of R_5 and R_6 can be optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-alkyl, halo-substituted-alkoxy, $-XNR_7R_8$, $-XOR_7$, $-XNR_7S(O)_2R_8$, $-XNR_7S(O)R_8$, $-XNR_7SR_8$, $-XC(O)NR_7R_8$, $-XC(O)NR_7XNR_7R_8$, $-XNR_7C(O)NR_7R_8$, $-XNR_7XNR_7R_8$, $-XNR_7XOR_7$, $-XNR_7C(=NR_7)NR_7R_8$, $-XS(O)_2R_9$, $-XNR_7C(O)R_8$, $-XNR_7C(O)R_9$, $-XR_9$, $-XC(O)OR_8$, $-XS(O)_2NR_7R_8$, $-XS(O)NR_7R_8$ and $-XSNR_7R_8$; wherein X is a bond or C_{1-4}alkylene; each R_7 and R_8 are independently selected from the group consisting of hydrogen and C_{1-4}alkyl, or R_7 and R_8 together with the nitrogen to which R_7 and R_8 are both attached form heteroaryl or heterocycloalkyl;; and R_9 is selected from C_{3-10}heterocycloalkyl and C_{1-10}heteroaryl; wherein

said heterocycloalkyl or heteroaryl of R_9 is optionally substituted with a radical selected from the group consisting of C_{1-4}alkyl, $-XNR_7XNR_7R_7$, XNR_7XOR_7 and $-XOR_7$;

R_2 is selected from $-R_{11}$, $-CONR_{10}R_{11}$, $SO_2NR_{10}R_{11}$, $-NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}S(O)_{0-2}R_{11}$ and $-NR_{10}C(O)NR_{10}R_{11}$; wherein R_{10} is selected from hydrogen and C_{1-6}alkyl; R_{11} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein R_{10} and R_{11} together with the nitrogen to which R_{10} and R_{11} are both attached can optionally form heteroaryl or heterocycloalkyl, and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{11} is optionally substituted by 1 to 3 radicals selected from halo, nitro, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-X_2R_{13}$, $-X_2NR_{12}C(O)R_{13}$, $-X_2NR_{12}C(O)NR_{12}R_{13}$, $-X_2NR_{12}R_{12}$, $-X_2NR_{12}R_{13}$, $-X_2NR_{12}X_2R_{13}$, $-X_2NR_{12}NR_{12}R_{12}$, $-X_2NR_{12}X_2OR_{12}$, $-X_2C(O)NR_{12}R_{13}$, $-X_2S(O)_{0-2}R_{12}$, $-X_2NR_{12}S(O)_{0-2}R_{13}$ and $-X_2S(O)_{0-2}NR_{12}R_{13}$; wherein X_2 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{12} is selected from hydrogen, C_{1-6}alkyl and hydroxy-substituted-C_{1-6}alkyl; R_{13} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein two R_{12} of $NR_{12}R_{12}$ or R_{12} and R_{13} of $NR_{12}R_{13}$ together with the nitrogen to which both are attached optionally form heteroaryl or heterocycloalkyl, and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{13} is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, hydroxy, nitro, amino, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-X_3NR_7R_8$, $-X_3NR_7X_3OR_7$, C_{6-10}aryl-C_{0-4}alkyl, C_{1-10}heteroaryl-C_{0-4}alkyl, C_{3-10}cycloalkyl-C_{0-4}alkyl, C_{3-10}heterocycloalkyl-C_{0-4}alkoxy and C_{3-10}heterocycloalkyl-C_{0-4}alkyl; wherein X_3 is selected from a bond and C_{1-4}alkyelene; R_7 and R_8 are as described above and wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituents of R_{13} is further optionally substituted by 1 to 3 radicals independently selected from halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-10}heterocycloalkyl and halo-substituted-C_{1-6}alkoxy;

R_3 is selected from hydrogen, halo, halo-substituted-C_{1-6}alkyl, C_{1-6}alkyl, $-XOR_{4a}$, -XCN, $-XC(O)OR_{4a}$, $-XC(O)R_{4b}$, $-XNR_{4a}R_{4a}$, $-XNR_{4a}R_{4b}$, $-XNR_{4a}XNR_{4a}R_{4a}$, $-XC(O)NR_{4a}XNR_{4a}R_{4a}$, $-XC(O)NR_{4a}XR_{4b}$, $-XC(O)NR_{4a}XNR_{4a}R_{4b}$, $-XC(O)NR_{4a}XOR_{4a}$, $-XNR_{4a}XNR_{4a}R_{4b}$, $-XNR_{4a}XOR_{4a}$, $-XNR_{4a}XCF_3$, $-XC(O)NR_{4a}R_{4a}$, and $-XR_{4b}$; wherein X is

selected from a bond and C_{1-4}alkylene; R_{4a} is selected from hydrogen and C_{1-6}alkyl; and R_{4b} is selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-10}cycloalkyl and C_{3-10}heterocycloalkyl; wherein two R_{4a} of $NR_{4a}R_{4a}$ together with the nitrogen to which both are attached optionally form heteroaryl or heterocycloalkyl, and any cycloalkyl, heterocycloalkyl, aryl or heteroaryl of R_{4b} is optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl and -$NR_{4c}R_{4d}$; wherein each R_{4c} and R_{4d} is independently selected from hydrogen and C_{1-6}alkyl, and R_{4c} and R_{4d} of $NR_{4c}R_{4d}$ together with the nitrogen to which R_{4c} and R_{4d} are attached optionally form a heteroaryl or heterocycloalkyl; and

Y is selected from CH and N.

4. The compound of claim 3 in which R_3 is selected from hydrogen, methyl, morpholino-ethyl, ethoxy-carbonyl, chloro, trifluoromethyl, (methyl-piperidinyl)(methyl)amino-methyl, methyl-amino-carbonyl, hydroxy-methyl, dimethyl-amino-methyl, methyl-amino-methyl, morpholino-methyl, diethyl-amino-ethyl-amino-methyl, methyl-piperazinyl-methyl, methyl-piperazinyl-ethyl-amino-methyl, dimethyl-amino-propyl-amino-methyl, ((2-hydroxyethyl)(methyl)amino)methyl, ethyl-amino-methyl, trifluoromethyl-amino-methyl, dimethyl-amino-ethyl-amino-carbonyl, piperidinyl-ethyl-amino-carbonyl, morpholino-ethyl-amino-carbonyl, morpholino-carbonyl, amino-carbonyl, dimethyl-amino-carbonyl, dimethyl-amino-pyrrolidinyl-methyl, dimethyl-amino-pyrrolidinyl-carbonyl, thiomorpholino-methyl, methoxy-ethyl-piperazinyl-methyl, methoxy-ethyl-amino-carbonyl, cyano-methyl, (2,6-dimethylmorpholino)methyl, (2,6-dimethyl-piperidinyl)ethyl-amino-carbonyl and cyclopropyl-amino-carbonyl.

5. The compound of claim 4 in which R_1 is selected from morpholino-ethyl-amino, methyl-amino, methyl-piperazinyl-ethyl-amino, cyclopropyl-amino, hydroxy-ethyl-piperazinyl-amino, isopropyl-amino, dimethyl-amino-ethyl-amino, methyl-piperazinyl-amino, amino, 2,6-dimethyl-morpholino-ethyl-amino, hydroxy-pyridinyl-ethyl-amino, amino-ethyl-amino, 3-oxopiperazin-1-yl-ethyl-amino, hydroxy-ethyl-amino, hydroxy-propyl-amino, methyl-sulfanyl, methoxy, sulfanyl, pyridinyl-ethyl-amino, pyridinyl-methyl-amino, morpholino-methyl-pyridinyl-amino, carboxy-propyl-amino, carboxy-methyl-amino, azetidin-3-yl-amino, azetidin-3-yl-methyl-amino, carboxy-ethyl-amino and hydroxy-pyrrolidinyl.

6. The compound of claim 5 in which R_2 is selected from $-R_{11}$, $-CONHR_{11}$, SO_2NHR_{11}, $-NHR_{11}$, $-NHC(O)R_{11}$, $-NHS(O)_{0-2}R_{11}$ and $-NHC(O)NHR_{11}$; wherein R_{11} is selected from phenyl, pyridinyl, thiazolyl, benzimidazolyl, isoxazolyl, 1,2,3,4-tetrahydronaphthyl, benzothiazolyl, benzo[d][1,2,3]triazole, 2,3-dihydrobenzofuran and 2,3-dihydro-3,3-dimethylbenzofuran-5-yl; wherein said phenyl, pyridinyl, thiazolyl, isoxazolyl and 2,3-dihydro-3,3-dimethylbenzofuran-5-yl of R_2 are optionally substituted with 1 to 3 radicals independently selected from halo, isopropyl, methyl-sulfonyl, hydroxy, methyl-sulfonyl-amino, 1-(2-hydroxyethylamino)cyclopropyl, 3-(3-hydroxypropylamino)cyclobutyl, isopropyl-amino-cyclobutyl, 2-(2-hydroxyethylamino)propan-2-yl, 3-aminoprop-1-enyl, isopropyl-3-aminoprop-1-enyl, isopropyl-amino-propyl, isopropyl-amino-ethyl, hydroxyethyl-3-aminoprop-1-enyl, methyl-amino, 1,2-dihydroxyethyl, 2-hydroxy-ethyl, (3-hydroxyazetidin-1-yl)methyl, (3-methoxyazetidin-1-yl)methyl, 2-methyl-morpholino-methyl, (3-methoxypyrrolidin-1-yl)methyl, (2-hydroxy-2-methylpropylamino)methyl, 1-methyl-1,2,3,6-tetrahydropyridin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, piperidin-4-yl, (4-ethylpiperazin-1-yl)methyl, pyrrolidiny-1-yl-methyl, 1-(ethylamino)ethyl, 4-(2-hydroxypropyl)-1-piperazinyl, 3-trifluoromethyl-4-methyl-1-piperazinyl, difluoro-methyl, 4-methyl-1-imidazolyl, methyl-sulfonyl-ethyl-amino-carbonyl, hydroxy-propyl-amino-carbonyl, 4-t-butoxy-carbonyl-1-piperazinyl, 4-(1-carboxyethyl)piperazin-1-yl, 4,7-diazaspiro[2.5]octan-7-yl, ethoxy, 4-(tert-butoxycarbonyl)-2-oxopiperazin-1-yl, 4-methyl-2-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, methoxy, ethyl, pyrazolyl, trifluoromethyl, 2-cyanobutan-2-yl, 1-cyanocyclopropyl, 2-hydroxypropan-2-yl, difluoromethyl, 3-ethylpentan-3-yl, methyl-piperazinyl, ethyl-piperazinyl, t-butyl, t-butoxy, 1,2-dihydroxypropyl, 2-hydroxymethyl-ethyl, cyclopropyl-1-piperazinyl, 4-methyl-sulfonyl-ethyl-1-piperazinyl, 2-hydroxy-propyl-amino-methyl, (tetrahydrofuran-2-ylamino)methyl, (2,3-dihydroxypropylamino)methyl), (1,3-dihydroxypropan-2-ylamino)methyl, (1-hydroxy-2-methylpropan-2-ylamino)methyl, cyclobutyl-amino-methyl, 4-hydroxy-piperidinyl, (1-hydroxypropan-2-ylamino)methyl, dimethyl-amino-amino-methyl, methoxy-amino-methyl,hydroxy-amino-methyl,2-hydroxy-methyl-pyrrolidin-1-yl-methyl, pyrrolidinyl-ethoxy, 3-hydroxy-pyrrolidinyl, 3-hydroxyazetidin-1-yl, 3-(methoxy-carbonyl)- 4-methylpiperazin-1-yl, 4-methylpiperazin-1-yl, 4-methyl-3-hydroxymethyl-piperazin-1-yl, 4-

methoxy-carbonyl-piperidinyl, 4-carboxy-piperidinyl, piperazinyl, 4-(2,2,2-trifluoroethyl)piperazin-1-yl, 2-hydroxy-cyclopent-1-yl-amino-methyl, amino-carbonyl-methyl, dimethyl-amino-propyl(methyl)-amino, (2-(dimethylamino)ethyl)(methyl)amino, methoxy-ethyl(methyl)amino, dimethyl-amino-ethoxy, nitro, 1-methyl-4-piperidinyloxy, morpholino, 2-methyl-morpholino, 4-ethyl-piperazin-1-yl-methyl, ethyl-amino-methyl, cyclopropyl-amino-methyl, diethyl-amino-ethyl, azetidin-1-ylmethyl, 3-hydroxy-pyrrolidin-1-yl-methyl, hydroxy-ethyl-amino-methyl, propyl-amino-methyl, 3-hydroxy-azetidin-1-ylmethyl, 4-methoxyethyl-1-piperazinyl, methoxy-ethyl-amino-methyl, butyl-amino-ethyl, t-butyl-amino-methyl, hydroxy-cyclohexyl-amino-methyl, amino-methyl, hydroxy-propyl-amino-methyl, hydroxy-ethyl(methyl)amino-methyl, 4-hydroxypropyl-1-piperazinyl, 4-carboxy-methyl-piperazinyl, dimethyl-amino-methyl, isopropyl-amino-methyl, 4-dimethyl-amino-carbonyl-methyl-1-piperazinyl, 4-(2-hydroxypropyl)piperazin-1-yl, hydroxy-ethyl-piperazinyl, methyl, cyclopropyl, halo, trifluoromethoxy, difluoromethoxy, 2-fluoropropan-2-yl, 2-methoxy-propan-2-yl, 1,1-difluoroethyl, 1-methyl-1-fluoroethyl, 1-methyl-1-methoxy-ethyl, 2-hydroxypropan-2-yl, 2-methoxypropan-2-yl, 2-cyanopropan-2-yl, 3-cyanopropan-2-yl, 2,3-difluoropropan-2-yl and cyano-cyclopropyl.

7. The compound of claim 1 selected from N-(4-Methyl-3-{2-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{1-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(5-methyl-2-{6-[2-(4-methyl-piperazin-1-yl)-ethylamino]-pyrimidin-4-yl}-2H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[4-(6-Cyclopropylamino-pyrimidin-4-yl)-2-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(2-methyl-4-{6-[2-(4-methyl-piperazin-1-yl)-ethylamino]-pyrimidin-4-yl}-2H-pyrazol-3-ylamino)-

phenyl]-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{2-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-{3-[4-(6-Cyclopropylamino-pyrimidin-4-yl)-1-methyl-1H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(1-methyl-4-{6-[2-(4-methyl-piperazin-1-yl)-ethylamino]-pyrimidin-4-yl}-1H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{1-methyl-4-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-{4-Methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(4-ethyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, 3-(4-Ethyl-piperazin-1-yl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-5-trifluoromethyl-benzamide, 3-(4-Ethyl-piperazin-1-yl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-5-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, 3-(4-Ethyl-piperazin-1-yl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-5-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 5-Methyl-6-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-pyridine-2-carboxylic acid (3-trifluoromethyl-phenyl)-amide, 5-Methyl-6-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-pyridine-2-carboxylic acid (3-trifluoromethyl-phenyl)-amide, 5-Methyl-6-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-pyridine-2-carboxylic acid (3-trifluoromethyl-phenyl)-amide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(4-

methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-[3-(2-{6-[2-(2,6-Dimethyl-morpholin-4-yl)-ethylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-3-trifluoromethyl-benzamide, N-[3-(2-{6-[2-(4-Hydroxy-piperidin-1-yl)-ethylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(5-methyl-2-{6-[2-(3-oxo-piperazin-1-yl)-ethylamino]-pyrimidin-4-yl}-2H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, N-(3-{2-[6-(2-Amino-ethylamino)-pyrimidin-4-yl]-5-methyl-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, 2-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-tert-Butyl-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, N-{4-Methyl-3-[4-(6-methylamino-pyrimidin-4-yl)-1H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[4-(6-methylamino-pyrimidin-4-yl)-1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[1-methyl-4-(6-methylamino-pyrimidin-4-yl)-1H-pyrazol-3-ylamino]-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, 3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-N-{4-methyl-3-[1-methyl-4-(6-methylamino-pyrimidin-4-yl)-1H-pyrazol-3-ylamino]-phenyl}-5-trifluoromethyl-benzamide, N-{3-[4-(6-Cyclopropylamino-pyrimidin-4-yl)-1-methyl-1H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzamide, N-{3-[4-(6-Cyclopropylamino-pyrimidin-4-yl)-1-methyl-1H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-5-trifluoromethyl-benzamide, N-(3-{2-[6-(2-Hydroxy-ethylamino)-pyrimidin-4-yl]-5-methyl-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[5-methyl-2-(6-methylsulfanyl-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(2,3-Dihydro-imidazo[1,2-c]pyrimidin-7-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, 2-tert-Butyl-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, N-{3-[2-(6-Methoxy-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-

{3-[2-(6-Mercapto-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-pyridin-3-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 4-(6-{3-Methyl-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-pyrazol-1-yl}-pyrimidin-4-ylamino)-butyric acid, (6-{3-Methyl-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-pyrazol-1-yl}-pyrimidin-4-ylamino)-acetic acid, N-(3-{2-[6-(Azetidin-3-ylamino)-pyrimidin-4-yl]-5-methyl-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, 3-(6-{3-Methyl-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-pyrazol-1-yl}-pyrimidin-4-ylamino)-propionic acid, N-(3-{2-[6-(3-Hydroxy-pyrrolidin-1-yl)-pyrimidin-4-yl]-5-methyl-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, N-[3-(2-{6-[(Azetidin-3-ylmethyl)-amino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(5-methyl-2-{6-[(pyridin-2-ylmethyl)-amino]-pyrimidin-4-yl}-2H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, 4-Methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-N-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-phenyl]-benzamide, (4-Methyl-3-{5-methyl-2-[6-(5-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-carbamic acid tert-butyl ester, 5-Methyl-N-(4-methyl-3-{5-methyl-2-[6-(5-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 3-Cyclopropyl-isoxazole-5-carboxylic acid (4-methyl-3-{5-methyl-2-[6-(5-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-amide, 3,4-Dichloro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-Fluoro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-5-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-4-trifluoromethyl-benzamide, 3,5-Dichloro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-Fluoro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, N-(4-Methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethoxy-benzamide, 3-Bromo-4-chloro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-

Difluoromethoxy-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-Chloro-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 3-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Cyano-cyclopropyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3,3-Dimethyl-2,3-dihydro-benzofuran-5-carboxylic acid (4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-amide, 4-Methyl-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 3-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Cyano-cyclopropyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 2-(1-Cyano-cyclopropyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid ethyl ester, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-

phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-hydroxymethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-dimethylaminomethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-methylaminomethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-(3-{2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[(2-diethylamino-ethylamino)-methyl]-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-(4-methyl-piperazin-1-ylmethyl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-[3-(2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-{[2-(4-methyl-piperazin-1-yl)-ethylamino]-methyl}-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-3-trifluoromethyl-benzamide, N-(3-{2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[(3-dimethylamino-propylamino)-methyl]-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-ethylaminomethyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-(3-{2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[(2,2,2-trifluoro-ethylamino)-methyl]-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-3-trifluoromethyl-benzamide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid (2-dimethylamino-ethyl)-amide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid (2-piperidin-1-yl-ethyl)-amide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-(morpholine-4-carbonyl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid amide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid dimethylamide, N-{3-[2-(6-Cyclopropylamino-pyrimidin-4-yl)-5-(3-dimethylamino-pyrrolidine-1-carbonyl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, 1-(6-Cyclopropylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic

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acid (2-methoxy-ethyl)-amide, 1-(6-Methylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, N-{4-Methyl-3-[5-methylaminomethyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, 1-(6-Methylamino-pyrimidin-4-yl)-5-{2-methyl-5-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzoylamino]-phenylamino}-1H-pyrazole-3-carboxylic acid methylamide, 1-(6-Methylamino-2-morpholin-4-yl-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1-Cyano-cyclopropyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, N-{3-[5-Cyanomethyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, 1-(6-Methylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 1-(6-Methylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid cyclopropylamide, 5-tert-Butyl-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-tert-Butyl-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, N-[5-(1-Fluoro-1-methyl-ethyl)-pyridin-3-yl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-[5-(1-Methoxy-1-methyl-ethyl)-pyridin-3-yl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-[5-(1-Fluoro-1-methyl-ethyl)-pyridin-3-yl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-[5-(1-Methoxy-1-methyl-ethyl)-pyridin-3-yl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, 4-Methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-N-(4-trifluoromethyl-pyridin-2-yl)-

benzamide, N-(3-tert-Butyl-phenyl)-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-(2-tert-Butyl-pyridin-4-yl)-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-(3-tert-Butyl-phenyl)-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-[3-(Cyano-dimethyl-methyl)-phenyl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, 4-Methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-N-(4-trifluoromethyl-pyridin-2-yl)-benzamide, (6-{5-[5-(6-tert-Butyl-1H-benzoimidazol-2-yl)-2-methyl-phenylamino]-3-methyl-pyrazol-1-yl}-pyrimidin-4-yl)-(4-methyl-piperazin-1-yl)-amine, (6-{3-Methyl-5-[2-methyl-5-(6-trifluoromethyl-1H-benzoimidazol-2-yl)-phenylamino]-pyrazol-1-yl}-pyrimidin-4-yl)-(4-methyl-piperazin-1-yl)-amine, N-[3-(1,1-Difluoro-ethyl)-phenyl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-[3-(1,1-Difluoro-ethyl)-phenyl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, 4-Fluoro-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, 4-Fluoro-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 5-[5-(4-Fluoro-3-trifluoromethyl-benzoylamino)-2-methyl-phenylamino]-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-[5-(4-Fluoro-3-trifluoromethyl-benzoylamino)-2-methyl-phenylamino]-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-[5-(4-Fluoro-3-trifluoromethyl-benzoylamino)-2-methyl-phenylamino]-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 5-[5-(2-tert-Butyl-pyridin-4-ylcarbamoyl)-2-methyl-phenylamino]-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, N-(4-Methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-

morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 2-tert-Butyl-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 5-tert-Butyl-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(Cyano-dimethyl-methyl)-N-{3-[5-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-isonicotinamide, 3-(Cyano-dimethyl-methyl)-N-{3-[5-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-benzamide, 2-tert-Butyl-N-{3-[5-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-isonicotinamide, 2-tert-Butyl-N-{3-[5-[2-(2,6-dimethyl-piperidin-1-yl)-ethylcarbamoyl]-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-isonicotinamide, 2-(Cyano-dimethyl-methyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 3-(Cyano-dimethyl-methyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Cyano-cyclopropyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-(1-Cyano-cyclopropyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 3-(1-Cyano-1-methyl-propyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-tert-Butyl-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 3-(1,1-Difluoro-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Hydroxy-1-methyl-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Methoxy-1-methyl-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 5-tert-Butyl-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, 2-tert-Butyl-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2,2-Dimethyl-2,3-dihydro-benzofuran-7-carboxylic acid {4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-amide, 2-(1-Fluoro-

1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Fluoro-1-methyl-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Fluoro-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Methoxy-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(1-Hydroxy-1-methyl-ethyl)-N-{4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 3-(1-Cyano-cyclopropyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(Cyano-dimethyl-methyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-(Cyano-dimethyl-methyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Cyano-cyclopropyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 3-(1,1-Difluoro-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Methoxy-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 3-(1-Hydroxy-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-(1-Fluoro-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Methoxy-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-(1-Hydroxy-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 5-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, N-[3-(Cyano-dimethyl-methyl)-phenyl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-

ylamino}-benzamide, N-(2-tert-Butyl-pyridin-4-yl)-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, 5-(1-Fluoro-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-(1-Hydroxy-1-methyl-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 2-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-(1,1-difluoro-ethyl)-benzamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(5-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{5-methyl-2-[6-(4-morpholin-4-ylmethyl-pyridin-2-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-benzamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-5-methyl-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-2-tert-butyl-isonicotinamide, 2-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-tert-Butyl-N-[3-(2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-ylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-isonicotinamide, 5-tert-Butyl-N-[3-(2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-ylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-phenyl]-nicotinamide, N-(2-tert-Butyl-pyridin-4-yl)-3-(2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-ylamino]-pyrimidin-4-yl}-5-methyl-2H-pyrazol-3-ylamino)-4-methyl-benzamide, N-(5-tert-Butyl-pyridin-3-yl)-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-[2-(1-Methoxy-1-methyl-ethyl)-pyridin-4-yl]-4-methyl-3-{5-methyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, N-[3-(1,1-Difluoro-ethyl)-phenyl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, N-[2-(Cyano-dimethyl-methyl)-pyridin-4-yl]-4-methyl-3-[5-methyl-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-benzamide, 5-(1-Fluoro-1-methyl-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, N-{3-[2-(6-Amino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-2-tert-butyl-isonicotinamide, 3-(1,1-Difluoro-ethyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-benzamide, 2-tert-

Butyl-N-(3-{2-[6-(2-dimethylamino-acetylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-4-methyl-phenyl)-isonicotinamide, N-[2-(1,1-Difluoro-ethyl)-pyridin-4-yl]-4-methyl-3-{5-methyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-benzamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 5-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, 5-tert-Butyl-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 1-(6-Methylamino-pyrimidin-4-yl)-5-{2-methyl-5-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-benzoylamino]-phenylamino}-1H-pyrazole-3-carboxylic acid methylamide, 1-(6-Methylamino-2-morpholin-4-yl-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1-Cyano-cyclopropyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 1-(6-Methylamino-pyrimidin-4-yl)-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid cyclopropylamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 2-tert-Butyl-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-tert-Butyl-N-{4-methyl-3-[2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-tert-Butyl-N-{4-

methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-methylcarbamoyl-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 5-[5-(3-tert-Butyl-benzoylamino)-2-methyl-phenylamino]-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 2-Chloro-6-methoxy-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-Chloro-6-methoxy-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 2-Chloro-6-methoxy-N-{4-methyl-3-[2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-Chloro-6-methoxy-N-{4-methyl-3-[2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-Chloro-6-methoxy-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-isonicotinamide, 2-Chloro-6-methoxy-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, N-(4-Methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-6-pyrazol-1-yl-nicotinamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-methylcarbamoyl-2H-pyrazol-3-ylamino]-phenyl}-6-pyrazol-1-yl-nicotinamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-6-pyrazol-1-yl-nicotinamide, N-(4-Methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-6-pyrazol-1-yl-nicotinamide, 5-[2-Methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 5-[2-Methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 1-[6-(4-Methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenylamino]-1H-pyrazole-3-carboxylic acid methylamide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-6-trifluoromethoxy-nicotinamide, N-{4-

Methyl-3-[2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-6-trifluoromethoxy-nicotinamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-methylcarbamoyl-2H-pyrazol-3-ylamino]-phenyl}-6-trifluoromethoxy-nicotinamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-(2-morpholin-4-yl-ethylcarbamoyl)-2H-pyrazol-3-ylamino]-phenyl}-6-trifluoromethoxy-nicotinamide, N-(4-Methyl-3-{5-methylcarbamoyl-2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-6-trifluoromethoxy-nicotinamide, 2-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 5-{5-[3-(1-Cyano-1-methyl-propyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 3-(1-Cyano-1-methyl-propyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 5-{5-[3-(1-Cyano-1-methyl-propyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1-Cyano-1-methyl-propyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(1-Methoxy-1-methyl-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 3-(1-Methoxy-1-methyl-ethyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-(Cyano-dimethyl-methyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 5-tert-Butyl-N-(4-methyl-3-{5-methylcarbamoyl-2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 3-(1,1-Difluoro-ethyl)-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-1H-pyrazole-3-carboxylic acid methylamide, 2-tert-Butyl-N-(4-methyl-3-{5-methylcarbamoyl-

2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 4-tert-Butyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-Methanesulfonyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-Chloro-3-methanesulfonyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-tert-Butoxy-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 4-Methoxy-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethyl-benzamide, 3-tert-Butoxy-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, 3-Methanesulfonyl-N-(4-methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-benzamide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-4-trifluoromethoxy-benzamide, N-(4-Methyl-3-{2-[6-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-3-trifluoromethoxy-benzamide, 5-{5-[3-(1,1-Difluoro-ethyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid methylamide, 5-{5-[3-(Cyano-dimethyl-methyl)-benzoylamino]-2-methyl-phenylamino}-1-(6-methylamino-pyrimidin-4-yl)-1H-pyrazole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide, 5-tert-Butyl-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-nicotinamide, 2-tert-Butyl-N-(4-methyl-3-{2-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-yl]-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino}-phenyl)-isonicotinamide, 5-tert-Butyl-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-nicotinamide, 1-Isopropyl-1H-benzotriazole-5-carboxylic acid {4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-amide, 5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid {4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-amide, 2-Methyl-benzothiazole-5-carboxylic acid {4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-amide, 3-(1,1-Diethyl-propyl)-N-{4-methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-

morpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-benzamide, N-{3-[5-(3-Dimethylamino-pyrrolidin-1-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[5-[4-(2-Methoxy-ethyl)-piperazin-1-ylmethyl]-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[5-(2,6-Dimethyl-morpholin-4-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{3-[5-(2,6-Dimethyl-morpholin-4-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-[4-Methyl-3-(2-(6-methylamino-pyrimidin-4-yl)-5-{[methyl-(1-methyl-piperidin-4-yl)-amino]-methyl}-2H-pyrazol-3-ylamino)-phenyl]-3-trifluoromethyl-benzamide, N-{3-[5-(1,1-Dioxo-1l6-thiomorpholin-4-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-phenyl}-3-trifluoromethyl-benzamide, N-{4-Methyl-3-[2-(6-methylamino-pyrimidin-4-yl)-5-thiomorpholin-4-ylmethyl-2H-pyrazol-3-ylamino]-phenyl}-3-trifluoromethyl-benzamide, 5-tert-butyl-N-(3-(3-(((2-hydroxyethyl)(methyl)amino)methyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)nicotinamide, -(2-(2-fluoropropan-2-yl)pyridin-4-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 5-tert-butyl-N-(3-(3-(((2-hydroxyethyl)(methyl)amino)methyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)nicotinamide, 5-tert-butyl-N-(3-(3-(2-(2,6-dimethylpiperidin-1-yl)ethylcarbamoyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)nicotinamide, 5-(2-methoxypropan-2-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)nicotinamide, 5-(2-fluoropropan-2-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)nicotinamide, N-(4-tert-butylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-(2-fluoropropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 5-(5-(2-tert-butylpyridin-4-ylcarbamoyl)-2-methylphenylamino)-1-(6-(isopropylamino)pyrimidin-4-yl)-N-methyl-1H-pyrazole-3-carboxamide, 5-(5-(2-tert-butylpyridin-4-ylcarbamoyl)-2-methylphenylamino)-N-methyl-1-(6-(méthylamino)pyrimidin-4-yl)-1H-pyrazole-3-carboxamide, N-(2-tert-butylpyridin-4-yl)-4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-(morpholinomethyl)-1H-pyrazol-5-ylamino)benzamide, N-(2-tert-Butyl-pyridin-4-yl)-3-[5-(1,1-dioxo-1lambda*6*-

thiomorpholin-4-ylmethyl)-2-(6-methylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-benzamide, 2-tert-butyl-N-(3-(1-(6-(isopropylamino)pyrimidin-4-yl)-3-(methylcarbamoyl)-1H-pyrazol-5-ylamino)-4-methylphenyl)isonicotinamide, N-(2-tert-butylpyridin-4-yl)-3-(1-(6-(isopropylamino)pyrimidin-4-yl)-3-(morpholinomethyl)-1H-pyrazol-5-ylamino)-4-methylbenzamide, N-(2-tert-Butyl-pyridin-4-yl)-3-[5-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-2-(6-isopropylamino-pyrimidin-4-yl)-2H-pyrazol-3-ylamino]-4-methyl-benzamide, 2-tert-butyl-N-(3-(1-(6-(isopropylamino)pyrimidin-4-yl)-3-(morpholinomethyl)-1H-pyrazol-5-ylamino)-4-methylphenyl)isonicotinamide, N-(4-(2-fluoropropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(5-tert-butyl-4-methylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(5-tert-butyl-4-methylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-(2-cyanopropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(2-(2-methoxypropan-2-yl)pyridin-4-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-tert-butylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-(2-morpholinoethylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(5-tert-butyl-4-methylthiazol-2-yl)-4-methyl-3-(3-methyl-1-(6-(2-morpholinoethylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, -(4-(1,1-difluoroethyl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-(1,1-difluoroethyl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-tert-butylpyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-tert-butylpyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 3-(1-(6-aminopyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(5-tert-butyl-4-methylthiazol-2-yl)-4-methylbenzamide, 3-(1-(6-aminopyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(4-tert-butylthiazol-2-yl)-4-methylbenzamide, N-(4-(2-methoxypropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-(2-methoxypropan-2-yl)pyridin-2-yl)-4-methyl-3-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(6-methyl-5-(3-methyl-1-(6-

(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)-3-(trifluoromethyl)benzamide, N-(6-methyl-5-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)-3-(trifluoromethyl)benzamide, 2-tert-butyl-N-(6-methyl-5-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)isonicotinamide, 2-tert-butyl-N-(6-methyl-5-(3-methyl-1-(6-(4-methylpiperazin-1-ylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)isonicotinamide, N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-(1-oxo-thiomorpholinomethyl)-1H-pyrazol-5-ylamino)phenyl)-3-(trifluoromethyl)benzamide, N-(3-(1-(6-aminopyrimidin-4-yl)-3-methyl-1H-pyrazol-5-ylamino)-4-methylphenyl)-3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)benzamide, 3-(4-hydroxypiperidin-1-yl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(4-hydroxypiperidin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1-methylpiperidin-4-yloxy)-5-(trifluoromethyl)benzamide, 3-(4-(2-hydroxyethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-morpholino-5-(trifluoromethyl)benzamide, (S)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(2-methylmorpholino)-5-(trifluoromethyl)benzamide, (R)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(2-methylmorpholino)-5-(trifluoromethyl)benzamide, 1-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(3-(trifluoromethyl)phenyl)urea, 1-(4-fluoro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(3-(4-ethylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1,1-dioxo-thiomorpholino)-5-(trifluoromethyl)benzamide, (R)-3-(3,4-dimethylpiperazin-1-yl)-N-(4-

methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(3,4-dimethylpiperazin-1-yl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-(2-(dimethylamino)ethoxy)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(2-(pyrrolidin-1-yl)ethoxy)-5-(trifluoromethyl)phenyl)benzamide, N-(3-(3-hydroxypyrrolidin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-(3-hydroxyazetidin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 2-(1,1-difluoroethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)isonicotinamide, methyl 1-methyl-4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamido)-5-(trifluoromethyl)phenyl)piperazine-2-carboxylate, N-(3-((2-methoxyethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-((2-(dimethylamino)ethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 3-(1,1-difluoroethyl)-N-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)benzamide, N-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)-3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)benzamide, 4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-(trifluoromethyl)-1H-pyrazol-5-ylamino)-N-(3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)benzamide, methyl 1-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamido)-5-(trifluoromethyl)phenyl)piperidine-4-carboxylate, 1-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamido)-5-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid, N-(3-(3-(hydroxymethyl)-4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-((2-

hydroxyethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(3-(4-(hydroxymethyl)piperidin-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 1-(3-(1,1-difluoroethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(2-(1,1-difluoroethyl)pyridin-4-yl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, N-(3-fluoro-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(methylsulfonamido)-5-(trifluoromethyl)phenyl)benzamide, 2-methoxy-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-(trifluoromethyl)isonicotinamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(trifluoromethyl)phenyl)benzamide, N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, N-(4-fluoro-3-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 3-((3-(dimethylamino)propyl)(methyl)amino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-nitro-5-(trifluoromethyl)benzamide, 3-amino-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((2-methoxyethyl)(methyl)amino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 1-(4-bromo-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(6-methyl-5-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)pyridin-3-yl)urea, 3-((2-(dimethylamino)ethyl)(methyl)amino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 1-(3-(4-(2-hydroxyethyl)piperazin-1-yl)-5-

(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)urea, methyl 3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamido)-5-(trifluoromethyl)benzoate, 3-(2-(dimethylamino)ethoxy)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(3-(dimethylamino)propoxy)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-hydroxy-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1-(6-(2-(dimethylamino)ethylamino)pyrimidin-4-yl)-3-methyl-1H-pyrazol-5-ylamino)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(1-(6-(2-(dimethylamino)ethylamino)pyrimidin-4-yl)-3-methyl-1H-pyrazol-5-ylamino)-4-methylphenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(2-morpholinoethylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 3-(1-(6-(3-hydroxypropylamino)pyrimidin-4-yl)-3-methyl-1H-pyrazol-5-ylamino)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide, 3-(difluoromethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-(difluoromethyl)-N-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)benzamide, 1-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 3-(4-methyl-1H-imidazol-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide, N-(3-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(2-methyl-5-(trifluoromethyl)phenyl)benzamide, 1-(3-(1,1-difluoroethyl)phenyl)-3-(3-(3-(hydroxymethyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-

methylphenyl)urea, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(2-(methylsulfonyl)ethylcarbamoyl)-5-(trifluoromethyl)phenyl)benzamide, N-(3-(3-hydroxypropylcarbamoyl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-methyl-5-(trifluoromethyl)phenyl)benzamide, 1-(3-((2-methoxyethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(3-((2-(dimethylamino)ethyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-(morpholinomethyl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(3-((dimethylamino)methyl)-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-4-methylphenyl)urea, 3-bromo-5-(1,1-difluoroethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, (R)-1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-3-((2-methylmorpholino)methyl)-1H-pyrazol-5-ylamino)phenyl)urea, tert-butyl 4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamoyl)-5-(trifluoromethyl)phenyl)piperazine-1-carboxylate, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(piperazin-1-yl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)-5-(trifluoromethyl)benzamide, 3-(4-(2-amino-2-oxoethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(4-(2-methoxyethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(4-(3-hydroxypropyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 2-(4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamoyl)-5-(trifluoromethyl)phenyl)piperazin-1-yl)acetic acid, 3-(4-(2-(dimethylamino)-2-oxoethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-

(trifluoromethyl)benzamide, 3-(4-(2-hydroxypropyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)-5-(trifluoromethyl)benzamide, 3-(4-cyclopropylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-2-(4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamoyl)-5-(trifluoromethyl)phenyl)piperazin-1-yl)propanoic acid, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4,7-diazaspiro[2.5]octan-7-yl)-5-(trifluoromethyl)benzamide, 2-ethoxy-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-(trifluoromethyl)isonicotinamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(trifluoromethyl)-5-(3-(trifluoromethyl)piperazin-1-yl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-5-(trifluoromethyl)benzamide, tert-butyl 4-(3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenylcarbamoyl)-5-(trifluoromethyl)phenyl)-3-oxopiperazine-1-carboxylate, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(2-oxopiperazin-1-yl)-5-(trifluoromethyl)benzamide, 3-(4-methyl-2-oxopiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-2-(methylamino)-6-(trifluoromethyl)isonicotinamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(4-methyl-3-(trifluoromethyl)piperazin-1-yl)-5-(trifluoromethyl)benzamide, 2-(2-(dimethylamino)ethylamino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-(trifluoromethyl)isonicotinamide, 2-(2-hydroxyethylamino)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-(trifluoromethyl)isonicotinamide, 3-(4-hydroxypiperidin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (*R*)-3-(4-(2-hydroxypropyl)piperazin-1-yl)-

N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (*S*)-3-(4-(2-hydroxypropyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(3-((4-ethylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)-N-(3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)phenyl)benzamide, N-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)benzamide, 3-((dimethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)benzamide, 3-((isopropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((methylamino)methyl)-5-(trifluoromethyl)benzamide, 1-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 1-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)phenyl)urea, 1-(3-((4-ethylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-3-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)urea, 3-((ethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((cyclopropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,1-difluoroethyl)-5-((isopropylamino)methyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-(1,1-difluoroethyl)-5-((isopropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((diethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(azetidin-1-ylmethyl)-N-(4-

methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(azetidin-1-ylmethyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3-hydroxyazetidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3-hydroxypyrrolidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((2-hydroxyethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((propylamino)methyl)-5-(trifluoromethyl)benzamide, 3-(1,1-difluoroethyl)-5-((dimethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((cyclopropylamino)methyl)-5-(1,1-difluoroethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((3-hydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,1-difluoroethyl)-5-((ethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((2-methoxyethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((butylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((tert-butylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,1-difluoroethyl)-5-((4-hydroxycyclohexylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-((cyclopropylamino)methyl)-5-(1,1-difluoroethyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-(aminomethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 2-((dimethylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-6-

(trifluoromethyl)isonicotinamide, 3-(((2-hydroxyethyl)(methyl)amino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,2-dihydroxyethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((1-hydroxypropan-2-ylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((1-hydroxypropan-2-ylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((2,2-dimethylhydrazinyl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((methoxyamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((hydroxyamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-((2-hydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(((tetrahydrofuran-2-yl)methylamino)methyl)-5-(trifluoromethyl)benzamide, (R)-3-((2,3-dihydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-((2,3-dihydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((1,3-dihydroxypropan-2-ylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((1-hydroxy-2-methylpropan-2-ylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((cyclobutylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((dimethylamino)methyl)-N-(4-methyl-3-(1-(6-

(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(((2-methoxyethyl)(methyl)amino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(((1S,2R)-2-hydroxycyclopentylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(((tetrahydrofuran-2-yl)methylamino)methyl)-5-(trifluoromethyl)benzamide, (R)-3-((2-hydroxypropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(morpholinomethyl)-5-(trifluoromethyl)benzamide, 3-((3-methoxyazetidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide 3-((3-methoxypyrrolidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3-hydroxyazetidin-1-yl)methyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-chloro-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((dimethylamino)methyl)-5-(trifluoromethyl)benzamide, N-(4-chloro-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((isopropylamino)methyl)-5-(trifluoromethyl)benzamide, N-(4-chloro-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)benzamide, 3-((isopropylamino)methyl)-N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)benzamide, 3-(1-(ethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (*S*)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((2-methylmorpholino)methyl)-5-(trifluoromethyl)benzamide, (*R*)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-((2-

methylmorpholino)methyl)-5-(trifluoromethyl)benzamide, 3-((2-hydroxy-2-methylpropylamino)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-5-(trifluoromethyl)benzamide, N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(piperidin-4-yl)-5-(trifluoromethyl)benzamide, 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1,2-dihydroxyethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(1-hydroxyethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(3-(2-hydroxyethylamino)cyclobutyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(3-(isopropylamino)cyclobutyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (E)-3-(3-aminoprop-1-enyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (E)-3-(3-(isopropylamino)prop-1-enyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (E)-3-(3-(2-hydroxyethylamino)prop-1-enyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(3-(isopropylamino)propyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(2-(isopropylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(2-(2-hydroxyethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-(1-(ethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (*R*)-3-(1-(ethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-

pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(1-(dimethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-(1-(dimethylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1-(pyrrolidin-1-yl)ethyl)-5-(trifluoromethyl)benzamide, (R)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-3-(1-(pyrrolidin-1-yl)ethyl)-5-(trifluoromethyl)benzamide, (S)-3-(1-(isopropylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(1-(isopropylamino)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-(4-(2,2-difluoroethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-chloro-5-(4-(2-methoxyethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-chloro-5-(4-(2-ethoxyethyl)piperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)benzamide, 3-chloro-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(4-methylpiperazin-1-yl)benzamide, (S)-3-(4-(2-methoxyethyl)-2-methylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(4-(2-methoxyethyl)-2-methylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(2,4-dimethylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (S)-3-(2,4-dimethylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3,3-difluoroazetidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, 3-((3,3-difluoropyrrolidin-1-yl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, (R)-3-(4-(2,2-difluoroethyl)-2-methylpiperazin-1-yl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, *rac*-3-(2-(3,3-difluoropyrrolidin-1-yl)ethyl)-N-

(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, *rac*-3-(2-(3,3-difluoroazetidin-1-yl)ethyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide, and 3-((2,2-difluoroethyl)methyl)-N-(4-methyl-3-(3-methyl-1-(6-(methylamino)pyrimidin-4-yl)-1H-pyrazol-5-ylamino)phenyl)-5-(trifluoromethyl)benzamide.

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

9. A method for treating a disease in an animal in which inhibition of kinase activity can inhibit or ameliorate the pathology and/or symptomology of the kinase mediated disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

10. The method of claim 9 in which the kinase is selected from the group consisting of Abl, ARG, BCR-Abl, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 and TrkB.

11. The use of a compound of claim 1 in the manufacture of a medicament for treating a disease in an animal in which the kinase activity of Abl, ARG, BCR-Abl, BRK, EphB, Fms, Fyn, KDR, c-Kit, LCK, PDGF-R, b-Raf, c-Raf, SAPK2, Src, Tie2 and TrkB contributes to the pathology and/or symptomology of the disease.

COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE PROTEINQUINASAS

REFERENCIA RECIPROCA A SOLICITUDES RELACIONADAS

Esta solicitud reivindica el beneficio de prioridad de la Solicitud de Patente Provisional US No. 60/827,873, presentada el 02 de octubre de 2006. La divulgación completa de esta solicitud se incorpora en la presente como referencia en su totalidad y para todo propósito.

FUNDAMENTO DEL INVENTO

Campo del invento

El invento proporciona una nueva clase de compuestos, composiciones farmacéuticas comprendiendo tales compuestos y métodos de utilización de tales compuestos para tratar o prevenir enfermedades o trastornos asociados con la actividad anormal o desregulada de las quinasas, particularmente enfermedades o trastornos que involucran activación anormal de las quinasas Abl, ARG, BCR- Abl, BRK, EphB, Fms, Fyn, KDR, c- Kit, LCK, PDGF- R, b- Raf, c- Raf, SAPK2, Src, Tie2 y TrkB.

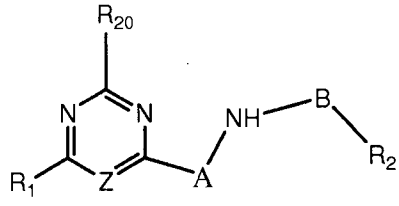
Fundamento

Las proteinquinasas representan una gran familia de proteínas, las cuales juegan un papel principal en la regulación de una amplia variedad de procesos celulares y mantenimiento de control sobre la función celular. Una lista no limitante parcial de estas quinasas incluyen: tirosin quinasas receptoras tal como la quinasa del receptor de factor de crecimiento derivado de las plaquetas (PDGF- R), el receptor del factor de crecimiento nervioso (trkB), y el receptor del factor de crecimiento de fibroblastos (FGFR3); tirosin quinasas no receptoras tal como Abl y la quinasa de fusión BCR- Abl, Lck, Bmx y c- src; y serina/treonina quinasas tal como las quinasas b- RAF, c- RAF, sgk, MAP (ej., MKK4, MKK6, etc.) y SAPK2α y SAPK2β. Se ha observado actividad aberrante de las quinasas en muchos estados patológicos incluyendo trastornos proliferativos benignos y malignos así como también enfermedades que resultan a partir de la activación inapropiada de los sistemas inmune y nervioso.

Los compuestos novedosos de este invento inhiben la actividad de una o más proteinquinasas y por lo tanto se espera que sean útiles en el tratamiento de enfermedades asociadas con quinasas.

RESUMEN DEL INVENTO

En un aspecto, el presente invento proporciona compuestos de Formula I:



I

en los cuales:

A es un anillo no saturado o parcialmente saturado de 5 miembros que contiene entre 1 y 3 heteroátomos seleccionados a partir de - N=, - NR_3- , - O- y - S- ; en donde R_3 se selecciona a partir de hidrógeno, halo, C_1- $_6$alquilo sustituido o no sustituido, C2-6alquenilo sustituido o no sustituido, C_2- $_6$ alquinilo sustituido o no sustituido, - XOR_{4a}, - XCN, - $XC(O)OR_{4a}$, - $XC(O)R_{4b}$, - XNR_{4a}R4a, - $XNR_{4a}XNR_{4a}R4_a$, - XC(O) $nR_{4a}XNR4_aR4_a$, - XC(O) $nR_{4a}XR4_b$, - XC(O) $nR_{4a}XNR4_aR_{4b}$, - XC(O) $nR_{4a}XOR4_a$, - $XNR_{4a}XNR_{4a}R_{4b}$, - $XNR_{4a}XOR_{4a}$, - $XNR_{4a}XCF_3$, - XC(O) $nR_{4a}R_{4a}$, y - XR_{4b}; en donde cada X es independientemente seleccionado a partir de un enlace y C_1- $_4$alquileno; R_{4a} se selecciona a partir de hidrógeno y C_1- $_6$alquilo sustituido o no sustituido, y dos R_{4a} sobre los mismos átomos o átomos adyacentes se pueden opcionalmente unir para formar un anillo de 5- 6 miembros que contiene hasta dos heteroátomos seleccionados a partir de N, O y S como miembros cíclicos; y R_{4b} se selecciona a partir de C_6-$_{10}$arilo, C_1- $_{10}$heteroarilo, C_3- $_{10}$cicloalquilo y C_3- $_{10}$heterocicloalquilo; en donde cualquier cicloalquilo, heterocicloalquilo, arilo o heteroarilo de R_{4b} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de C_1- $_6$alquilo y –$NR_{4c}R_{4d}$; en donde cada R_{4c} y R_{4d} es independientemente seleccionado a partir de hidrógeno y C_1- $_6$alquilo sustituido o no sustituido, y R_{4c} y R_{4d} se pueden opcionalmente unir juntas para formar un anillo de 5- 6 miembros que contiene N y opcionalmente conteniendo un heteroátomo adicional seleccionado a partir de N, O y S; con la condición que el anillo A no sea imidazol;

en donde cualquier anillo A se puede opcionalmente sustituir por uno o dos radicales R3, con la condición que R3 no sea halo cuando se une directamente a un átomo de nitrógeno;

B es un anillo no saturado o parcialmente saturado de 5 o 6 miembros que contiene entre 0 y 3 heteroátomos seleccionados a partir de - N=, - NR21- , - O- y - S- ; en

donde R21 se selecciona a partir de hidrógeno, C_{1-6}alquilo, C_{1-6}alquilo halo- sustituido y halo; en donde B se puede opcionalmente sustituir por 1 a 3 radicales independientemente seleccionados a partir de C_{1-6}alquilo, C_{1-6}alquilo halo- sustituido y halo;

Z se selecciona a partir de CH y N;

R_1 se selecciona a partir de - XNR_5R_6, - $XNR_5XNR_5R_6$, - XNR5XR5, - XNR_5XOR_6, - $XNR_6XC(O)OR_5$, - $XNR_6XC(O)$ nR_6R_6, - XOR_5, - $XC(O)R_5$, - XR_5 y - XS(O)o-2R5; en donde X se selecciona a partir de un enlace y C_{1-4}alquileno opcionalmente sustituido por 1 a 2 radicales de C_{1-6}alquilo; R_5 se selecciona a partir de hidrógeno, C_{1-6}alquilo sustituido o no sustituido, C_{6-10}aril- C_{0-4}alquilo, C_{1-10}heteroaril- C_{0-4}alquilo, C_{3-10}cicloalquil- C_{0-4}alquil y C_{3-10}heterocicloalquil- C_{0-4}alquilo; y cada R_6 es independientemente seleccionado a partir de hidrógeno y C_{1-6}alquilo sustituido o no sustituido; o R_5 y R_6 junto con el nitrógeno al cual R^5 y R^6 están unidos forman heteroarilo o heterocicloalquilo que pueden contener un heteroátomo adicional seleccionado a partir de N, O y S como un miembro cíclico; o R_1 junto con el N1 del anillo de pirimidina al cual R_1 está fijado forma 2,3- dihidroimidazol[1,2- f]pirimidina;

en donde cualquier arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R^5 o la combinación de R_5 y R_6 se puede opcionalmente sustituir por 1 a 3 radicales independientemente seleccionados a partir de halo, nitro, ciano, hidroxilo, C_{1-6}alquilo, C_{1-6}alcoxilo alquilo halo-sustituido, alcoxilo halo- sustituido - XNR_7R_8, - XOR_7, - $XNR_7S(O)_2R_8$, - $XNR_7S(O)R_8$, - XNR_7SR_8, - $XC(O)$ nR_7R_8, - $XC(O)$ $nR_7XNR_7R_8$, - $XNR_7C(O)$ nR_7R_8, - $XNR_7XNR_7R_8$, - XNR_7XOR_7, - $XNR_7C(=NR_7)$ nR_7R_8, - $XS(O)_2R_9$, - $XNR_7C(O)R_8$, - $XNR_7C(O)R_9$, - XR_9, - $XC(O)OR_8$, - $XS(O)_2NR_7R_8$, - $XS(O)$ nR_7R_8 y - $XSNR_7R_8$; en donde X es un enlace o C_{1-4}alquileno; R_7 y R_8 son independientemente seleccionados a partir del grupo que consta de hidrógeno y C_{1-4}alquilo sustituido o no sustituido, y en donde R_7 y R_8 sobre un nitrógeno pueden opcionalmente ciclar para formar un anillo de 5- 6 miembros que puede contener un heteroátomo adicional seleccionado a partir de N, O y S como un miembro cíclico; y R_9 se selecciona a partir de C_{3-10}heterocicloalquilo y C_{1-10}heteroarilo; en donde dicho heterocicloalquilo o heteroarilo de R9 es opcionalmente sustituido por una radical seleccionado a partir del grupo que consta de C_{1-4}alquilo, - $XNR_7XNR_7R_7$, XNR_7XOR_7 y - XOR_7;

R_2 se selecciona a partir de $-R_{11}$,- $CONR_{10}R_{11}$, $SO_2NR_{10}R_{11}$, - $NR_{10}R_{11}$,- $NR_{10}C(O)R_{11}$, - $NR_{10}S(O)_{0-2}R_{11}$ y $-NR_{10}C(O)$ $nR_{10}Rn$; en donde R_{10} se selecciona a partir de hidrógeno y C_{1-6}alquilo sustituido o no sustituido; R_{11} se selecciona a partir de C_{6-10}arilo, C_{1-}

$_{10}$heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde R_{10} y R_{11} sobre el mismo nitrógeno pueden opcionalmente ciclar para formar un anillo de 5- 6 miembros que puede contener un heteroátomo adicional seleccionado a partir de N, O y S como un miembro cíclico, y cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{11} es opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halo, nitro, ciano, hidroxilo, C_{1-6}alquilo sustituido o no sustituido, C_{1-6}alcoxilo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo ciano- sustituido, C_{1-6}alquilo hidroxilo- sustituido, C_{1-6}alcoxilo halo- sustituido, - X_2R_{13}, - $X_2NR_{12}C(O)R_{13}$, - $X_2NR_{12}C(O)$ $nR_{12}R_{13}$, - $X_2NR_{12}R12$, - $X_2NR_{12}R_{13}$, - $X_2NR_{12}X_2R_{13}$, - $X_2NR_{12}NR_{12}R_{12}$, - $X_2NR_{12}X_2OR12$, - $X_2C(O)$ $nR_{12}R_{13}$, - $X_2NR_{12}S(O)_{0-2}R_{13}$ y - $X_2S(O)_{0-2}NR_{12}R_{13}$; en donde X_2 se selecciona a partir de un enlace, C_{1-4}alquileno y C_{2-4}alquenileno; R_{12} se selecciona a partir de hidrógeno, C_{1-6}alquilo y C_{1-6}alquilo hidroxilo- sustituido; R_{13} se selecciona a partir de C_{1-6} alquilo sustituido o no sustituido, C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde dos grupos R_{12} o R_{12} y R_{13} sobre el mismo nitrógeno pueden opcionalmente ciclar para formar un anillo de 5- 6 miembros que puede contener un heteroátomo adicional seleccionado a partir de N, O y S como un miembro cíclico, cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, ciano, hidroxilo, nitro, amino, C_{1-6}alquilo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo hidroxilo- sustituido, C_{1-6}alquilo ciano- sustituido, C_{1-6}alquilo hidroxilo- sustituido, C_{1-6}alcoxilo, C_{1-6}alcoxilo halo- sustituido - $X_3NR_7R_8$, - $X_3NR_7X_3OR_7$, C_{6-10}aril- C_{0-4}alquilo, C_{1-10}heteroaril- C_{0-4}alquilo, C_{3-10}cicloalquil- C_{0-4}alquilo, C_{3-10}heterocicloalquil- C_{0-4}alkoxilo y C_{3-10}heterocicloalquil- C_{0-4}alquilo; en donde X_3 se selecciona a partir de un enlace y C_{1-4}alquileno; R_7 y R_8 son como se describió anteriormente y en donde cualquier sustituyente de arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es adicionalmente opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, hidroxilo, C_{1-6}alquilo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo hidroxilo- sustituido, C_{1-6}alcoxilo, C_{3-10}heterocicloalquilo y C_{1-6}alcoxilo halo- sustituido;

R_{20} se selecciona a partir de hidrógeno, C_{1-6}alquilo sustituido o no sustituido, y $N(R_{21})_2$, en donde cada R_{21} es independientemente H o C_{1-6} alquilo sustituido o no sustituido, y en donde dos R_{21} sobre el mismo nitrógeno pueden ciclar para formar un anillo de 5- 6 miembros que puede contener un heteroátomo adicional seleccionado a partir de N, O y S;

y los derivados de N- óxido, derivados de profármacos, derivados protegidos,

isómeros individuales y mezcla de isómeros de los mismos; y las sales y solvatos farmacéuticamente aceptables (ej. hidratos) de tales compuestos.

En un segundo aspecto, el presente invento proporciona una composición farmacéutica la cual contiene un compuesto de la Formula I o un Derivado de N- óxido, isómeros individuales y mezcla de isómeros de los mismos; o una sal farmacéuticamente aceptable de los mismos, en mezcla con uno o más excipientes apropiados.

En un tercer aspecto, el presente invento proporciona un método de tratar una enfermedad en un animal en el cual la inhibición de la actividad de quinasa, particularmente actividad de Abl, ARG, BCR- Abl, BRK, EphB, Fms, Fyn, KDR, c- Kit, LCK, PDGF- R, b- Raf, c- Raf, SAPK2, Src, Tie2 y/o TrkB, puede prevenir, inhibir o aliviar la patología y/o sintomatología de las enfermedades, tal método comprende administrar al animal una cantidad terapéuticamente efectiva de un compuesto de Formula I o un derivado de N- óxido, isómeros individuales y mezcla de isómeros de los mismos, o una sal farmacéuticamente aceptable de los mismos.

En un cuarto aspecto, el presente invento proporciona el uso de un compuesto de la Formula I en la fabricación de un medicamento para tratar una enfermedad en un animal en la cual actividad de la quinasa, particularmente la actividad de Abl, ARG, BCR- Abl, BRK, EphB, Fms, Fyn, KDR, c- Kit, LCK, PDGF- R, b- Raf, c- Raf, SAPK2, Src, Tie2 y/o TrkB, contribuye a la patología y/o sintomatología de la enfermedad.

En un quinto aspecto, el presente invento proporciona un proceso para preparar compuestos de Fórmula I y los derivados de N- óxido, derivados de profármacos, derivados protegidos, isómeros individuales y mezcla de isómeros de los mismos, y las sales farmacéuticamente aceptables de los mismos.

DESCRIPCION DETALLADA DEL INVENTO

Definiciones

Como se utilizan en la presente, los términos "alquilo," "alquenilo" y "alquinilo" tienen sus significados comunes e incluyen radicales de hidrocarbonos de cadena lineal, de cadena ramificada y monovalentes cíclicos, y combinaciones de estos, las cuales contienen solamente C y H cuando no son sustituidos. Los grupos “alquilo” son saturados de manera que no contienen múltiples enlaces carbono- carbono; los grupos “alquenilo” contienen al menos un enlace doble carbono- carbono; y los grupos "alquinilo" contienen al menos un enlace triple carbono- carbono.

Ejemplos incluyen metilo, etilo, isobutilo, ciclohexilo, ciclopentiletilo, 2- propenilo, 3- butinilo, y similares. El número total de átomos de carbono en cada uno de éstos grupos algunas veces se describe en la presente, *ej.*, cuando el grupo puede contener hasta diez átomos de carbono éste se puede representar como $_{1-10}$C o como C_1- C_{10} o C_{1-10}.

Típicamente, los sustituyentes de alquilo, alquenilo y alquinilo del invento contienen $_{1-10}$C (alquilo) o $_{2-10}$C (alquenilo o alquinilo). Preferiblemente contienen $_{1-6}$C (alquilo) o $_{2-6}$C (alquenilo o alquinilo). Algunas veces contienen $_{1-4}$C (alquilo) o 2- 4C (alquenilo o alquinilo). Un grupo alquenilo o alquinilo sencillo puede incluir más de un tipo de enlace múltiple, o más de un enlace múltiple; tales grupos se incluyen dentro de la definición del término "alquenilo" cuando contienen al menos un enlace doble carbono- carbono, y se incluyen dentro del término "alquinilo" cuando contienen al menos un enlace triple carbono- carbono.

Mientras "alquilo" como se utiliza en la presente incluye grupos cicloalquilo y cicloalquilalquilo, el término "cicloalquilo" se puede utilizar en la presente para describir un grupo carbocíclico no aromático que está conectado vía un átomo de carbono cíclico, y "cicloalquilalquilo" se puede utilizar para describir un grupo carbocíclico no aromático que está conectado a la molécula a través de un enlazador de alquilo. De manera similar, "heterociclilo" se puede utilizar para describir un grupo cíclico no aromático que contiene al menos un heteroátomo como un miembro cíclico y que está conectado a la molécula vía un átomo cíclico, el cual puede ser C o N; y "heterociclilalquilo" se puede utilizar para describir tal grupo que está conectado a otra molécula a través de un enlazador. Los tamaños y sustituyentes que son adecuados para los grupos cicloalquilo, cicloalquilalquilo, heterociclilo, y heterociclilalquilo son iguales a aquellos descritos anteriormente para grupos alquilo. Como se utilizan en la presente, estos términos también incluyen anillos que contienen un enlace doble o dos, siempre y cuando el anillo no sea aromático.

"Heteroalquilo", "heteroalquenilo", y "heteroalquinilo" y similares se definen de manera similar a los grupos hidrocarbilo (alquilo, alquenilo y alquinilo) correspondientes, pero los términos 'hetero' se refieren a grupos que contienen 1- 3 O, S o N heteroátomos o combinaciones de los mismos dentro del residuo del esqueleto; por lo tanto al menos un átomo de carbono de un grupo alquilo, alquenilo, o alquinilo correspondiente es reemplazado por uno de los heteroátomos especificados para formar un grupo heteroalquilo, heteroalquenilo, o heteroalquinilo. Los tamaños típicos y preferidos para heteroformas de grupos alquilo, alquenilo

y alquinilo generalmente son los mismos que para los grupos hidrocarbilo correspondientes, y los sustituyentes que pueden estar presentes sobre las heteroformas son iguales a aquellos descritos anteriormente para los grupos hidrocarbilo. Por razones de estabilidad química, también se entiende que, a menos que se especifique lo contrario, tales grupos no incluyen más de dos heteroátomos contiguos excepto donde un grupo oxo está presente sobre N o S como en un grupo nitro o sulfonilo.

Los grupos alquilo, alquenilo y alquinilo y los correspondientes grupos cíclicos, heteroformas de estos grupos, y anillos formados al unir juntos dos de estos grupos a menudo se sustituyen en la medida que tal sustitución tenga sentido químicamente. Sustituyentes típicos incluyen, pero no están limitados a, halo, =0, =N- CN, =N- O, =NR, O, NR_2, SR, $S0_2R$, $S0_2NR_2$, $NRS0_2R$, $NRCONR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, y $N0_2$, en donde cada R es independientemente H, C1- C8 alquilo, C2- C8 heteroalquilo, C1- C8 acilo, C2- C8 heteroacilo, C2- C8 alquenilo, C2- C8 heteroalquenilo, C2- C8 alquinilo, C2- C8 heteroalquinilo, C6- C10 arilo, o C5- C10 heteroarilo, y cada R es opcionalmente sustituido por halo, =0, =N- CN, =N- O', =NR', O', NR'_2, SR', $S0_2R'$, $S0_2NR'_2$, $NR'S0_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', y $N0_2$, en donde cada R' es independientemente H, C1- C8 alquilo, C2- C8 heteroalquilo, C1- C8 acilo, C2- C8 heteroacilo, C6- C10 arilo o C5- C10 heteroarilo. Los grupos alquilo, alquenilo y alquinilo también se pueden sustituir por C1- C8 acilo, C2- C8 heteroacilo, C6- C10 arilo o C5- C10 heteroarilo, cada de estos se puede sustituir por los sustituyentes que son apropiados para el grupo particular.

"Alcoxilo" como se utiliza en la presente se refiere a un grupo alquilo conectado a través de oxígeno. Por ejemplo, C_1- $_4$- alcoxilo incluye, metoxilo, etoxilo, y similares. Otros grupos alquilo sustituidos se describen de manera similar. C_1- $_6$alquilo halo- sustituido, como se utiliza en esta solicitud, incluye trifluorometilo, pentafluoroetilo, difluorometilo, difluorometilo, y similares, así como también las combinaciones de isómeros de los mismos. Alquileno, como se utiliza en esta solicitud, es un radical de alquilo divalente que puede ser de cadena sencilla, ramificado o ciclado. Por ejemplo C_1- $_4$alquileno incluye ciclobutilo, y similares.

Como se utiliza en la presente, "acilo" incluye grupos que comprenden un radical de alquilo, alquenilo, alquinilo, arilo o arilalquilo fijado en una de las dos posiciones de valencia disponibles de un átomo de carbono carbonilo, y heteroacilo se refiere a los grupos correspondientes en donde al menos un carbono diferente al carbono carbonilo se ha reemplazado

por un heteroátomo elegido a partir de N, O y S. Por lo tanto heteroacilo incluye, por ejemplo, - C(=O)OR y - C(=O) nR_2 así como también - C(=O)- heteroarilo.

Los grupos acilo o heteroacilo se unen a cualquier grupo o molécula al cual están unidos a través de la valencia abierta del átomo carbono carbonilo. Típicamente, son grupos Cl- C8 acilo, los cuales incluyen grupos formilo, acetilo, pivaloilo, y benzoilo, y C2- C8 heteroacilo, los cuales incluyen metoxiacetilo, etoxicarbonilo, y 4- piridinoilo. Los grupos hidrocarbilo, grupos arilo, y heteroformas de tales grupos que comprenden un grupo acilo o heteroacilo se pueden sustituir por los sustituyentes descritos en la presente como sustituyentes generalmente adecuados para cada componente correspondiente del grupo acilo o heteroacilo.

Fracción "aromática" o fracción "arilo" se refiere a una fracción monocíclica o bicíclica fusionada con características bien conocidas de aromaticidad; ejemplos incluyen fenilo y naftilo. De manera similar, "heteroaromático" y "heteroarilo" se refieren a tales sistemas monocíclicos o bicíclicos fusionados los cuales contienen como miembros cíclicos uno o más heteroátomos seleccionados a partir de O, S y N. La inclusión de una heteroátomo permite aromaticidad en anillos de 5 miembros así como también anillos de 6 miembros. Sistemas heteroaromáticos típicos incluyen grupos monocíclicos C5- C6 aromáticos tal como piridilo, pirimidilo, pirazinilo, tienilo, furanilo, pirrolilo, pirazolilo, tiazolilo, oxazolilo, y imidazolilo y las fracciones bicíclicas fusionadas formadas mediante al fusionar uno de estos grupos monocíclicos con un anillo fenilo o con cualquiera de los grupos monocíclicos heteroaromáticos para formar un grupo C8- C10 bicíclico tal como indolilo, benzimidazolilo, indazolilo, benzotriazolilo, isoquinolilo, quinolilo, benzotiazolilo, benzofuranilo, pirazolopiridilo, quinazolinilo, quinoxalinilo, cinolinilo, y similares. Cualquier sistema monocíclico o bicíclico fusionado el cual tiene las características de aromaticidad en términos de distribución de electrones a través del sistema cíclico se incluye en esta definición. También incluye grupos bicíclicos donde al menos el anillo la cual está directamente unido al resto de la molécula tiene las características de aromaticidad. Típicamente, el sistemas cíclicos contienen átomos con 5- 12 miembros cíclicos. Preferiblemente los heeroarilos monocíclicos contienen 5- 6 miembros cíclicos, y los heteroarilos bicíclicos contienen 8- 10 miembros cíclicos.

Las fracciones arilo y heteroarilo se pueden sustituir mediante una variedad de sustituyentes incluyendo C1- C8 alquilo, C2- C8 alquenilo, C2- C8 alquinilo, C5- C12 arilo, C1- C8 acilo, y heteroformas de estos, cada uno de los cuales se pueden por sí mismos sustituir

adicionalmente; otros sustituyentes para las fracciones arilo y heteroarilo incluyen halo, O, NR_2, SR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, y NO_2, en donde cada R es independientemente H, C1- C8 alquilo, C2- C8 heteroalquilo, C2- C8 alquenilo, C2- C8 heteroalquenilo, C2- C8 alquinilo, C2- C8 heteroalquinilo, C6- C10 arilo, C5- C10 heteroarilo, C7- C12 arilalquilo, o C6- C12 heteroarilalquilo, y cada R es opcionalmente sustituido como se describió anteriormente para grupos alquilo. Los grupos sustituyentes sobre un grupo arilo o heteroarilo pueden naturalmente ser adicionalmente sustituidos por los grupos descritos en la presente como adecuados para cada tipo de tales sustituyentes o para cada componente del sustituyente. Por lo tanto, por ejemplo, un sustituyente arilalquilo puede ser sustituido sobre la porción arilo por los sustituyentes descritos en la presente como típicos para grupos arilo, y se puede sustituir adicionalmente sobre la porción alquilo por sustituyentes descritos en la presente como típicos o adecuados para grupos alquilo.

De manera similar, "arilalquilo" y "heteroarilalquilo" se refieren a sistemas cíclicos aromáticos y heteroaromáticos los cuales se unen a su punto de fijación a través de un grupo enlazador tal como un alquileno, incluyendo enlazadores sustituidos o no sustituidos, saturados o no saturados, cíclicos o acíclicos. Típicamente el enlazador es C1- C8 alquilo o una forma hetero del mismo. Estos enlazadores también pueden incluir un grupo carbonilo, haciéndolos así capaces de proporcionar sustituyentes como una fracción acilo o heteroacilo. Un anillo arilo o heteroarilo en un grupo arilalquilo o heteroarilalquilo se pueden sustituir por los mismos sustituyentes descritos anteriormente para grupos arilo. Preferiblemente, un grupo arilalquilo incluye un anillo fenilo opcionalmente sustituido por los grupos definidos anteriormente para grupos arilo y un C1- C4 alquileno que no es sustituido o es sustituido por uno o dos grupos C1- C4 alquilo o grupos heteroalquilo, donde los grupos alquilo o heteroalquilo pueden opcionalmente ciclar para formar un anillo tal como ciclopropano, dioxolano, o oxaciclopentano. De manera similar, un grupo heteroarilalquilo preferiblemente incluye un Grupo heteroarilo C5- C6 monocíclico que es opcionalmente sustituido por los grupos descritos anteriormente como sustituyentes típicos sobre grupos arilo y un C1- C4 alquileno que no es sustituido o es sustituido por uno o dos grupos C1- C4 alquilo o grupos heteroalquilo, o incluye un anillo fenilo opcionalmente sustituido o Heteroarilo C5- C6 monocíclico y un C1- C4 heteroalquileno que no es sustituido o es sustituido por uno o dos grupos C1- C4 alquilo o heteroalquilo, donde los grupos alquilo o heteroalquilo pueden opcionalmente ciclar para formar un anillo tal como ciclopropano, dioxolano, o

oxaciclopentano.

Donde un grupo arilalquilo o heteroarilalquilo se describe como opcionalmente sustituido, los sustituyentes pueden estar sobre cualquiera la porción alquilo o heteroalquilo o sobre la poción arilo o heteroarilo del grupo. Los sustituyentes opcionalmente presentes sobre la porción alquilo o heteroalquilo son iguales a aquellos descritos anteriormente para grupos alquilo generalmente; los sustituyentes opcionalmente presentes sobre la poción arilo o heteroarilo son iguales a aquellos descritos anteriormente para grupos arilo generalmente.

Grupos "Arilalquilo" como se utilizan en la presente son grupos hidrocarbilos si no son sustituidos, y se describen por el número total de átomos de carbono en el anillo y alquileno o enlazador similar. Por lo tanto un grupo bencilo es un grupo C7 arilalquilo, y feniletilo es un C8-arilalquilo.

"Heteroarilalquilo" como se describió anteriormente se refiere a una fracción comprendiendo un grupo arilo que está fijado a través de un grupo enlazador, y difiere de "arilalquilo" en que al menos un átomo cíclico de la fracción arilo o un átomo en el grupo enlazador es un heteroátomo seleccionado a partir de N, O y S. El grupo heteroarilalquilo se describe en la presente según el número total de átomos en el anillo y enlazador combinados, e incluyen grupos arilo enlazados a través de un enlazador de heteroalquilo; grupos heteroarilo enlazados a través de un enlazador de hidrocarbilo tal como un alquileno; y grupos heteroarilo enlazados a través de un enlazador de heteroalquilo. Por lo tanto, por ejemplo, C7-heteroarilalquilo incluiría piridilmetilo, fenoxilo, y N- pirrolilmetoxilo.

"Arileno" significa un radical divalente derivado de un grupo arilo. Un anillo descrito como "no saturado" contiene al menos un enlace múltiple carbono- carbono, y puede ser aromático; un anillo descrito como "parcialmente no saturado" contiene al menos un enlace múltiple carbono- carbono pero no es aromático.

"Heteroarilo" es como se definió para arilo anteriormente donde uno o más de los miembros cíclicos es un heteroátomo. Por ejemplo C_{1-10}heteroarilo, como se utiliza en esta solicitud, incluye piridilo, indolilo, indazolilo, quinoxalinilo, quinolinilo, benzofuranilo, benzopiranilo, benzotiopiranilo, benzo[1,3]dioxol, imidazolilo, benzo- imidazolilo, pirimidinilo, furanilo, oxazolilo, isoxazolilo, triazolilo, tetrazolilo, pirazolilo, tienilo, etc. Heteroarilo también puede incluir sistemas cíclicos parcialmente no saturados tal como 1,2,3,6- tetrahidropiridin- 4-ilo, y similares.

"Cicloalquilo" significa un ensamble anular saturado o parcialmente no saturado, monocíclico, bicíclico fusionado o policíclico puenteado que contiene el número de átomos cíclicos indicado. Por ejemplo, C_{3-10}cicloalquilo incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etc.

"Heterocicloalquilo" significa cicloalquilo, como se define en esta solicitud, siempre y cuando uno o más de los carbonos cíclicos indicados, son reemplazados por una fracción seleccionad a partir de - 0- , - N=, - NR- , - C(0>, - S- , - S(O) - o - $S(O)_2$- , en donde R es hidrógeno, C_{1-4}alquilo o un grupo protector de nitrógeno. Por ejemplo, C3- 8heterocicloalquilo como se utiliza en esta solicitud para describir compuestos del invento incluye morfolino, pirrolidinilo, pirrolidinil- 2- ona, piperazinilo, piperidinilo, piperidinil- ona, 1,4- dioxa- 8- aza- spiro[4.5]dec- 8- ilo, etc.

"Halógeno" (o halo) preferiblemente representa cloro o fluoro, pero también puede ser bromo o yodo.

En general, cualquier grupo alquilo, alquenilo, alquinilo, acilo, o arilo o arilalquilo o cualquier heteroforma de uno de estos grupos que está contenida en un sustituyente puede por sí mismo opcionalmente ser sustituido por sustituyentes adicionales. La naturaleza de estos sustituyentes es similar a aquellos citados con respecto a los sustituyentes primarios mismos si los sustituyentes no se describen de otra manera. Por lo tanto, donde una realización de, por ejemplo, R^7 es alquilo, este alquilo opcionalmente se puede sustituir por los sustituyentes restantes listados como realizaciones para R^7 donde esto tenga sentido químico, y donde esto no socave el límite de tamaño proporcionado para el alquilo *per se; ej.*, alquilo sustituido por alquilo o por alquenilo simplemente extendería el límite superior de átomos de carbono para estas realizaciones, y no se incluye. Sin embargo, alquilo sustituido por arilo, amino, alcoxilo =O, y similares se incluiría dentro del alcance del invento, y los átomos de estos grupos sustituyentes no se cuentan en el número utilizado para describir el grupo alquilo, alquenilo, etc. grupo que se está describiendo. Donde no se especifica el número de sustituyentes, cada grupo alquilo, alquenilo, alquinilo, acilo, o arilo se puede sustituir por un número de sustituyentes según sus valencias disponibles; en particular, cualquiera de estos grupos se puede sustituir por átomos de flúor en cualquiera o todas sus valencias disponibles, por ejemplo.

"Sustituido" como se utiliza en la presente indica que el grupo particular o grupos siendo descritos tendrán uno o más sustituyentes no hidrógenos. "Opcionalmente sustituido" indica que

el grupo puede o no tener sustituyentes no hidrógenos. Si no se especifica lo contrario, el número total de tales sustituyentes que pueden estar presentes es igual al número de átomos H presentes sobre la forma no sustituida del grupo descrito. Donde un sustituyente opcional está fijado vía una enlace doble, tal como un oxigeno de carbonilo (=O), el grupo toma hasta dos valencias disponibles, de manera que el número total de sustituyentes que se pueden incluir se reduce según el número de valencias disponibles.

"Panel de quinasas" es una lista de quinasas comprendiendo Abl(humano), Abl(T3151), JAK2, JAK3, ALK, JNKlal, ALK4, KDR, Aurora- UNA, Lck, Blk, MAPK1, Bmx, MAPKAP-K2, BRK, MEK1, CaMKII(rata), Met, CDKl/ciclinaB, p70S6K, CHK2, PAK2, CK1, PDGFRa, CK2, PDK1, c- kit, Pim- 2, c- RAF, PKA(h), CSK, PKBa, cSrc, PKCa, DYRK2, Plk3, EGFR, ROCK- I, Fes, Ron, FGFR3, Ros, Flt3, SAPK2a, Fms, SGK, Fyn, SIK, GSK3 3, Syk, IGF- 1R, Tie- 2, IKKB, TrKB, IR, WNK3, IRAK4, ZAP- 70, ITK, AMPK(rata), LIMK1, Rsk2, Axl, LKB1, SAPK2 3, BrSK2, Lin (h), SAPK3, BTK, MAPKAP- K3, SAPK4, CaMKIV, MARK1, Snk, CDK2/ciclinaA, MINK, SRPK1, CDK3/ciclinaE, MKK4(m), TAK1, CDK5/p25, MKK6(h), TBK1, CDK6/ciclinaD3, MLCK, TrkA, CDK7/ciclinaH/MATl, MRCKp, TSSK1, CHK1, MSK1, Yes, CKld, MST2, ZIPK, c- Kit (D816V), MuSK, DAPK2, NEK2, DDR2, NEK6, DMPK, PAK4, DRAK1, PAR- lBa, EphAl, PDGFRP, EphA2, Pim- 1, EphA5, PKBp, EphB2, PKCpi, EphB4, PKC5, FGFR1, PKCr , FGFR2, PKC9, FGFR4, PKD2, Fgr, PKGip, Fltl, PRK2, Hck, PYK2, HIPK2, Ret, IKKα, RIPK2, IRR, ROCK- II(humana), JNK2α2, Rse, JNK3, Rskl(h), PI3 Kγ, P13 Kδ y P13- Kβ. Los compuestos del invento fueron seleccionados con respecto al panel de quinasas (tipo silvestre y/o mutación de los mismos) e inhiben la actividad de al menos uno de tales miembros del panel.

"Formas mutantes de BCR- Abl" significa cambios aminoácidos sencillos o múltiples desde la secuencia de tipos silvestre. Las mutaciones en BCR- ABL actúan al alterar puntos de contacto críticos entre proteína e inhibidor (por ejemplo, Gleevec, y similares), a menudo, induciendo una transición desde el estado inactivo al estado activo, es decir a una conformación a la cual BCR- ABL y Gleevec no pueden unirse. A partir de análisis de muestras clínicas, el repertorio de mutaciones encontradas en asociación con el fenotipo resistente ha estado creciendo lentamente pero inexorablemente con el tiempo. Las mutaciones parecen agruparse en cuatro regiones principales. Uno grupo de mutaciones (G250E, Q252R, Y253F/H, E255K/V) incluye los aminoácidos que forman el asa fijadora de fosfato para ATP (asa P). Un segundo grupo

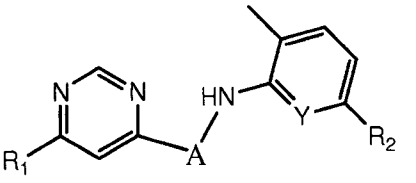
(V289A, F311L, T315I, F317L) puede ser encontrado en el sitio de fijación Gleevec e interactúa directamente con el inhibidor vía enlaces de hidrógeno o interacciones de Van der Waals. El tercer grupo de mutaciones (M351T, E355G) se junta en proximidad estrecha al dominio catalítico. El cuarto grupo de mutaciones (H396R/P) está localizados en el asa de activación, cuya conformación es el interruptor molecular que controla activación/desactivación de quinasas, mutaciones puntuales BCR- ABL asociadas con resistencia de Gleevec detectadas en pacientes CML y ALL incluyen: M224V, L248V, G250E, G250R, Q252R, Q252H, Y253H, Y253F, E255K, E255V, D276G, T277A, V289A, F311L, T315I, T315N, F317L, M343T, M315T, E355G, F359V, F359A, V379I, F382L, L387M, L387F, H396P, H396R, A397P, S417Y, E459K, y F486S (las posiciones aminoácidas, indicadas por el código de letra única, son aquellas para la Secuencia GenBank, número de acceso AAB60394, y corresponden al tipo ABL la; Martinelli et al., Haematologica/The Hematology Journal, 2005, Abrill; 90- 4). A menos que se indique lo contrario para este invento, Bcr- Abl se refiere a formas tipo silvestre y mutante de la enzima.

"Tratar", "tratando" y "tratamiento" se refieren a un método de aliviar o abatir una enfermedad y/o sus síntomas concomitantes.

Descripción de las Realizaciones preferidas

La proteína de fusión BCR- Abl es un resultado de una translocación recíproca que fusiona el Abl proto- oncogeno con el gen Bcr. BCR- Abl luego es capaz de transformar células B a través del aumento de actividad mitogénica. Este aumento produce una reducción de la sensibilidad a apoptosis, así como también alteración de la adhesión y anidamiento de células CML progenitoras. El presente invento proporciona compuestos, composiciones y métodos para el tratamiento de enfermedad relacionada con quinasas, particularmente enfermedades relacionadas con las quinasas Abl, ARG, BCR- Abl, BRK, EphB, Fms, Fyn, KDR, c- Kit, LCK, PDGF- R, b- Raf, c- Raf, SAPK2, Src, Tie2 y TrkB. Por ejemplo, leucemia y otros trastornos proliferativos relacionados con BCR- Abl se pueden tratar mediante la inhibición de formas tipo silvestre y mutante de Bcr- Abl.

En una realización, con referencia a compuestos de la Formula I, son compuestos de la Formula Ia:



Ia

en la cual: A es un anillo no saturado o parcialmente saturado de 5 miembros que contiene entre 1 y 3 heteroátomos seleccionados de - N=, - NR3- , - O- y - S- ; en donde R3 se selecciona a partir de hidrógeno, halo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo, - $XOR4_a$, - XCN, - $XC(O)OR_{4a}$, - $XC(O)R_{4b}$, - $XNR_{4a}R4a$, - $XNR_{4a}R_{4b}$, - $XNR_{4a}XNR_{4a}R_{4a}$, - $XC(O)\ nR_{4a}XNR4_aR4_a$, - $XC(O)\ nR_{4a}XR4_b$, - $XC(O)\ nR_{4a}XNR_{4a}R_{4b}$, - $XC(O)\ nR_{4a}XOR_{4a}$, - $XNR_{4a}XNR_{4a}R4_b$, $XNR_{4a}XOR_{4a}$,- $XNR_{4a}XCF_3$, - $XC(O)\ nR_{4a}R_{4a}$, y - XR_{4b}; en donde X se selecciona a partir de un enlace y C_{1-4}alquileno; R_{4a} se selecciona a partir de hidrógeno y C_{1-6}alquilo; y R_{4b} se selecciona a partir de C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde cualquier cicloalquilo, heterocicloalquilo, arilo o heteroarilo de R_{4b} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de C_{1-6}alquilo y - $NR_{4C}R_{4d}$; en donde cada R_{4C} y R_{4d} es independientemente seleccionado a partir de hidrógeno y C_{1-6}alquilo; con la condición que el anillo A no sea imidazol; en donde cualquier anillo A se puede opcionalmente sustituir por un radical R3;

R_1 se selecciona a partir de - XNR_5R_6, - $XNR_5XNR_5R_6$, - XNR5XR5, - XNR_5XOR_6, - $XNR_6XC(O)OR_5$, - $XNR_6XC(O)\ nR_6R_6$, - XOR_5, - $XC(O)R_5$, - XR_5 y - $XS(O)_{0-2}R5$; en donde X se selecciona a partir de un enlace y $_{1-4}$alquileno opcionalmente sustituido por 1 a 2 radicales de C_{1-6}alquilo; R5 se selecciona a partir de hidrógeno, C_{1-6}alquilo, C_{6-10}aril- C_{0-4}alquilo, C_{1-10} heteroaril- C_{0-4}alquilo, C_{3-10}cicloalquil- C_{0-4}alquilo y C_{3-10}heterocicloalquil- C_{0-4}alquilo; y cada R6 es independientemente seleccionado a partir de hidrógeno y C_{1-6}alquilo; o R5 y R6 junto con el nitrógeno al cual R5 y R6 están unidos forman heteroarilo o heterocicloalquilo; o R_1 junto con la N1 del anillo de pirimidina al cual R_1 está fijado forma 2,3- dihidroimidazol[1,2-f]pirimidina;

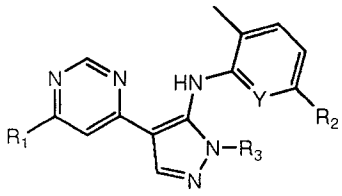
en donde cualquier arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R5 o la combinación de R5 y R6 se puede opcionalmente sustituir por 1 a 3 radicales independientemente seleccionados a partir de halo, nitro, ciano, hidroxilo, C_{1-6}alquilo, C_{1-6}alcoxilo, alquilo halo-sustituido, alcoxilo halo- sustituido - XNR_7R_8, - XOR_7, - $XNR_7S(O)_2R_8$, - $XNR_7S(O)R_8$, -

XNR_7SR_8, - $XC(O)\ nR_7R_8$, - $XC(O)\ nR_7XNR_7R_8$, - $XNR_7C(O)\ nR_7R_8$, - $XNR_7XNR_7R_8$, - XNR_7XOR_7, - $XNR_7C(=NR_7)\ nR_7R_8$, - $XS(O)_2R_9$, - $XNR_7C(O)R_8$, - $XNR_7C(O)R_9$, - XR_9, - $XC(O)OR_8$, - $XS(O)_2NR_7R_8$, - $XS(O)\ nR_7R_8$ y - $XSNR_7R_8$; en donde X es un enlace o C_{1-4}alquileno; R_7 y R_8 son independientemente seleccionados a partir del grupo que consta de hidrógeno y C_{1-4}alquilo; y R_9 se selecciona a partir de C_{3-10}heterocicloalquil y C_{1-10}heteroarilo; en donde dicho heterocicloalquilo o heteroarilo de R_9 es opcionalmente sustituido por un radical seleccionado a partir del grupo que consta de C_{1-4}alquilo, - $XNR_7XNR_7R_7$, XNR_7XOR_7 y - XOR_7;

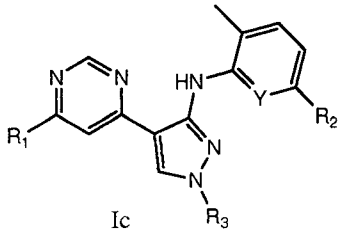
R_2 se selecciona a partir de $-R_{11}$,- $CONR_{10}R_{11}$,- $SO_2NR_{10}R_{11}$, - $NR_{10}R_{11}$,- $NR_{10}C(O)R_{11}$, - $NR_{10}S(O)_{0-2}R_{11}$ y $-NR_{10}C(O)\ nR_{10}R_{11}$; R_{10} se selecciona a partir de hidrógeno y C_{1-6}alquilo; R11 se selecciona a partir de C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{11} es opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halo, nitro, ciano, hidroxilo, C_{1-6}alquilo, C_{1-6}alcoxilo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo ciano- sustituido, C_{1-6}alquilo hidroxilo- sustituido, C_{1-6}alcoxilo halo- sustituido, - X_2R_{13}, - $X_2NR_{12}C(O)R_{13}$, - $X2NR_{12}C(O)\ nR_{12}R_{13}$, - $X_2NR_{12}R_{12}$, —$X_2NR_{12}R_{13}$, —$X_2NR_{12}X_2R_{13}$, —$X_2NR_{12}NR_{12}R_{12}$, — $X_2NR_{12}X_2OR_{12}$, — $X_2C(O)\ nR_{12}R_{13}$, - $X_2NR_{12}S(O)_{0-2}R_{13}$ y - $X_2S(O)_{0-2}NR_{12}R_{13}$; en donde R_{12} se selecciona a partir de hidrógeno, C_{1-6}alquilo y C_{1-6}alquilo hidroxilo- sustituido; en donde X_2 se selecciona a partir de un enlace, C_{1-4}alquileno y C_{2-4}alquenileno; R_{13} se selecciona a partir de C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, ciano, hidroxilo, nitro, amino, C_{1-6}alquilo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo hidroxilo- sustituido, C_{1-6}alquilo ciano-sustituido, C_{1-6}alquilo hidroxilo- sustituido, C_{1-6}alcoxilo, C_{1-6}alcoxilo halo- sustituido - $X_3NR_7R_8$, - $X_3NR_7X_3OR_7$, C_{6-10}aril- C_{0-4}alquilo, C_{1-10}heteroaril- C_{0-4}alquilo, C_{3-10}cicloalquil- C_{0-4}alquilo, C_{3-10}heterocicloalquil- C_{0-4}alcoxilo y C_{3-10}heterocicloalquil- C_{0-4}alquilo; en donde X_3 se selecciona a partir de un enlace y C_{1-4}alquileno; R_7 y R_8 son como se describió antes y en donde cualquier sustituyente arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es además opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, hidroxilo, C_{1-6}alquilo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo hidroxilo- sustituido, C_{1-6}alcoxilo, C_{3-10}heterocicloalquilo y C_{1-6}alcoxilo halo- sustituido; y

Y se selecciona a partir de C y N.

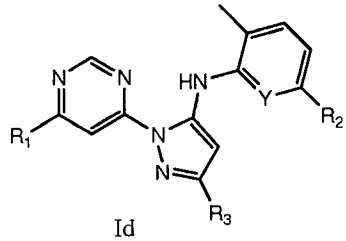
En otra realización, es un compuesto seleccionado a partir de la Formula Ib, Ic y Id:



Ib



Ic



Id

en la cual:

R_1 se selecciona a partir de - XNR_5R_6, - $XNR_5XNR_5R_6$, - XNR5XR5, - XNR_5XOR_6, - $XNR_6XC(O)OR_5$, - $XNR_6XC(O)\ nR_6R_6$, - XOR_5, - $XC(O)R_5$, - XR_5 y - $XS(O)_{0-2}R_5$; en donde X se selecciona a partir de un enlace y C_{1-4}alquileno opcionalmente sustituido por 1 a 2 radicales de C_{1-6}alquilo; R_5 se selecciona a partir de hidrógeno, C_{1-6}alquilo, C_{6-10}aril- C_{0-4}alquilo, C_{1-10}heteroaril- C_{0-4}alquilo, C_{3-10}cicloalquil- C_{0-4}alquilo y C_{3-10}heterocicloalquil- C_{0-4}alquilo; y cada R6 es independientemente seleccionado a partir de hidrógeno y C_{1-6}alquilo; o R_5 y R_6 junto con el nitrógeno al cual R_5 y R_6 están unidos forman heteroarilo o heterocicloalquilo; o R_1 junto con el N1 del anillo de pirimidina al cual R_1 está fijado forma 2,3- dihidroimidazol[1,2-f]pirimidina;

en donde cualquier arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R_5 o la combinación de R_5 y R_6 se puede opcionalmente sustituir por 1 a 3 radicales independientemente seleccionados a partir de halo, nitro, ciano, hidroxilo, C_{1-6}alquilo, C_{1-6}alcoxilo, alquilo halo-sustituido, alcoxilo halo- sustituido - XNR_7R_8, - XOR_7, - $XNR_7S(O)_2R_8$, - $XNR_7S(O)R_8$, - XNR_7SR_8, - $XC(O)\ nR_7R_8$, - $XC(O)\ nR_7XNR_7R_8$, - $XNR_7C(O)\ nR_7R_8$, - $XNR_7XNR_7R_8$, - XNR_7XOR_7, - $XNR_7C(=NR_7)\ nR_7R_8$, - $XS(O)_2R_9$, - $XNR_7C(O)R_8$, - $XNR_7C(O)R_9$, - XR_9, - $XC(O)OR_8$, - $XS(O)_2NR_7R_8$, - $XS(O)\ nR_7R_8$ y - $XSNR_7R_8$; en donde X es un enlace o C_{1-4}alquileno; cada R_7 y R_8 son independientemente seleccionados a partir del grupo que consta de hidrógeno y C_{1-4}alquilo, o R_7 y R_8 junto con el nitrógeno al cual R_7 y R_8 están unidos forman heteroarilo o heterocicloalquilo; y R9 se selecciona a partir de C_{3-10}heterocicloalquilo y C_{1-10}heteroarilo; en donde dicho heterocicloalquilo o heteroarilo de R9 es opcionalmente sustituido por un radical seleccionado a partir del grupo que consta de C_{1-4}alquilo, - $XNR_7XNR_7R_7$, XNR_7XOR_7 y - XOR_7;

R_2 se selecciona a partir de $-R_{11}$, - $CONR_{10}R_{11}$, $SO_2NR_{10}R_{11}$, - $NR_{10}R_{11}$, -

$NR_{10}C(O)R_{11}$, - $NR_{10}S(O)0$- $2R_{11}$ y $-NR_{10}C(O)$ $nR_{10}R_{11}$; en donde R_{10} se selecciona a partir de hidrógeno y C_1- $_6$alquilo; R11 se selecciona a partir de C_6- $_{10}$arilo, C_1- $_{10}$heteroarilo, C_3- $_{10}$cicloalquilo y C_3- $_{10}$heterocicloalquilo; en donde R_{10} y R_{11} junto con el nitrógeno al cual R_{10} y R_{11} están unidos pueden opcionalmente formar heteroarilo o heterocicloalquilo, y cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R11 es opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halo, nitro, ciano, hidroxilo, C_1- $_6$alquilo, C_1- $_6$alcoxilo C_1- $_6$alquilo halo- sustituido, C_1- $_6$alquilo ciano- sustituido, C_1- $_6$alquilo hidroxilo- sustituido, C_1- $_6$alcoxilo halo- sustituido - X_2R_{13}, - $X_2NR_{12}C(O)R_{13}$, - $X_2NR_{12}C(O)$ $nR_{12}R_{13}$, - $X_2NR_{12}R_{12}$, - $X_2NR_{12}R_{13}$, - $X_2NR_{12}X_2R_{13}$, - $X_2NR_{12}NR_{12}R_{12}$, - $X_2NR_{12}X_2OR_{12}$, - $X_2C(O)$ $nR_{12}R_{13}$, - $X_2S(O)_0$- $_2R_{12}$, - $X_2NR_{12}S(O)_0$- $_2R_{13}$ y - $X_2S(O)0$- $2NR_{12}R_{13}$; en donde X_2 se selecciona a partir de un enlace, C_1- $_4$alquileno y C_2- $_4$alquenileno; R_{12} se selecciona a partir de hidrógeno, C_1- $_6$alquilo y C_1- $_6$alquilo hidroxilo- sustituido; R_{13} se selecciona a partir de C_6- $_{10}$arilo, C_1- $_{10}$heteroarilo, C_3- $_{10}$cicloalquilo y C_3- $_{10}$heterocicloalquilo; en donde dos R_{12} de $NR_{12}R_{12}$ o R_{12} y R_{13} de $NR_{12}R_{13}$ junto con el nitrógeno al cual ambos están fijados opcionalmente formar heteroarilo o heterocicloalquilo, y cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, ciano, hidroxilo, nitro, amino, C_1- $_6$alquilo, C_1- $_6$alquilo halo- sustituido, C_1- $_6$alquilo hidroxilo- sustituido, C_1- $_6$alquilo ciano- sustituido, C_1- $_6$alquilo hidroxilo- sustituido, C_1- $_6$alcoxilo, C_1- $_6$alcoxilo halo- sustituido, $X_3NR_7R_8$, - $X_3NR_7X_3OR_7$, C_6- $_{10}$aril- C_0- $_4$alquilo, C_1- $_{10}$heteroaril- C_0- $_4$alquilo, C_3- $_{10}$cicloalquil- C_0- $_4$alquilo, C_3- $_{10}$heterocicloalquil- C_0- $_4$alcoxilo y C_3- $_{10}$heterocicloalquil- C_0- $_4$alquilo; en donde X_3 se selecciona a partir de un enlace y C_1- $_4$alquileno; R_7 y R_8 son como se describió anteriormente y en donde cualquier sustituyente arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es adicionalmente opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, hidroxilo, C_1- $_6$alquilo, C_1- $_6$alquilo halo- sustituido, C_1- $_6$alquilo hidroxilo- sustituido, C_1- $_6$alcoxilo C_3- $_{10}$heterocicloalquilo y C_1- $_6$alcoxilo halo- sustituido;

R_3 se selecciona a partir de hidrógeno, halo, C_1- $_6$alquilo halo- sustituido, C_1- $_6$alquilo, - XOR_{4a}, - XCN, - $XC(O)OR_{4a}$, - $XC(O)R_{4b}$, - $XNR_{4a}R4a$, - $XNR_{4a}R4_b$, - $XNR_{4a}XNR_{4a}R4_a$, - $XC(O)$ $nR_{4a}XNR_{4a}R4_a$, - $XC(O)$ $nR_{4a}XR4_b$, - $XC(O)$ $nR_{4a}XNR_{4a}R_{4b}$, - $XC(O)$ $nR_{4a}XOR4_a$, - $XNR4_aXNR_{4a}R4_b$, - $XNR_{4a}XOR_{4a}$, - $XNR_{4a}XCF_3$, - $XC(O)$ $nR_{4a}R4_a$, y - XR_{4b}; en donde X se selecciona a partir de un enlace y C_1- $_4$alquileno; R_{4a} se selecciona a partir de hidrógeno y C_1-

$_4$alquilo; y R_{4b} se selecciona a partir de C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde dos R_{4a} de $NR_{4a}R_{4a}$ junto con el nitrógeno al cual ambos están fijados opcionalmente forman heteroarilo o heterocicloalquilo, y cualquier cicloalquilo, heterocicloalquilo, arilo o heteroarilo de R_{4b} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de C_{1-6}alquilo y - $NR_{4c}R_{4d}$; en donde cada R_{4c} y R_{4d} es independientemente seleccionado a partir de hidrógeno y C_{1-6}alquilo, y R_{4c}; y R_{4d} de $NR_{4c}R_{4d}$ junto con el nitrógeno al cual R_{4c} y R_{4d} están fijados opcionalmente forman una heteroarilo o heterocicloalquilo,; y Y se selecciona a partir de CH y N.

En otra realización, R3 se selecciona a partir de hidrógeno, metilo, morfolino- etilo, etoxi- carbonilo, cloro, trifluorometilo, (metil- piperidinil) (metil) amino- metilo, metil- amino- carbonilo, hidroxi- metilo, dimetil- amino- metilo, metil- amino- metilo, morfolino- metilo, dietil- amino- etil- amino- metilo, metil- piperazinil- metilo, metil- piperazinil- etil- amino- metilo, dimetil- amino- propil- amino- metilo, ((2- hidroxietil) (metil) amino) metilo, etil- amino- metilo, trifluorometil- amino- metilo, dimetil- amino- etil- amino- carbonilo, piperidinil- etil- amino- carbonilo, morfolino- etil- amino- carbonilo, morfolino- carbonilo, amino- carbonilo, dimetil- amino- carbonilo, dimetil- amino- pirrolidinil- metilo, dimetil- amino- pirrolidinil- carbonilo, tiomorfolino- metilo, metoxi- etil- piperazinil- metilo, metoxi- etil- amino- carbonilo, ciano- metilo, (2,6- dimetilmorfolino) metilo, (2,6- dimetil- piperidinil) etil- amino- carbonilo y ciclopropil- amino- carbonilo.

En otra realización, R_1 se selecciona a partir de morfolino- etil- amino, metil- amino, metil- piperazinil- etil- amino, ciclopropil- amino, hidroxi- etil- piperazinil- amino, isopropil- amino, dimetil- amino- etil- amino, metil- piperazinil- amino, amino, 2,6- dimetil- morfolino- etil- amino, hidroxi- piridinil- etil- amino, amino- etil- amino, 3- oxopiperazin- 1- il- etil- amino, hidroxi- etil- amino, hidroxi- propil- amino, metil- sulfanilo, metoxilo, sulfanilo, piridinil- etil- amino, piridinil- metil- amino, morfolino- metil- piridinil- amino, carboxi- propil- amino, carboxi- metil- amino, azetidin- 3- il- amino, azetidin- 3- il- metil- amino, carboxi- etil- amino y hidroxi- pirrolidinilo.

En otra realización, R_2 se selecciona a partir de $-R_{11}$, - $CONHR_{11}$, $S0_2NHR_{11}$, - NHR_{11}, - $NHC(O)R_{11}$, - $NHS(O)_{0-2}R_{11}$ y - NHC(O) nHR_{11}; en donde R_{11} se selecciona a partir de fenilo, piridinilo, tiazolilo, benzimidazolilo, isoxazolilo, 1,2,3,4- tetrahidronaftilo, benzotiazolilo, benzo[d][1,2,3]triazol, 2,3- dihidrobenzofurano y 2,3- dihidro- 3,3-

dimetilbenzofuran- 5- ilo; en donde dicho fenilo, piridinilo, tiazolilo, isoxazolilo y 2,3- dihidro- 3,3- dimetilbenzofuran- 5- ilo de R_2 son opcionalmente sustituidos por 1 a 3 radicales independientemente seleccionados a partir de halo, isopropilo, metil- sulfonilo, hidroxilo, metil- sulfonil- amino, 1- (2- hidroxietilamino) ciclopropilo, 3- (3- hidroxipropilamino) ciclobutilo, isopropil- amino- ciclobutilo, 2- (2- hidroxietilamino) propan- 2- ilo, 3- aminoprop- 1- enilo, isopropil- 3- aminoprop- 1 - enilo, isopropil- amino- propilo, isopropil- amino- etilo, hidroxietil- 3- aminoprop- 1- enilo, metil- amino, 1,2- dihidroxietilo, 2- hidroxi- etilo, (3- hidroxiazetidin- 1- il) metilo, (3- metoxiazetidin- 1- il) metilo, 2- metil- morfolino- metilo, (3- metoxipirrolidin- 1- il) metilo, (2- hidroxi- 2- metilpropilamino) metilo, 1- metil- 1,2,3,6- tetrahidropiridin- 4- ilo, 1,2,3,6- tetrahidropiridin- 4- ilo, piperidin- 4- ilo, (4- etilpiperazin- 1- il) metilo, pirrolidin- 1- il- metilo, 1- (etilamino) etilo, 4- (2- hidroxipropil)- 1- piperazinilo, 3- trifluorometil- 4- metil- 1- piperazinilo, difluoro- metilo, 4- metil- 1- imidazolilo, metil- sulfonil- etil- amino- carbonilo, hidroxi- propil- amino- carbonilo, 4- t- butoxi- carbonil- 1- piperazinilo, 4- (1- carboxietil) piperazin- 1- ilo, 4,7- diazaspiro[2.5]octan- 7- ilo, etoxilo, 4- (tert- butoxicarbonil)- 2- oxopiperazin- 1- ilo, 4- metil- 2- oxopiperazin- 1- ilo, 2- oxopiperazin- 1- ilo, metoxilo, etilo, pirazolilo, trifluorometilo, 2- cianobutan- 2- ilo, 1- cianociclopropilo, 2- hidroxipropan- 2- ilo, difluorometilo, 3- etilpentan- 3- ilo, metil- piperazinilo, etil- piperazinilo, t- butilo, t- butoxi, 1,2- dihidroxipropilo, 2- hidroximetil- etilo, ciclopropil- 1- piperazinilo, 4- metil- sulfonil- etil- 1- piperazinilo, 2- hidroxi- propil- amino- metilo, (tetrahidrofuran- 2- ilamino) metilo, (2,3- dihidroxipropilamino) metil), (1,3- dihidroxipropan- 2- ilamino) metilo, (1- hidroxi- 2- metilpropan- 2- ilamino) metilo, ciclobutil- amino- metilo, 4- hidroxi- piperidinilo, (1- hidroxipropan- 2- ilamino) metilo, dimetil- amino- amino- metilo, metoxi- amino- metilo, hidroxi- amino- metilo, 2- hidroxi- metil- pirrolidin- 1- il- metilo, pirrolidinil- etoxilo, 3- hidroxi- pirrolidinilo, 3- hidroxiazetidin- 1- ilo, 3- (metoxi- carbonil)- 4- metilpiperazin- 1- ilo, 4- metilpiperazin- 1- ilo, 4- metil- 3- hidroximetil- piperazin- 1- ilo, 4- metoxi- carbonil- piperidinilo, 4- carboxi- piperidinilo, piperazinilo, 4- (2,2,2- trifluoroetil) piperazin- 1- ilo, 2- hidroxi- ciclopent- 1- il- amino- metilo, amino- carbonil- metilo, dimetil- amino- propil(metil)- amino, (2- (dimetilamino) etil) (metil) amino, metoxi- etil(metil) amino, dimetil- amino- etoxilo, nitro, 1- metil- 4- piperidiniloxilo, morfolino, 2- metil- morfolino, 4- etil- piperazin- 1- il- metilo, etil- amino- metilo, ciclopropil- amino- metilo, dietil- amino- etilo, azetidin- 1- ilmetilo, 3- hidroxi- pirrolidin- 1- il- metilo, hidroxi- etil- amino- metilo, propil- amino- metilo, 3- hidroxi- azetidin- 1- ilmetilo, 4- metoxietil- 1- piperazinilo, metoxi- etil- amino-

metilo, butil- amino- etilo, t- butil- amino- metilo, hidroxi- ciclohexil- amino- metilo, amino-metilo, hidroxi- propil- amino- metilo, hidroxi- etil(metil) amino- metilo, 4- hidroxipropil- 1-piperazinilo, 4- carboxi- metil- piperazinilo, dimetil- amino- metilo, isopropil- amino- metilo, 4-dimetil- amino- carbonil- metil- 1 - piperazinilo, 4- (2- hidroxipropil) piperazin- 1- ilo, hidroxi-etil- piperazinilo, metilo, ciclopropilo, halo, trifluorometoxilo, difluorometoxilo, 2- fluoropropan-2- ilo, 2- metoxi- propan- 2- ilo, 1,1- difluoroetilo, 1- metil- 1- fluoroetilo, 1- metil- l- metoxi-etilo, 2- hidroxipropan- 2- ilo, 2- metoxipropan- 2- ilo, 2- cianopropan- 2- ilo, 3- cianopropan- 2-ilo, 2,3- difluoropropan- 2- ilo y ciano- ciclopropilo.

Compuestos preferidos son seleccionados a partir de N- (4- Metil- 3- {2- metil- 4- [6- (2-morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifiuorometil-benzamida, N- (4- Metil- 3- {1- metil- 4- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 1H-pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (2-morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifiuorometil-benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]-fenil}- 3- (4- metil- piperazin- 1 - il)- 5- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2-[6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3-trifluorometil- benzamida, N- [4- Metil- 3- (5- metil- 2- {6- [2- (4- metil- piperazin- l- il)-etilamino]- pirimidin- 4- il}- 2H- pirazol- 3- ilamino)- fenil]- 3- trifluorometil- benzamida, N- {3-[2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3-trifluorometil- benzamida, N- {3- [4- (6- Ciclopropilamino- pirimidin- 4- il)- 2- metil- 2H-pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- [4- Metil- 3- (2- metil- 4-{6- [2- (4- metil- piperazin- l- il)- etilamino]- pirimidin- 4- il}- 2H- pirazol- 3- ilamino)- fenil]- 3-trifluorometil- benzamida, N- (4- Metil- 3- {2- metil- 4- [6- (2- morfolin- 4- il- etilamino)-pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- {3- [4- (6-Ciclopropilamino- pirimidin- 4- il)- l- metil- lH- pirazol- 3- ilamino]- 4- metil- fenil}- 3-trifluorometil- benzamida, N- [4- Metil- 3- (l- metil- 4- {6- [2- (4- metil- piperazin- l- il)-etilamino] - pirimidin- 4- il}- 1H- pirazol- 3 - ilamino)- fenil]- 3- trifluorometil- benzamida, N-(4- Metil- 3- {1- metil- 4- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- 3 -ilamino}- fenil)- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)-5- metil- 2H- pirazol- 3 - ilamino] - 4- metil- fenil}- 3- (4- metil- piperazin- 1- il)- 5-trifluorometil- benzamida, N- {4- Metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H-

pirazol- 3- ilamino]- fenil}- 3- (4- metil- piperazin- 1 - il)- 5- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3 - ilamino] - 4- metil- fenil}- 3- (4- etil- piperazin- 1 - il)- 5- trifluorometil- benzamida, 3- (4- Etil- piperazin- 1 - il)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3 - ilamino] - fenil}- 5- trifluorometil- benzamida, 3- (4- Etil- piperazin- l- il)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 5- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- (4- metil- piperazin- 1 - il)- 5- trifluorometil- benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- (4- metil- piperazin- l- il)- 5- trifluorometil- benzamida, 3- (4- Etil- piperazin- l- il)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 5- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, (3- trifluorometil- fenil)- amida del ácido 5- Metil- 6- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- piridina- 2- carboxílico, (3- trifluorometil- fenil)- amida del ácido 5- Metil- 6- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- piridina- 2- carboxílico, (3- trifluorometil- fenil)- amida del ácido 5- Metil- 6- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- piridina- 2- carboxílico, N- (4- Metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3 - [2- (6- amino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 2H- pirazol- 3 - ilamino] - 4- metil- fenil}- 3- (4- metil- piperazin- l- il)- 5- trifluorometil- benzamida, N- [3- (2- {6- [2- (2,6- Dimetil- morfolin- 4- il)- etilamino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3 - ilamino)- 4- metil- fenil]- 3- trifluorometil- benzamida, N- [3- (2- {6- [2- (4- Hidroxi- piperidin- 1- il)- etilamino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- 3- trifluorometil- benzamida, N- [4- Metil- 3 - (5- metil- 2- {6- [2- (3- oxo- piperazin- 1- il)- etilamino]- pirimidin- 4- il} - 2H- pirazol- 3 - ilamino)- fenil]- 3- trifluorometil- benzamida, N- (3- {2- [6- (2- Amino- etilamino)- pirimidin- 4- il]- 5- metil- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, 2- tert- Butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- tert- Butil- N- (4- metil- 3- {5- metil- 2- [6-

(2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, N- {4- Metil- 3- [4- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [4- (6- metilamino- pirimidin- 4- il)- l- (2- morfolin- 4- il- etil)- lH- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [1- metil- 4- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- ilamino]- fenil}- 3- (4- metil- piperazin- l- il)- 5- trifluorometil- benzamida, 3- [4- (2- Hidroxi- etil)- piperazin- 1 - il]- N- {4- metil- 3- [1- metil- 4- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- ilamino]- fenil}- 5- trifluorometil- benzamida, N- {3- [4- (6- Ciclopropilamino- pirimidin- 4- il)- l- metil- lH- pirazol- 3- ilamino]- 4- metil- fenil}- 3- (4- metil- piperazin- 1 - il)- 5- trifluorometil- benzamida, N- {3- [4- (6- Ciclopropilamino- pirimidin- 4- il)- 1 - metil- 1 H- pirazol- 3 - ilamino] - 4- metil- fenil}- 3- [4- (2- hidroxi- etil)- piperazin- l- il]- 5- trifluorometil- benzamida, N- (3- {2- [6- (2- Hidroxi- etilamino)- pirimidin- 4- il]- 5- metil- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, N- {4- Metil- 3- [5- metil- 2- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (2,3- Dihidro- imidazo[1,2- c]pirimidin- 7- il)- 5- metil- 2H- pirazol- 3 - ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, 2- tert- Butil- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, N- {3- [2- (6- metoxi- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- Amino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3 - ilamino] - 4- metil- fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- Mercapto- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (2- piridin- 3- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, ácido 4- (6- {3- Metil- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- pirazol- l- il}- pirimidin- 4- ilamino)- butírico, ácido (6- {3- Metil- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- pirazol- 1- il}- pirimidin- 4- ilamino)- acético, N- (3- {2- [6- (Azetidin- 3- ilamino)- pirimidin- 4- il]- 5- metil- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, ácido 3- (6- {3- Metil- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- pirazol- 1 - il}- pirimidin- 4- ilamino)- propiónico, N- (3- {2- [6- (3- Hidroxi- pirrolidin- 1- il)- pirimidin- 4- il]- 5- metil- 2H-

pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, N- [3- (2- {6- [(Azetidin- 3- ilmetil)- amino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- 3- trifluorometil- benzamida, N- [4- Metil- 3- (5- metil- 2- {6- [(piridin- 2- ilmetil)- amino]- pirimidin- 4- il} - 2H- pirazol- 3 - ilamino)- fenil]- 3- trifluorometil- benzamida, 4- Metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- N- [3- (4- metil- piperazin- 1 - il)- 5- trifluorometil- fenil]- benzamida, éster tert- butílico del ácido (4- Metil- 3- {5- metil- 2- [6- (5- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- carbámico, 5- Metil- N- (4- metil- 3- {5- metil- 2- [6- (5- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, (4- metil- 3- {5- metil- 2- [6- (5- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- amida del ácido 3- Ciclopropil- isoxazol- 5- carboxílico, 3,4- Dicloro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- Fluoro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 5- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 4- trifluorometil- benzamida, 3,5- Dicloro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- Fluoro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino}- fenil)- 3- trifluorometoxi- benzamida, 3- Bromo- 4- cloro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- Difluorometoxi- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- Cloro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (l- Hidroxi- l- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1- Metoxi- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 2- (Ciano- dimetil- metil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 3- (Ciano- dimetil- metil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)-

benzamida, 3- (1,1- Difluoro- etil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il-etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1- Ciano-ciclopropil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il-etilamino)- pirimidin- 4- il]- 2H- pirazol- 3 - ilamino }- fenil)- amida del ácido 3,3- Dimetil- 2,3-dihidro- benzofuran- 5- carboxílico, 4- Metil- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il-etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, 2-(Ciano- dimetil- metil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)-pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 3- (Ciano- dimetil- metil)- N-(4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il]- 2H- pirazol- 3-ilamino}- fenil)- benzamida, 3- (1 - Ciano- ciclopropil)- N- (4- metil- 3- {5- metil- 2- [6- (4-metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 2- (1-Ciano- ciclopropil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin-4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 3- (1,1- Difluoro- etil)- N- (4- metil- 3-{5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}-fenil)- benzamida, 3- (1 - Hidroxi- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil-piperazin- 1- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1-Metoxi- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)-pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, éster etílico del ácido l- (6-ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)-fenilamino]- lH- pirazol- 3- carboxílico, metilamida del ácido l- (6- Ciclopropilamino- pirimidin-4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- hidroximetil- 2H- pirazol- 3- ilamino]- 4-metil- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5-dimetilaminometil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N-{3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- metilaminometil- 2H- pirazol- 3- ilamino]- 4-metil- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5-morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino] - 4- metil- fenil}- 3- trifluorometil- benzamida, N-(3- {2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [(2- dietilamino- etilamino)- metil]- 2H-pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, N- {3- [2- (6-Ciclopropilamino- pirimidin- 4- il)- 5- (4- metil- piperazin- l- ilmetil)- 2H- pirazol- 3- ilamino]-

4- metil- fenil}- 3- trifluorometil- benzamida, N- [3- (2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- {[2- (4- metil- piperazin- 1- il)- etilamino]- metil}- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- 3- trifluorometil- benzamida, N- (3- {2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [(3- dimetilamino- propilamino)- metil]- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- etilaminometil- 2H- pirazol- 3 - ilamino] - 4- metil- fenil}- 3- trifluorometil- benzamida, N- (3- {2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [(2,2,2- trifluoro- etilamino)- metil]- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, (2- dimetilamino- etil)- amida del ácido 1- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3- carboxílico, (2- piperidin- 1- il- etil)- amida del ácido 1- (6- ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3- carboxílico, (2- morfolin- 4- il- etil)- amida del ácido 1- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3- carboxílico, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- (morfolina- 4- carbonil)- 2H- pirazol- 3- ilamino] - 4- metil- fenil}- 3- trifluorometil- benzamida, amida del ácido 1- (6- ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (34rifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3- carboxílico, dimetilamida del ácido 1- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3- carboxílico, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- (3- dimetilamino- pirrolidina- 1- carbonil)- 2H- pirazol- 3- ilamino] - 4- metil- fenil}- 3- trifluorometil- benzamida, (2- metoxi- etil)- amida del ácido 1- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3- carboxílico, metilamida del ácido 1- (6- Metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3- carboxílico, N- {4- Metil- 3- [5- metilaminometil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3 - ilamino]- fenil}- 3- trifluorometil- benzamida, metilamida del ácido 1- (6- Metilamino- pirimidin- 4- il)- 5- {2- metil- 5- [3- (4- metil- piperazin- 1- il)- 5- trifluorometil- benzoilamino]- fenilamino}- 1H- pirazol- 3- carboxílico, metilamida del ácido 1- (6- Metilamino- 2- morfolin- 4- il- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (1,1- Difluoro- etil)- benzoilamino]- 2- metil-

fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- 1 H- pirazol- 3 - carboxílico, metilamida del ácido 5- {5- [3- (Ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- l- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (l - Ciano- ciclopropil)- benzoilamino] - 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, N- {3- [5- Cianometil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, (2- morfolin- 4- il- etil)- amida del ácido l- (6- Metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- l H- pirazol- 3- carboxílico, ciclopropilamida del ácido 1- (6- Metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, 5- tert- Butil- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino} - fenil)- nicotinamida, N- [5- (l- Fluoro- l- metil- etil)- piridin- 3- il]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [5- (1- Metoxi- 1- metil- etil)- piridin- 3- il]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [5- (l- Fluoro- l- metil- etil)- piridin- 3- il]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- [5- (l- Metoxi- l- metil- etil)- piridin- 3- il]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino}- benzamida, 4- Metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- N- (4- trifluorometil- piridin- 2- il)- benzamida, N- (3- tert- Butil- fenil)- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- (2- tert- Butil- piridin- 4- il)- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- (3- tert- Butil- fenil)- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [3- (Ciano- dimetil- metil)- fenil]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, 4- Metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- N- (4- trifluorometil- piridin- 2- il)- benzamida, (6- {5- [5- (6- tert- Butil- lH- benzoimidazol- 2- il)- 2- metil- fenilamino]- 3- metil- pirazol- 1 - il}- pirimidin- 4- il)- (4- metil- piperazin- 1 - il)- amine, (6- {3- Metil- 5- [2- metil- 5- (6- trifluorometil- 1 H-

fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- 1 H- pirazol- 3 - carboxílico, metilamida del ácido 5- {5- [3- (Ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- l- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (l - Ciano- ciclopropil)- benzoilamino] - 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, N- {3- [5- Cianometil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, (2- morfolin- 4- il- etil)- amida del ácido l- (6- Metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- l H- pirazol- 3- carboxílico, ciclopropilamida del ácido 1- (6- Metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, 5- tert- Butil- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino} - fenil)- nicotinamida, N- [5- (l- Fluoro- l- metil- etil)- piridin- 3- il]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [5- (1- Metoxi- 1- metil- etil)- piridin- 3- il]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [5- (l- Fluoro- l- metil- etil)- piridin- 3- il]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- [5- (l- Metoxi- l- metil- etil)- piridin- 3- il]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino}- benzamida, 4- Metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- N- (4- trifluorometil- piridin- 2- il)- benzamida, N- (3- tert- Butil- fenil)- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- (2- tert- Butil- piridin- 4- il)- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- (3- tert- Butil- fenil)- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [3- (Ciano- dimetil- metil)- fenil]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, 4- Metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- N- (4- trifluorometil- piridin- 2- il)- benzamida, (6- {5- [5- (6- tert- Butil- lH- benzoimidazol- 2- il)- 2- metil- fenilamino]- 3- metil- pirazol- 1 - il}- pirimidin- 4- il)- (4- metil- piperazin- 1 - il)- amine, (6- {3- Metil- 5- [2- metil- 5- (6- trifluorometil- 1 H-

benzoimidazol- 2- il)- fenilamino]- pirazol- 1 - il}- pirimidin- 4- il)- (4- metil- piperazin- 1- il)-amina, N- [3- (1,1- Difluoro- etil)- fenil]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1-ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- [3- (1,1 - Difluoro- etil)-fenil]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H-pirazol- 3- ilamino}- benzamida, 4- fluoro- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)-5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, 4- Fluoro-N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 5- morfolin- 4- ilmetil-2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, metilamida del ácido 5- [5- (4-Fluoro- 3- trifluorometil- benzoilamino)- 2- metil- fenilamino]- 1- [6- (2- morfolin- 4- il-etilamino)- pirimidin- 4- il]- 1H- pirazol- 3- carboxílico, metilamida del ácido 5- [5- (4- Fluoro-3- trifluorometil- benzoilamino)- 2- metil- fenilamino]- 1- [6- (4- metil- piperazin- 1- ilamino)-pirimidin- 4- il]- 1H- pirazol- 3- carboxílico, (2- morfolin- 4- il- etil)- amida del ácido 5- [5- (4-Fluoro- 3- trifluorometil- benzoilamino)- 2- metil- fenilamino]- 1- (6- metilamino- pirimidin- 4-il)- 1H- pirazol- 3- carboxílico, metilamida del ácido 5- [5- (2- tert- Butil- piridin- 4- ilcarbamoil)-2- metil- fenilamino]- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 1H- pirazol- 3-carboxílico, (2- morfolin- 4- il- etil)- amida del ácido 5- {5- [3- (1,1- Difluoro- etil)-benzoilamino]- 2- metil- fenilamino}- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]-1H- pirazol- 3- carboxílico, N- (4- Metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4-il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, 3 - (1,1 - Difluoro- etil)- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il]- 5-morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (Ciano- dimetil- metil)- N-(4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H-pirazol- 3- ilamino}- fenil)- benzamida, 2- tert- Butil- N- (4- metil- 3- {2- [6- (4- metil-piperazin- 1- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)-isonicotinamida, 5- tert- Butil- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)-pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 2-(Ciano- dimetil- metil)- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]-5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- (Ciano- dimetil-metil)- N- {3- [5- {[(2- hidroxi- etil)- metil- amino]- metil}- 2- (6- metilamino- pirimidin- 4- il)-2H- pirazol- 3- ilamino]- 4- metil- fenil}- isonicotinamida, 3- (Ciano- dimetil- metil)- N- {3- [5-{[(2- hidroxi- etil)- metil- amino]- metil}- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3-

ilamino]- 4- metil- fenil}- benzamida, 2- tert- Butil- N- {3- [5- {[(2- hidroxi- etil)- metil- amino]- metil}- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- isonicotinamida, 2- tert- Butil- N- {3- [5- [2- (2,6- dimetil- piperidin- 1- il)- etilcarbamoil]- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- isonicotinamida, 2- (Ciano- dimetil- metil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 3- (Ciano- dimetil- metil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (1- Ciano- ciclopropil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 2- (1- Ciano- ciclopropil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3 - ilamino]- fenil}- isonicotinamida, 3- (1- Ciano- 1- metil- propil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 2- tert- Butil- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 3- (1,1 - Difluoro- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (1- Hidroxi- 1- metil- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (1 - Metoxi- 1 - metil- etil)- N- {4- metil- 3 - [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 5- tert- Butil- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- nicotinamida, 2- tert- Butil- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- amida del ácido 2,2- Dimetil- 2,3- dihidro- benzofuran- 7- carboxílico, 2- (1- Fluoro- 1 - metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- (1- Fluoro- 1 - metil- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3 - ilamino] - fenil}- isonicotinamida, 2- (1- Fluoro- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- (1- Metoxi- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- (1- Metoxi- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino] - fenil}- isonicotinamida, 2- (1 - Metoxi- 1 - metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3-

ilamino}- fenil)- isonicotinamida, 2- (1- Hidroxi- 1- metil - etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il] - 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- (1- Hidroxi- 1- metil- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- (l- Hidroxi- l- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil) isonicotinamida, 3- (l- ciano- ciclopropil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (Ciano- dimetil- metil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 2- (Ciano- dimetil- metil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- (l- Ciano- ciclopropil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 3 - (1,1- Difluoro- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (l- Metoxi- l- metil- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (1 - Hidroxi- 1- metil- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 2- (1- Fluoro- 1- metil- etil)- N- {4- metil- 3 - [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- (1- Metoxi- l- metil- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3 - ilamino]- fenil}- isonicotinamida, 2- (l- Hidroxi- l- metil- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 5- tert- Butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- nicotinamida, N- [3- (Ciano- dimetil- metil)- fenil]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino}- benzamida, N- (2- tert- Butil- piridin- 4- il)- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, 5- (1- Fluoro- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3 - ilamino}- fenil)- nicotinamida, 5- (1 - Metoxi- 1 - metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- (l- Hidroxi- l- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 2- (1,1- Difluoro- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, N- {3- [2- (6- Amino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3

- ilamino]- 4- metil- fenil}- 3- (1,1- difluoro- etil)- benzamida, 3- (1,1- Difluoro- etil)- N- (4- metil- 3- {5- metil- 2- [6- (5- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1,1- Difluoro- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, N- {3- [2- (6- Amino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino] - 4- metil- fenil}- 2- tert- butil- isonicotinamida, 2- tert- Butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- tert- Butil- N- [3- (2- {6- [4- (2- hidroxi- etil)- piperazin- l- ilamino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- isonicotinamida, 5- tert- Butil- N- [3- (2- {6- [4- (2- hidroxi- etil)- piperazin- l- ilamino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- nicotinamida, N- (2- tert- Butil- piridin- 4- il)- 3- (2- {6- [4- (2- hidroxi- etil)- piperazin- l- ilamino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- benzamida, N- (5- tert- Butil- piridin- 3- il)- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- [2- (1 - Metoxi- 1 - metil- etil)- piridin- 4- il]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- [3- (l,l- Difluoro- etil)- fenil]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [2- (Ciano- dimetil- metil)- piridin- 4- il]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, 5- (l- Fluoro- l- metil- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- nicotinamida, N- {3- [2- (6- Amino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 2- tert- butil- isonicotinamida, 3- (l,l- Difluoro- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 2- tert- Butil- N- (3- {2- [6- (2- dimetilamino- acetilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- isonicotinamida, N- [2- (l,l- Difluoro- etil)- piridin- 4- il]- 4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino} - benzamida, (2- morfolin- 4- il- etil)- amida del ácido 5- {5- [3- (l,l- Difluoro- etil)- benzoilamino]- 2- metil- fenilamino}- l- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, 5- tert- Butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino}- fenil)- nicotinamida, metilamida del ácido 1- (6- metilamino- pirimidin- 4- il)- 5- {2- metil- 5- [3- (4- metil- piperazin-

l- il)- 5- trifluorometil- benzoilamino]- fenilamino}- lH- pirazol- 3- carboxílico, metilamida del ácido l- (6- Metilamino- 2- morfolin- 4- il- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (l,l- Difluoro- etil)- benzoilamino]- 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- 1 H- pirazol- 3 - carboxílico, metilamida del ácido 5- {5- [3- (Ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- l- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (1- Ciano- ciclopropil)- benzoilamino] - 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, ciclopropilamida del ácido l- (6- Metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, 2- (Ciano- dimetil- metil)- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino}- fenil)- isonicotinamida, 2- (Ciano- dimetil- metil)- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino} - fenil)- isonicotinamida, metilamida del ácido 5- {5- [3- (Ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- l- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (Ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, 2- tert- Butil- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- tert- Butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- tert- Butil- N- {4- metil- 3- [2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- tert- Butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- metilcarbamoil- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- tert- Butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, metilamida del ácido 5- [5- (3- tert- Butil- benzoilamino)- 2- metil- fenilamino]- l- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, 2- Cloro- 6- metoxi- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- Cloro- 6- metoxi- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- Cloro- 6- metoxi- N- {4- metil- 3- [2- [6- (2- morfolin- 4- il- etilamino)-

pirimidin- 4- il]- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- Cloro- 6- metoxi- N- {4- metil- 3- [2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- Cloro- 6- metoxi- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- Cloro- 6- metoxi- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, N- (4- Metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino}- fenil)- 6- pirazol- 1- il- nicotinamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- metilcarbamoil- 2H- pirazol- 3 - ilamino] - fenil}- 6- pirazol- 1- il- nicotinamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- 6- pirazol- 1 - il- nicotinamida, N- (4- Metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 6- pirazol- 1- il- nicotinamida, metilamida del ácido 5- [2- Metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 1H- pirazol- 3- carboxílico, N- (4- Metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, (2- morfolin- 4- il- etil)- amida del ácido 5- [2- Metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 1H- pirazol- 3- carboxílico, metilamida del ácido 1- [6- (4- Metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3- carboxílico, N- (4- Metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 6- trifluorometoxi- nicotinamida, N- {4- Metil- 3- [2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- 6- trifluorometoxi- nicotinamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- metilcarbamoil- 2H- pirazol- 3- ilamino]- fenil}- 6- trifluorometoxi- nicotinamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- 6- trifluorometoxi- nicotinamida, N- (4- Metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 6- trifluorometoxi- nicotinamida, 2- (Ciano- dimetil- metil)- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, metilamida del ácido 5- {5- [3- (1- Ciano- 1- metil-

propil)- benzoilamino] - 2- metil- fenilamino}- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, 3- (l- Ciano- l- metil- propil)- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, metilamida del ácido 5- {5- [3- (1 - Ciano- 1 - metil- propil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 1 H- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (l- Ciano- l- metil- propil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 1H- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (l- Metoxi- l- metil- etil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 1 H- pirazol- 3- carboxílico, 3- (1 - Metoxi- 1 - metil- etil)- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (Ciano- dimetil- metil)- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 5- tert- Butil- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3 - ilamino}- fenil)- nicotinamida, metilamida del ácido 5- {5- [3- (l,l- Difluoro- etil)- benzoilamino]- 2- metil- fenilamino}- l- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, 3- (1,1- Difluoro- etil)- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, metilamida del ácido 5- {5- [3- (l,l- Difluoro- etil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il] - lH- pirazol- 3- carboxílico, 2- tert- Butil- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino}- fenil)- isonicotinamida, 4- tert- Butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- metanosulfonil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- Cloro- 3- metanosulfonil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- tert- Butoxi- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- Metoxi- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 5- morfolin- 4- ilmetil- 2H- pirazol- 3 - ilamino}-

fenil)- 3- trifluorometil- benzamida, 3 - tert- Butoxi- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- Metanosulfonil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, N- (4- Metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 4- trifluorometoxi- benzamida, N- (4- Metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometoxi- benzamida, metilamida del ácido 5- {5- [3- (1,1- Difluoro- etil)- benzoilamino]- 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- 1H- pirazol- 3- carboxílico, (2- morfolin- 4- il- etil)- amida del ácido 5- {5- [3- (Ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- 1H- pirazol- 3- carboxílico, 5- tert- Butil- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino }- fenil)- nicotinamida, 2- tert- Butil- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il] - 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 5- tert- Butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3 - ilamino]- fenil}- nicotinamida, {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- amida del ácido 1- Isopropil- 1H- benzotriazol- 5- carboxílico, {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- amida del ácido 5,5,8,8- Tetrametil- 5,6,7,8- tetrahidro- naftaleno- 2- carboxílico, {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- amida del ácido 2- Metil- benzotiazol- 5- carboxílico, 3- (1,1- Dietil- propil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- benzamida, N- {3- [5- (3- Dimetilamino- pirrolidin- 1- ilmetil)- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [5- [4- (2- Metoxi- etil)- piperazin- 1 - ilmetil]- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino] - 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [5- (2,6- Dimetil- morfolin- 4- ilmetil)- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [5- (2,6- Dimetil- morfolin- 4- ilmetil)- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- [4- Metil- 3- (2- (6- metilamino- pirimidin- 4- il)- 5- {[metil- (1 - metil- piperidin- 4- il)- amino] - metil}- 2H-

pirazol- 3 - ilamino)- fenil]- 3- trifluorometil- benzamida, N- {3- [5- (1,1 - Dioxo- 116-tiomorfolin- 4- ilmetil)- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil-fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5-tiomorfolin- 4- ilmetil- 2H- pirazol- 3-·ilamino]- fenil}- 3- trifluorometil- benzamida, 5- tert-butil- N- (3- (3- (((2- hidroxietil) (metil) amino) metil)- 1 - (6- (metilamino) pirimidin- 4- il)- lH-pirazol- 5- ilamino)- 4- metilfenil) nicotinamida, - (2- (2- fluoropropan- 2- il) piridin- 4- il)- 4-metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 5-tert- butil- N- (3- (3- (((2- hidroxietil) (metil) amino) metil)- 1- (6- (metilamino) pirimidin- 4- il)-lH- pirazol- 5- ilamino)- 4- metilfenil) nicotinamida, 5- tert- butil- N- (3- (3- (2- (2,6-dimetilpiperidin- l- il) etilcarbamoil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5-ilamino)- 4- metilfenil) nicotinamida, 5- (2- metoxipropan- 2- il)- N- (4- metil- 3- (3- metil- l- (6-(metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) nicotinamida, 5- (2- fluoropropan-2- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) nicotinamida, N- (4- tert- butiltiazol- 2- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- (2- fluoropropan- 2- il) piridin- 2- il)-4- metil- 3- (3 - metil- 1- (6- (4- metilpiperazin- 1- ilamino) pirimidin- 4- il)- 1H- pirazol- 5-ilamino) benzamida, 5- (5- (2- tert- butilpiridin- 4- ilcarbamoil)- 2- metilfenilamino)- 1 - (6-(isopropilamino) pirimidin- 4- il)- N- metil- 1 H- pirazol- 3- carboxamida, 5- (5- (2- tert-butilpiridin- 4- ilcarbamoil)- 2- metilfenilamino)- N- metil- l- (6- (metilamino) pirimidin- 4- il)-lH- pirazol- 3- carboxamida, N- (2- tert- butilpiridin- 4- il)- 4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- 3- (morfolinometil)- lH- pirazol- 5- ilamino) benzamida, N- (2- tert- Butil-piridin- 4- il)- 3- [5- (1,1- dioxo- 1 lambda*6*- tiomorfolin- 4- ilmetil)- 2- (6- metilamino-pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- benzamida (ver ejemplo 295), 2- tert- butil-N- (3- (l- (6- (isopropilamino) pirimidin- 4- il)- 3- (metilcarbamoil)- lH- pirazol- 5- ilamino)- 4-metilfenil)isonicotinamida, N- (2- tert- butilpiridin- 4- il)- 3- (l- (6- (isopropilamino) pirimidin-4- il)- 3- (morfolinometil)- lH- pirazol- 5- ilamino)- 4- metilbenzamida, N- (2- tert- Butil- piridin-4- il)- 3- [5- (l,l- dioxo- lambda*6*- tiomorfolin- 4- ilmetil)- 2- (6- isopropilamino- pirimidin- 4-il)- 2H- pirazol- 3- ilamino]- 4- metil- benzamida (ver ejemplo 298), 2- tert- butil- N- (3- (l- (6-(isopropilamino) pirimidin- 4- il)- 3- (morfolinometil)- lH- pirazol- 5- ilamino)- 4-metilfenil)isonicotinamida, N- (4- (2- fluoropropan- 2- il) piridin- 2- il)- 4- metil- 3- (3- metil- l-(6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (5- tert- butil- 4-

metiltiazol- 2- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (5- tert- butil- 4- metiltiazol- 2- il)- 4- metil- 3- (3- metil- l- (6- (4- metilpiperazin- l- ilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- (2- cianopropan- 2- il) piridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (2- (2- metoxipropan- 2- il) piridin- 4- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- tert- butiltiazol- 2- il)- 4- metil- 3- (3- metil- l- (6- (2- morfolinoetilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (5- tert- butil- 4- metiltiazol- 2- il)- 4- metil- 3- (3- metil- l- (6- (2- morfolinoetilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, - (4- (l,l- difluoroetil) piridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- (l,l- difluoroetil) piridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (4- metilpiperazin- l- ilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- tert- butilpiridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- tert- butilpiridin- 2- il)- 4- metil- 3- (3- metil- 1- (6- (4- metilpiperazin- 1- ilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 3- (l- (6- aminopirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (5- tert- butil- 4- metiltiazol- 2- il)- 4- metilbenzamida, 3- (l- (6- aminopirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (4- tert- butiltiazol- 2- il)- 4- metilbenzamida, N- (4- (2- metoxipropan- 2- il) piridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- (2- metoxipropan- 2- il) piridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (4- metilpiperazin- l- ilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (6- metil- 5- (3- metil- l- (6- (4- metilpiperazin- l- ilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) piridin- 3- il)- 3- (trifluorometil) benzamida, N- (6- metil- 5- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) piridin- 3- il)- 3- (trifluorometil) benzamida, 2- tert- butil- N- (6- metil- 5- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) piridin- 3- il)isonicotinamida, 2- tert- butil- N- (6- metil- 5- (3- metil- l- (6- (4- metilpiperazin- l- ilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) piridin- 3- il)isonicotinamida, N- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- 3- (l- oxo- tiomorfolinometil)- lH- pirazol- 5- ilamino) fenil)- 3- (trifluorometil) benzamida, N- (3- (l- (6- aminopirimidin- 4- il)- 3- metil- lH- pirazol- 5- ilamino)- 4- metilfenil)- 3- (4- hidroxipiperidin- l- il)- 5- (trifluorometil) benzamida, 3- (4- hidroxipiperidin- l- il)- N- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5 - y lamino) fenil)- 5- (trifluorometil) benzamida,

3- (4- hidroxipiperidin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (l- metilpiperidin- 4- iloxi)- 5- (trifluorometil) benzamida, 3- (4- (2- hidroxietil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- morfolino- 5- (trifluorometil) benzamida, (S)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (2- metilmorfolino)- 5- (trifluorometil) benzamida, (R)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (2- metilmorfolino)- 5- (trifluorometil) benzamida, l- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (3- (trifluorometil) fenil)urea, l- (4- fluoro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (3- (4- etilpiperazin- l- il)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, N- (4- metil- 3- (3- metil- 1 - (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (1,1- dioxo- tiomorfolino)- 5- (trifluorometil) benzamida, (R)- 3- (3,4- dimetilpiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (3,4- dimetilpiperazin- l- il)- N- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il) - 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (3- (4- hidroxipiperidin- l- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (3- (2- (dimetilamino) etoxi)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (2- (pirrolidin- l- il) etoxi)- 5- (trifluorometil) fenil) benzamida, N- (3- (3- hidroxipirrolidin- l- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (3- (3- hidroxiazetidin- l- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 2- (l,l- difluoroetil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)isonicotinamida, l- metil- 4- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)-

lH- pirazol- 5- ilamino) benzamido)- 5- (trifluorometil) fenil) piperazina- 2- carboxilato de metilo, N- (3- ((2- metoxietil) (metil) amino)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (3- ((2- (dimetilamino) etil) (metil) amino)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 3- (l,l- difluoroetil)- N- (3- (3- (hidroximetil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil) benzamida, N- (3- (3- (hidroximetil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil)- 3- (4- hidroxipiperidin- l- il)- 5- (trifluorometil) benzamida, 4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- 3- (trifluorometil)- lH- pirazol- 5- ilamino)- N- (3- (4- metilpiperazin- l- il)- 5- (trifluorometil) fenil) benzamida, l- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamido)- 5- (trifluorometil) fenil) piperidina- 4- carboxilato de metilo, ácido l- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamido)- 5- (trifluorometil) fenil) piperidina- 4- carboxílico, N- (3- (3- (hidroximetil)- 4- metilpiperazin- l- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (3- ((2- hidroxietil) (metil) amino)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (3- (4- (hidroximetil) piperidin- l- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, l- (3- (l,l- difluoroetil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (2- (l,l- difluoroetil) piridin- 4- il)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (3- (4- hidroxipiperidin- l- il)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, N- (3- fluoro- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (metilsulfonamido)- 5- (trifluorometil) fenil) benzamida, 2- metoxi- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 6- (trifluorometil)isonicotinamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (trifluorometil) fenil) benzamida, N- (4- cloro- 3- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- fluoro- 3- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino)

pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 3- ((3- (dimetilamino) propil) (metil) amino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- nitro- 5- (trifluorometil) benzamida, 3- amino- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((2- metoxietil) (metil) amino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, l- (4- bromo- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (6- metil- 5- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) piridin- 3- il)urea, 3- ((2- (dimetilamino) etil) (metil) amino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, l- (3- (4- (2- hidroxietil) piperazin- l- il)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (3- (3- (hidroximetil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil)urea, 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamido)- 5- (trifluorometil) benzoato de metilo, 3- (2- (dimetilamino) etoxi)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (3- (dimetilamino) propoxi)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- hidroxi- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (l- (6- (2- (dimetilamino) etilamino) pirimidin- 4- il)- 3- metil- lH- pirazol- 5- ilamino)- 4- metil- N- (3- (trifluorometil) fenil) benzamida, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (3- (l- (6- (2- (dimetilamino) etilamino) pirimidin- 4- il)- 3- metil- lH- pirazol- 5- ilamino)- 4- metilfenil)urea, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (2- morfolinoetilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, 3- (l- (6- (3- hidroxipropilamino) pirimidin- 4- il)- 3- metil- lH- pirazol- 5- ilamino)- 4- metil- N- (3- (trifluorometil) fenil) benzamida, 3- (difluorometil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- (difluorometil)- N- (3- (3- (hidroximetil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil) benzamida, l- (3- (4- metil- lH- imidazol- l- il)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3-

metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, 3- (4- metil- lH- imidazol- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5-

(trifluorometil) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (4- metil- lH- imidazol- l- il)- 5- (trifluorometil) fenil) benzamida, N- (3- metoxi- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (2- metil- 5- (trifluorometil) fenil) benzamida, l- (3- (l,l- difluoroetil) fenil)- 3- (3- (3- (hidroximetil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil)urea, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (2- (metilsulfonil) etilcarbamoil)- 5- (trifluorometil) fenil) benzamida, N- (3- (3- hidroxipropilcarbamoil)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- metil- 5- (trifluorometil) fenil) benzamida, l- (3- ((2- metoxietil) (metil) amino)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (3- ((2- (dimetilamino) etil) (metil) amino)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- 3- (morfolinometil)- lH- pirazol- 5- ilamino) fenil)urea, 1- (4- cloro- 3- (trifluorometil) fenil)- 3- (3- (3- ((dimetilamino) metil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil)urea, 3- bromo- 5- (1,1 - difluoroetil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, (R)- l- (4- cloro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- 3- ((2- metilmorfolino) metil)- lH- pirazol- 5- ilamino) fenil)urea, 4- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenilcarbamoil)- 5- (trifluorometil) fenil) piperazina- 1- carboxilato tert- butílico, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (piperazin- l- il)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4- (2,2,2- trifluoroetil) piperazin- l- il)- 5- (trifluorometil) benzamida, 3- (4- (2- amino- 2- oxoetil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (4- (2- metoxietil) piperazin- l- il)- N- (4- metil-

3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (4- (3- hidroxipropil) piperazin- 1 - il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, ácido 2- (4- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenilcarbamoil)- 5- (trifluorometil) fenil) piperazin- 1- il) acético, 3- (4- (2- (dimetilamino)- 2- oxoetil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (4- (2- hidroxipropil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4- (2- (metilsulfonil) etil) piperazin- l- il)- 5- (trifluorometil) benzamida, 3- (4- ciclopropilpiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, ácido (S)- 2- (4- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenilcarbamoil)- 5- (trifluorometil) fenil) piperazin- l- il) propanóico, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4,7- diazaspiro[2.5]octan- 7- il)- 5- (trifluorometil) benzamida, 2- etoxi- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 6- (trifluorometil)isonicotinamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (trifluorometil)- 5- (3- (trifluorometil) piperazin- l- il) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4- metil- 4,7- diazaspiro[2.5]octan- 7- il)- 5- (trifluorometil) benzamida, 4- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenilcarbamoil)- 5- (trifluorometil) fenil)- 3- oxopiperazina- l- carboxilato tert- butílico, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (2- oxopiperazin- l- il)- 5- (trifluorometil) benzamida, 3- (4- metil- 2- oxopiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 2- (metilamino)- 6- (trifluorometil)isonicotinamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4- metil- 3- (trifluorometil) piperazin- l- il)- 5- (trifluorometil) benzamida, 2- (2- (dimetilamino) etilamino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 6-

(trifluorometil)isonicotinamida, 2- (2- hidroxietilamino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 6- (trifluorometil)isonicotinamida, 3- (4- hidroxipiperidin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (4- (2- hidroxipropil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (4- (2- hidroxipropil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (3- ((4- etilpiperazin- l- il) metil)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (pirrolidin- l- ilmetil)- 5- (trifluorometil) fenil) benzamida, N- (3- ((dimetilamino) metil)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 3- ((dimetilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (pirrolidin- l- ilmetil)- 5- (trifluorometil) benzamida, 3- ((isopropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((metilamino) metil)- 5- (trifluorometil) benzamida, 1- (3- ((dimetilamino) metil)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (3- (pirrolidin- l- ilmetil)- 5- (trifluorometil) fenil)urea, l- (3- ((4- etilpiperazin- l- il) metil)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, 3- ((etilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((ciclopropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (l,l- difluoroetil)- 5- ((isopropilamino) metil)- N- (4- metil- 3- (1 - (6- (metilamino) pirimidin- 4- il)- 1 H- pirazol- 5- ilamino) fenil) benzamida, 3- (1,1- difluoroetil)- 5- ((isopropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- ((dietilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH-

pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (azetidin- l- ilmetil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (azetidin- l- ilmetil)- N- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- 1 H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3- hidroxiazetidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3- hidroxipirrolidin- 1- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((2- hidroxietilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((propilamino) metil)- 5- (trifluorometil) benzamida, 3- (l,1- difluoroetil)- 5- ((dimetilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- ((ciclopropilamino) metil)- 5- (l,l- difluoroetil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- ((3- hidroxipropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (l,l- difluoroetil)- 5- ((etilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- ((2- metoxietilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((butilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((tert- butilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1 H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (1,1- difluoroetil)- 5- ((4- hidroxiciclohexilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- ((ciclopropilamino) metil)- 5- (l,l- difluoroetil)- N- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- (aminometil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 2- ((dimetilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 6- (trifluorometil)isonicotinamida, 3- (((2- hidroxietil) (metil) amino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (l,2- dihidroxietil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)-

1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((l- hidroxipropan- 2- ilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((l- hidroxipropan- 2- ilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((2,2- dimetilhidrazinil) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((metoxiamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((hidroxiamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- ((2- (hidroximetil) pirrolidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- ((2- hidroxipropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (((tetrahidrofuran- 2- il) metilamino) metil)- 5- (trifluorometil) benzamida, (R)- 3- ((2,3- dihidroxipropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- ((2,3- dihidroxipropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((l,3- dihidroxipropan- 2- ilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((l- hidroxi- 2- metilpropan- 2- ilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((ciclobutilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((dimetilamino) metil)- N- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (((2- metoxietil) (metil) amino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (((lS,2R)- 2- hidroxiciclopentilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (((tetrahidrofuran- 2- il) metilamino) metil)- 5- (trifluorometil) benzamida, (R)- 3- ((2- hidroxipropilamino) metil)- N- (4-

metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (morfolinometil)- 5- (trifluorometil) benzamida, 3- ((3- metoxiazetidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida 3- ((3- metoxipirrolidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3- hidroxiazetidin- 1- il) metil)- N- (4- metil- 3- (1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- cloro- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((dimetilamino) metil)- 5- (trifluorometil) benzamida, N- (4- cloro- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((isopropilamino) metil)- 5- (trifluorometil) benzamida, N- (4- cloro- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (pirrolidin- l- ilmetil)- 5- (trifluorometil) benzamida, 3- ((isopropilamino) metil)- N- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (1 - (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- (pirrolidin- l- ilmetil)- 5- (trifluorometil) benzamida, 3- (l- (etilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((2- metilmorfolino) metil)- 5- (trifluorometil) benzamida, (S)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((2- metilmorfolino) metil)- 5- (trifluorometil) benzamida, 3- ((2- hidroxi- 2- metilpropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (l,2,3,6- tetrahidropiridin- 4- il)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (piperidin- 4- il)- 5- (trifluorometil) benzamida, 3- (l- metil- l,2,3,6- tetrahidropiridin- 4- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (l,2- dihidroxietil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (l- hidroxietil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil)

benzamida, 3- (3- (2- hidroxietilamino) ciclobutil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (3- (isopropilamino) ciclobutil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (E)- 3- (3- aminoprop- l- enil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (E)- 3- (3- (isopropilamino) prop- l- enil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (E)- 3- (3- (2- hidroxietilamino) prop- l- enil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (3- (isopropilamino) propil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (2- (isopropilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (2- (2- hidroxietilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (l- (etilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, *(R)- 3* - (1 - (etilamino) etil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (l- (dimetilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (l- (dimetilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (1- (pirrolidin- 1 - il) etil)- 5- (trifluorometil) benzamida, (R)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (l- (pirrolidin- l- il) etil)- 5- (trifluorometil) benzamida, (S)- 3- (l- (isopropilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (1- (isopropilamino) etil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (4- (2,2- difluoroetil) piperazin- 1- il)- N- (4- metil- 3 - (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- cloro- 5- (4- (2- metoxietil) piperazin- 1 - il)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, 3- cloro- 5- (4- (2-

etoxietil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- cloro- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (4- metilpiperazin- l- il) benzamida, (S)- 3- (4- (2- metoxietil)- 2- metilpiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (4- (2- metoxietil)- 2- metilpiperazin- 1- il)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (2,4- dimetilpiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (2,4- dimetilpiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3- difluoroazetidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3,3- difluoropirrolidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (4- (2,2- difluoroetil)- 2- metilpiperazin- 1 - il)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1 H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, rac- 3- (2- (3,3- difluoropirrolidin- l- il) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, *rac*- 3- (2- (3,3- difluoroazetidin- l- il) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, y 3- ((2,2- difluoroetil) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida.

Compuestos preferidos adicionales del invento se presentan en detalle en los Ejemplos y Tabla I, *infra*.

Farmacología y Utilidad

Los compuestos del invento modulan la actividad de las quinasas y, como tal, son útiles para tratar enfermedades o trastornos en los cuales las quinasas, contribuyen a la patología y/o sintomatología de la enfermedad. Ejemplos de quinasas que son inhibidas por los compuestos y composiciones descritos en la presente y contra los cuales los métodos descritos en la presente son útiles incluyen, pero no están limitados a, Abl, BCR- Abl (formas tipo silvestre y mutantes), ARG, BRK, EphB, Fms, Fyn, KDR, c- Kit, LCK, PDGF- R, b- Raf, c- Raf, SAPK2,

Src, Tie2 y TrkB.

La tirosinquinasa Abelson (es decir Abl, c- Abl) está involucrada en la regulación del ciclo celular, en la respuesta celular a estrés genotóxico, y en la transmisión de información sobre el ambiente celular a través de señalización de integrina. Por lo general, parece que la proteína Abl cumple un papel complejo como un módulo celular que integra señales a partir de varias fuentes extracelulares e intracelulares y que influye sobre las decisiones con respecto a ciclo celular y apoptosis. La tirosinquinasa Abelson incluye derivados de sub- tipos tal como la fusión quimérica (oncoproteína) BCR- Abl con actividad de tirosinquinasa desregulada o la v- Abl. BCR- Abl es crítica en la patogénesis de 95% de leucemia mielógena crónica (CML) y 10% de leucemia linfocítica aguda. STI- 571 (Gleevec) es un inhibidor de la tirosinquinasa BCR- Abl oncogénica y se utiliza para el tratamiento de leucemia mieloide crónica (CML). Sin embargo, algunos pacientes en la fase de crisis blástica de CML son resistentes a STI- 571 debido a mutaciones en la quinasa BCR- Abl. Más de 22 mutaciones se han reportado hasta la fecha con las más comunes siendo G250E, E255V, T315I, F317L y M351T.

Los compuestos del presente invento inhiben la quinasa abl, especialmente la quinasa v-abl. Los compuestos del presente invento también inhiben la quinasa BCR- Abl tipo silvestre y las mutaciones de la quinasa BCR- Abl y por lo tanto son adecuados para el tratamiento de cáncer y enfermedades tumorales Bcr- abl- positivas, tal como leucemias (especialmente leucemia mieloide crónica y leucemia linfoblástica aguda, donde especialmente se encuentran los mecanismos de acción apoptótica), y también muestran efectos sobre el subgrupo de células madre leucémicas así como también potencial para la purificación de estas células *in vitro* después de retirar dichas células (por ejemplo, retiro de médula ósea) y reimplante de las células una vez hayan sido desprovistas de células de cáncer (por ejemplo, reimplante de células de médula ósea purificadas).

La malaria es producida por parásitos protozoarios del género plasmodium. Cuatro especies de Plasmodium pueden producir la enfermedad en sus diferentes formas: Plasmodium falciparum; Plasmodium vivax; Plasmodium ovale; y Plasmodium malaria. P. falciparum, la más diseminada y peligrosa, puede llevar a malaria cerebral fatal si no se trata. La actividad de la proteína tirosinquinasa está distribuida en todas las fases de maduración del parásito P. falciparum y los inhibidores de quinasa del presente invento se pueden utilizar para tratar Enfermedades relacionadas con Plasmodium. El ensayo in vitro, infra, se utiliza como un medio

para determinar la actividad de los compuestos del invento contra una variedad de cepas de parásitos productores de malaria.

La ruta de señalización Ras- Raf- MEK- ERK media la respuesta celular a señales de crecimiento. Ras es mutada a una forma oncogénica en ~15% de cáncer humano. La Familia Raf pertenece a la proteinquinasa e incluye tres miembros, A- Raf, B- Raf y c- Raf (o Raf- 1). El enfoque en Raf siendo un objetivo farmacológico se ha centrado en la relación de Raf como efector corriente abajo de Ras. Sin embargo, datos recientes indican que B- Raf puede tener un rol prominente en la formación de ciertos tumores sin requerimiento de un alelo activado por Ras (Nature 417, 949 - 954 (01 Jul 2002). En particular, las mutaciones B- Raf se han detectado en un gran porcentaje de melanomas malignos.

Los tratamientos médicos existentes para melanoma están limitados en su efectividad, especialmente para melanomas de fase tardía.

Los compuestos del presente invento también inhiben los procesos celulares que involucran la quinasa b- Raf, proporcionando una nueva oportunidad terapéutica para el tratamiento de cánceres humanos, especialmente para melanoma.

Los compuestos del presente invento también inhiben procesos celulares que involucran la quinasa c- Raf. c- Raf se activa por el oncógeno ras, el cual es mutado en un amplio número de cánceres humanos. Por lo tanto la inhibición de la actividad de la quinasa de c- Raf puede proporcionar una forma de prevenir crecimiento tumoral mediado por ras [Campbell, S. L., Oncogeno, 17, 1395 (1998)].

El PDGF (Factor de crecimiento derivado de plaquetas) es un factor de crecimiento muy común, el cual juega un papel importante tanto en crecimiento normal como también en proliferación celular patológica, tal como se observa en carcinogénesis y en enfermedades de las células de músculo liso de vasos sanguíneos, por ejemplo en aterosclerosis y trombosis. Los compuestos del invento pueden inhibir actividad de receptores PDGF (PDGFR), y por lo tanto, son adecuados para el tratamiento de enfermedades tumorales, tales como gliomas, sarcomas, tumores de próstata, y tumores del colon, seno, y ovarios.

Los compuestos del presente invento, se pueden utilizar no solamente como una sustancia inhibidora de tumores, por ejemplo en cáncer pulmonar de células pequeñas, sino también como un agente para tratar trastornos proliferativos no malignos, tal como aterosclerosis, trombosis, psoriasis, escleroderma y fibrosis, así como también para la protección de células madre, por

ejemplo para combatir el efecto hemotóxico de agentes quimioterapéuticos, tal como 5-fluoruracilo, y en asma. Los compuestos del invento se pueden especialmente utilizar para el tratamiento de enfermedades, las cuales responden a una inhibición de la quinasa del receptor del PDGF.

Los compuestos del presente invento muestran efectos útiles en el tratamiento de trastornos que se originan como un resultado de trasplante, por ejemplo, trasplante alogénico, especialmente rechazo de tejidos, tal como especialmente bronquiolitis obliterativa (OB), es decir un rechazo crónico de trasplantes pulmonares alogénicos. En contraste a pacientes sin OB, aquellos con OB a menudo muestran una concentración PDGF elevada en fluidos de lavado broncoalveolar.

Los compuestos del presente invento también son efectivos en enfermedades asociadas con migración y proliferación de células vasculares de músculo liso (donde PDGF y PDGF- R a menudo también juegan un papel), tal como restenosis y aterosclerosis. Estos efectos y las consecuencias de los mismos para la proliferación o migración de células vasculares de músculo liso *in vitro* y *in vivo* se pueden demostrar mediante la administración de los compuestos del presente invento, y también al investigar su efecto sobre el engrosamiento de la íntima vascular después de lesión mecánica *in vivo*.

La familia trk de receptores de neurotrofina (trkA, trkB, trkC) promueve la supervivencia, crecimiento y diferenciación de los tejidos neuronal y no neuronal. La proteína TrkB se expresa en células de tipo neuroendocrino en el intestino delgado y colon, en las células alfa del páncreas, en los monocitos y macrófagos de los nódulos 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 una progresión desfavorable de tumores Wilms y de neuroblastomas. Además, TkrB se expresa en células cancerosas de próstata pero no en células normales. La ruta de señalización corriente abajo de los receptores trk involucra la cascada de activación de la MAPK a través de la Shc, Ras activado, genes ERK- 1 y ERK- 2, y la vía de transducción de PLC- gama (Sugimoto et al., 2001).

La quinasa c- Src transmite señales oncogénicas de muchos receptores. Por ejemplo, la sobre expresión de EGFR o HER2/neu en tumores lleva a la activación constitutiva de c- src, la cual es característica para la célula maligna pero ausente a partir de la célula normal. Por otra parte, los ratones deficientes en la expresión de c- src exhiben un fenotipo osteopetrótico,

indicando una participación clave de c- src en función de osteoclastos y un posible papel en trastornos relacionados.

Bmx, una quinasa de la familia Tec, una proteína tirosinquinasa no receptora, controla la proliferación de células de cáncer epiteliales mamíferas.

Se mostró que el receptor del factor de crecimiento de fibroblastos 3 ejerce un efecto regulador negativo sobre crecimiento óseo y una inhibición de la proliferación de condrocitos. La displasia tanatofórica es producida por diferentes mutaciones en el receptor del factor de crecimiento de fibroblastos 3, y una mutación, TDIIF GFR3, tiene una actividad constitutiva de la tirosinquinasa la cual activa el factor de transcripción Statl, llevando a expresión de un inhibidor de ciclo celular, detención de crecimiento y desarrollo óseo anormal(Su et al., Nature, 1997, 386, 288- 292). FGFR3 a menudo también se expresa en múltiples cánceres tipo mieloma. Los inhibidores de actividad FGFR3 son útiles en el tratamiento de Enfermedades inflamatorias o autoinmunes mediadas por células T incluyendo pero sin limitar a artritis reumatoide (RA), artritis de colágeno II, esclerosis múltiple (MS), lupus eritematoso sistémico (SLE), psoriasis, diabetes de comienzo juvenil, Enfermedad de Sjogren, enfermedad tiroidea, sarcoidosis, uveítis autoinmune, enfermedad intestinal inflamatoria (colitis de Crohn y ulcerativa), enfermedad celiaca y miastenia grave.

La actividad de la quinasa sérica y regulada por glucocorticoides (SGK), está correlacionada con actividades de canales iónicos perturbados, en particular, aquellos de canales sódicos y/o potásicos y compuestos del invento pueden ser útiles para tratar hipertensión.

Lin et al (1997) J. Clin. Invest. 100, 8: 2072- 2078 y P. Lin (1998) PNAS 95, 8829- 8834, han mostrado una inhibición de crecimiento y vascularización tumoral y también una disminución en metástasis pulmonares durante infecciones adenovirales o durante inyecciones del dominio extracelular de Tie- 2 (Tek) en modelos tumorales de seno y xenoinjertos de melanoma. Los inhibidores Tie2 se pueden utilizar en situaciones donde la neovascularización tiene lugar inapropiadamente (es decir en retinopatía diabética, inflamación crónica, psoriasis, Sarcoma de Kaposi, neovascularización crónica debido a degeneración macular, artritis reumatoide, hemangioma infantil y cánceres).

Lck juega un papel en señalización de células T. Los ratones que carecen del gen Lck tienen un capacidad pobre para desarrollar timocitos. La función de Lck como un activador positivo de señalización de células T indica que los inhibidores Lck pueden ser útiles para tratar

enfermedad autoinmune tal como artritis reumatoide.

JNKs, junto con otras MAPKs, han sido implicadas en jugar un papel en mediación de la respuesta celular a cáncer, agregación de plaquetas inducida por trombina, trastornos de inmunodeficiencia, enfermedad autoinmune, muerte celular, alergias, osteoporosis y enfermedad cardiaca. Los objetivos terapéuticos relacionados con activación de la Ruta JNK incluyen leucemia mielógena crónica (CML), artritis reumatoide, asma, osteoartritis, isquemia, cáncer y enfermedades neurodegenerativas. Como un resultado de la importancia de la activación JNK asociada con enfermedad hepática o episodios de isquemia hepática, los compuestos del invento también pueden ser útiles para tratar varios trastornos hepáticos. Un papel para JNK en enfermedad cardiovascular tal como infarto del miocardio o falla cardiaca congestiva también se ha reportado ya que se ha mostrado que JNK interviene en respuestas hipertróficas a diferentes formas de estrés cardiaco. También se ha demostrado que la cascada JNK también juega un papel en activación de células T, incluyendo activación del promotor IL- 2. Por lo tanto, los inhibidores de JNK pueden tener valor terapéutico para alterar respuestas inmunes patológicas. También se ha establecido un papel para activación de JNK en diferentes cánceres, indicando el uso potencial de inhibidores JNK en cáncer. Por ejemplo, JNK activado de manera constitutiva está asociado con la tumorigénesis mediada por HTLV- 1 [Oncógeno 13:135- 42 (1996)]. JNK puede jugar un papel en Sarcoma de Kaposi (KS). Otros efectos proliferativos de otras citoquinas implicadas en proliferación KS, tal como factor de crecimiento endotelial vascular (VEGF), IL- 6 y TNFoc, también pueden ser meadiados por JNK. Además, la regulación del gen c- jun en células transformadas p210 BCR- ABL corresponde con actividad de JNK, indicando un papel para inhibidores JNK en el tratamiento para leucemia mielógena crónica (CML) [Blood 92:2450- 60 (1998)].

Se cree que ciertas condiciones proliferativas anormales están asociadas con expresión de raf, y por lo tanto, se cree que responden a inhibición de expresión raf. Niveles anormalmente altos de expresión de la proteína raf también están implicados en transformación y proliferación de células anormales. También se cree que éstas condiciones proliferativas anormales responden a la inhibición la expresión de raf. Por ejemplo, se cree que la expresión de la proteína c- raf proteína juega un papel en proliferación de células anormales puesto que se ha reportado que 60% de todas las líneas celulares de carcinoma pulmonar expresan niveles inusualmente altos de ARNm y proteína c-raf. Ejemplos adicionales de condiciones proliferativas

anormales son trastornos hiperproliferativos tal como cánceres, tumores, hiperplasia, fibrosis pulmonar, angiogénesis, psoriasis, aterosclerosis y proliferación de células de músculo liso en los vasos sanguíneos, tal como estenosis o restenosis después de angioplastia. La ruta de señalización celular de la cual raf es una parte también se ha implicado en trastornos inflamatorios caracterizados por Proliferación de células T (activación y crecimiento de células T), tal como rechazo de injerto de tejidos, choque de endotóxina, y nefritis glomerular, por ejemplo.

Las proteinquinasas activadas por estrés (SAPKs) son una familia de proteinquinasas que representan el penúltimo paso en rutas de transducción de señales que resultan en activación del factor de transcripción c- jun y expresión de genes regulados por c- jun. En particular, c- jun está involucrada en la transcripción de genes que codifican proteínas involucradas en la reparación de ADN que está dañado debido a los ataques genotóxicos. Por lo tanto, los agentes que inhiben la actividad SAPK en una célula evitan la reparación de ADN y sintetizan la célula a agentes que inducen daño de ADN o inhiben síntesis de ADN e inducen apoptosis de una célula o que inhiben proliferación celular.

Las proteinquinasas activadas por mitógenos (MAPKs) son miembros de rutas de transducción de señales conservadas que activan factores de transcripción, factores de traducción y otras moléculas objetivo en respuesta a una variedad de señales extracelulares. Las MAPKs son activadas por fosforilación en un motivo de fosforilación dual con la secuencia Thr- X- Tyr por proteinquinasas activadas por mitógenos (MKKs). En eucariontes mayores, el papel fisiológico de Señalización MAPK ha sido correlacionado con eventos celulares tal como proliferación, oncogénesis, desarrollo y diferenciación. Por consiguiente, la capacidad para regular la transducción de señales vía estas rutas (particularmente vía MKK4 y MKK6) podría llevar al desarrollo de tratamientos y terapias preventivas para enfermedades humanas asociadas con señalización MAPK, tal como enfermedades inflamatorias, enfermedades autoinmunes y cáncer.

La familia de proteinquinasas humanas ribosomales S6 consta de al menos 8 miembros (RSK1, RSK2, RSK3, RSK4, MSK1, MSK2, p70S6K y p70S6 Kb). Las proteinquinasas ribosomales S6 juegan un papel importante en funciones pleotróficas, entre ellas un papel clave en la regulación de traducción de ARNm durante biosíntesis de proteínas (Eur. J. Biochem 2000 Noviembre; 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). La fosforilación de la proteína ribosomal S6 por p70S6 también se ha implicado en la regulación de motilidad celular (Inmunol. Cell Biol.

2000 August;78(4):447- 51) y crecimiento celular (Prog. Nucleic Acid Res. Mol. Biol., 2000;65:101- 27), y por lo tanto, puede ser importante en metástasis tumoral, la respuesta inmune y reparación de tejidos así como también otras condiciones patológicas.

Las SAPKs (también conocidas como "quinasas terminales jun N" o "JNKs") son una familia de proteinquinasas que representan el penúltimo paso en rutas de transducción de señales que resultan en activación del factor de transcripción c- jun y expresión de genes regulada por c- jun. En particular, c- jun está involucrada en la transcripción de genes que codifican proteínas involucradas en la reparación de ADN que es dañado debido a ataques genotóxicos. Los agentes que inhiben la actividad SAPK en una célula evitan reparación de ADN y sintetizan la célula a aquellas modalidades terapéuticas de cáncer que actúan al inducir daño de ADN.

BTK juega un papel en enfermedad autoinmune y/o inflamatoria tal como lupus eritematoso sistémico (SLE), artritis reumatoide, vasculitis múltiples, púrpura idiopática trombocitopénica (ITP), miastenia grave, y asma. Debido al papel de BTK en activación de células B, los inhibidores de BTK son útiles como inhibidores de actividad patogénica mediada por células B, tal como producción de anticuerpos, y son útiles para el tratamiento de linfoma y leucemia de células B.

CHK2 es un miembro de la familia de quinasas de punto de comprobación de proteinquinasas serina/treonina y está involucrada en un mecanismo utilizado para vigilancia de daño de ADN, tal como daño producido por mutágenos ambientales y especies reactivas de oxígeno endógeno. Como un resultado, está implicado como un supresor tumoral y blanco para terapia contra el cáncer.

CSK influye sobre el potencial metastático de células de cáncer, particularmente cáncer de colon.

Fes es una proteína tirosinquinasa no receptora que ha sido implicada en una variedad de rutas de transducción de señales de citoquinas, así como también diferenciación de células mieloides. Fes también es un componente clave de la maquinaria de diferenciación de granulocitos.

La actividad del receptor tirosinquinasa Flt3 está implicada en leucemias y síndrome mielodisplásico. En aproximadamente 25% de AML las células de leucemia expresan una forma constitutivamente activa de tirosin quinasa auto- fosforilada (p) FLT3 sobre la superficie celular. La actividad de p- FLT3 confiere ventaja de crecimiento y supervivencia sobre

las células leucémicas. Los pacientes con leucemia aguda, cuyas células de leucemia expresan actividad de la quinasa p- FLT3 actividad, tienen un resultado clínico general pobre. La inhibición de la actividad de la quinasa p- FLT3 induce apoptosis (muerte celular programada) de las células leucémicas.

Los inhibidores de IKKα y IKKβ (1 & 2) son terapéuticos para enfermedades las cuales incluyen artritis reumatoide, rechazo de trasplantes, enfermedad intestinal inflamatoria, osteoartritis, asma, enfermedad pulmonar obstructiva crónica, aterosclerosis, psoriasis, esclerosis múltiple, accidente cerebrovascular, lupus eritematoso sistémico, enfermedad de Alzheimer, isquemia cerebral, lesión cerebral traumática, enfermedad de Parkinson, esclerosis lateral amiotrófica, hemorragia subaracnoide u otras enfermedades o trastornos asociados con producción excesiva de mediadores inflamatorios en el cerebro y sistema nervioso central.

Met está asociada con la mayoría de tipos de los principales cánceres humanos y la expresión a menudo está correlacionada con prognosis pobre y metástasis. Los inhibidores de de Met son terapéuticos para enfermedades las cuales incluyen cánceres tal como cáncer pulmonar, NSCLC (cáncer pulmonar de células no pequeñas), cáncer óseo, cáncer pancreático, cáncer de piel, cáncer de cabeza y cuello, melanoma cutáneo o intraocular, cáncer uterino, cáncer ovárico, cáncer rectal, cáncer de la región anal, cáncer de estomago, cáncer de colon, cáncer de seno, tumores ginecológicos (ej., sarcomas uterinos, carcinoma de las trompas de Falopio, carcinoma del endometrio, carcinoma de la cerviz, carcinoma de la vagina o carcinoma de la vulva), Enfermedad de Hodkin, cáncer del esófago, cáncer del intestino delgado, cáncer del sistema endócrino (ej., cáncer de la tiroides, glándulas paratiroides o adrenales), sarcomas de tejidos suaves, cáncer de la uretra, cáncer del pene, cáncer de la próstata, leucemia crónica o aguda, tumores sólidos de la niñez, linfomas linfociticos, cáncer de la vejiga, cáncer del riñón o uretra (ej., carcinoma de células renales, carcinoma de la pelvis renal), malignidad pediátrica, neoplasmas del sistema nervioso central (ej., linfoma del sistema nervioso central primario, tumores del eje espinal, glioma de tallo cerebral o adenomas pituitarios), cánceres de la sangre tal como leucemia mieloide aguda, leucemia mieloide crónica, etc., esófago de Barret (síndrome pre-maligno), enfermedad cutánea neoplásica, psoriasis, micosis fungoides y hipertrofia prostática benigna, enfermedades relacionadas con diabetes tales como retinopatía diabética, isquemia retinal y neovascularilación retinal, cirrosis hepática, enfermedad cardiovascular tal como aterosclerosis, enfermedad inmunológica tal como enfermedad autoinmune y enfermedad renal.

Preferiblemente, la enfermedad es cáncer tal como leucemia mieloide aguda y cáncer colorectal.

La quinasa Nima relacionada 2 (Nek2) es una proteinquinasa regulada mediante el ciclo celular con actividad máxima al comienzo de la mitosis que se localiza al centrosoma. Los estudios funcionales han implicado Nek2 en regulación de separación de centrosoma y formación de husos. La proteína Nek2 es elevada de 2- a 5- veces en líneas celulares derivadas a partir de un rango de tumores humanos incluyendo aquellos tumores cervicales, ováricos, prostáticos, y particularmente de seno.

Enfermedades o condiciones mediadas por p70S6K incluyen, pero no están limitadas a, trastornos proliferativos, tales como cáncer y esclerosis tuberosa.

Según lo anterior, el presente invento además proporciona un método para evitar o tratar cualquiera de las enfermedades o trastornos descritos anteriormente en un sujeto en necesidad de tal tratamiento, tal método comprende administrar a dicho sujeto una cantidad terapéuticamente efectiva *(*Ver, *"Administración y Composiciones farmacéuticas ", infra)* de un compuesto de la Formula I o una sal farmacéuticamente aceptable de los mismos. Para cualquiera de los anteriores usos, la dosificación requerida variará dependiendo del modo de administración, la condición particular a ser tratada y el efecto deseado.

Administración y Composiciones farmacéuticas

En general, los compuestos del invento serán administrados en cantidades terapéuticamente efectivas vía cualquier de los modos usuales y aceptables conocidos en el estado de la técnica, bien sea de manera sencilla o 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 salud relativa del sujeto, la potencia del compuesto utilizado y otros factores. En general, se indican resultados satisfactorios para ser obtenidos de manera sistemática a dosis diarias de entre 0.03 y 2.5mg/kg aproximadamente por peso corporal. Una dosificación diaria indicada en el mamífero más grande, ej. humanos, está en el rango entre 0.5mg y 100mg, convenientemente administrada, ej. en dosis divididas hasta cuatro veces al día o en forma retardada. Las formas de dosificación unitaria apropiadas para administración oral comprenden de 1 a 50mg de ingrediente activo.

Los compuestos del invento se pueden administrar como composiciones farmacéuticas mediante cualquier ruta convencional, en particular de manera enteral, ej., oralmente, ej., en la

forma de tabletas o cápsulas, o de manera parenteral, ej., en la forma de soluciones inyectables o suspensiones, tópicamente, ej., en la forma de lociones, geles, ungüentos o cremas, o en una forma nasal o supositoria. Las composiciones farmacéuticas que comprenden un compuesto del presente invento en forma libre o en una forma de sal farmacéuticamente aceptable en asociación con al menos un portador o diluyente farmacéuticamente aceptable se pueden fabricar en una manera convencional mediante métodos de mezclado, granulación o recubrimiento. Por ejemplo, las composiciones orales pueden ser tabletas o cápsulas de gelatina que comprenden el ingrediente activo junto con a) diluyentes, ej., lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa y/o glicina; b) lubricantes, ej., sílice, talco, ácido esteárico, su sal de magnesio o calcio y/o glicol de polietileno; para tabletas también c) aglomerantes, ej., silicato de aluminio de magnesio, pasta de almidón, gelatina, tragacanto, metilcelulosa, carboximetilcelulosa de sodio y/o polivinilpirrolidona; si se desea d) desintegrantes, ej., almidones, agar, ácido algínico o su sal de sodio, o mezclas efervescentes; y/o e) absorbentes, colorantes, saborizantes y endulzantes. Las composiciones inyectables pueden ser soluciones o suspensiones isotónicas acuosas, y supositorios se pueden preparar a partir de emulsiones o suspensiones grasosas. Las composiciones pueden ser esterilizadas y/o contienen adjuvantes, tales como agentes preservativos, estabilizantes, humectantes o emulsificantes, promotores de solución, sales para regular la presión osmótica y/o amortiguadores. Además, también pueden contener otras sustancias terapéuticamente valiosas. Formulaciones adecuadas para aplicaciones transdermales incluyen un cantidad efectiva de un compuesto del presente invento con una portador. Un portador puede incluir solventes farmacéuticamente aceptables absorbibles para asistir paso a través de la piel del huésped. Por ejemplo, dispositivos transdermales son en la forma de una bandeja que comprende un miembro de fondo, un deposito que contiene el compuesto opcionalmente con portadores, opcionalmente una barrera controladora de tasa para suministrar el compuesto a la piel del huésped a una tasa controlada y predeterminada a lo largo de un periodo prolongado de tiempo , y maneras de asegurar el dispositivo a la piel. Formulaciones transversales de matriz también se pueden utilizar. Formulaciones adecuadas para aplicación tópica, ej., en piel y ojos, son preferiblemente soluciones acuosas, ungüentos, cremas o geles bien conocidos en el estado de la técnica. Estos pueden contener agentes solubilizan tés, estabilizantes, mejoradores de tonicidad, amortiguadores y preservativos.

Los compuestos del invento se pueden administrar en cantidades terapéuticamente efectivas

en combinación con uno o más agentes terapéuticos (combinaciones farmacéuticas). Por ejemplo, pueden ocurrir efectos sinergísticos con otras sustancias inmunomoduladoras o anti-inflamatorias, por ejemplo cuando se utilizan en combinación con ciclosporina, rapamicina, o ascomicina, o análogos inmunosupresivos de los mismos, por ejemplo ciclosporina A (CsA), ciclosporina G, FK- 506, rapamicina, o compuestos comparables, corticosteroides, ciclofosfamida, azatioprina, metotrexato, brequinar, leflunomida, mizoribina, ácido micofenólico, mofetilo de micofenolato, 15- desoxispergualina, anticuerpos inmunosupresivos, anticuerpos especialmente monoclonales para receptores de leucocitos , por ejemplo MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, CD58 o sus ligandos, u otros compuestos inmunomoduladores, tales como CTLA41g. Donde los compuestos del invento se administran en conjunción con otras terapias, dosificación de los compuestos co- administrados variaran naturalmente dependiendo del tipo de co- fármaco empleado, sobre el fármaco especifico empleado, sobre la condición en tratamiento y demás.

El invento también proporciona para una combinación farmacéutica, ej. un kit, que comprende) un primer agente el cual es un compuesto del invento como se divulga en la presente, en forma libre o en forma de sal farmacéuticamente aceptable, y b) al menos un co-agente. El kit puede comprender instrucciones para su administración.

Los términos "co- administración" o "administración combinada" o similares como se utilizan en la presente para incluir administración de los agentes terapéuticos seleccionados a un solo paciente, y están diseñados para incluir regímenes de tratamiento en los cuales los agentes no se administran necesariamente mediante la misma ruta de administración o al mismo tiempo.

El término "combinación farmacéutica" como se utiliza en la presente se refiere a un producto que resulta de mezclar o combinar más de un ingrediente activo e incluye ambas combinaciones fijas y no fijas de los ingredientes activos. El término "combinación fija" significa que el ingrediente activo, ej. un compuesto de la Formula I y un co- agente, son ambos administrados a un paciente simultáneamente en la forma de una sola entidad o dosificación. El término "combinación no fija " significa que los ingrediente activos, ej. un compuesto de la Formula I y un co- agente, son ambos administrados a un paciente como entidades separadas ya sea simultáneamente, concurrentemente o secuencialmente sin límites de tiempo específicos, en donde tal administración proporciona niveles terapéuticamente efectivos de los dos compuestos

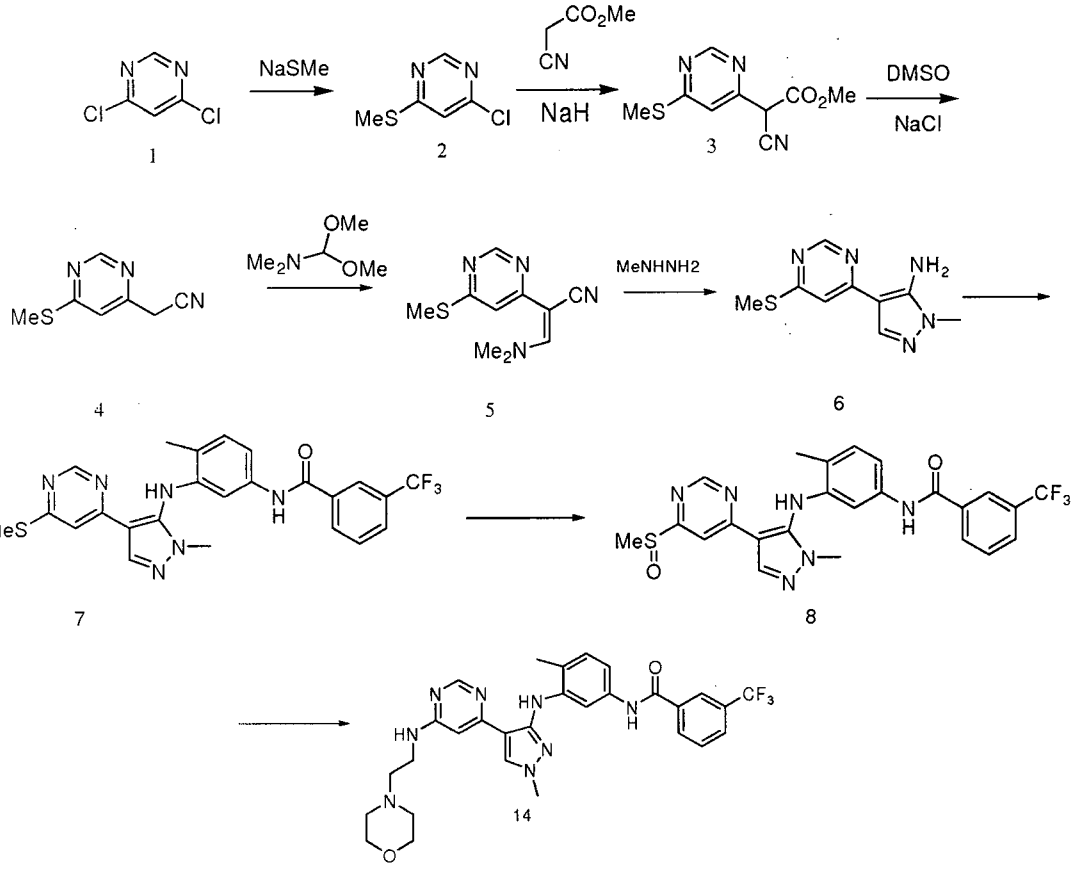
en el cuerpo del paciente. Esto último también aplica a terapia de coctel , ej. la administración de 3 o más ingredientes activos.

Procesos para Preparar los Compuestos del invento

El presente invento también incluye procesos para la preparación de compuestos del invento. En las reacciones descritas, puede ser necesario proteger los grupos funcionales reactivos, por ejemplo grupos hidroxilo, amino, imino, tiol o carboxilo, donde estos se desean en el producto final, para evitar su participación indeseada en las reacciones. Se pueden utilizar grupos protectores convencionales según la practica estándar, por ejemplo, ver T.W. Greene y P. G. M. Wuts en "Grupos Protectores en Química Orgánica ", John Wiley y Hijos, 1991.

Los compuestos de la Formula I se pueden preparar al proceder como en los Siguientes Esquemas de Reacciones I - V:

Esquema de Reacciones I

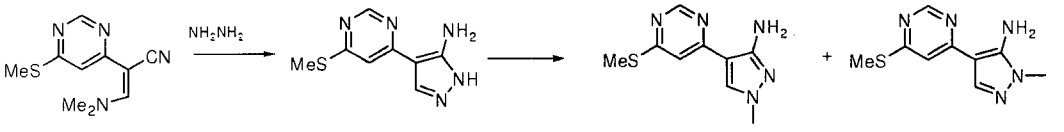


Un compuesto de la Formula 2 puede ser preparado al reaccionar un compuesto de

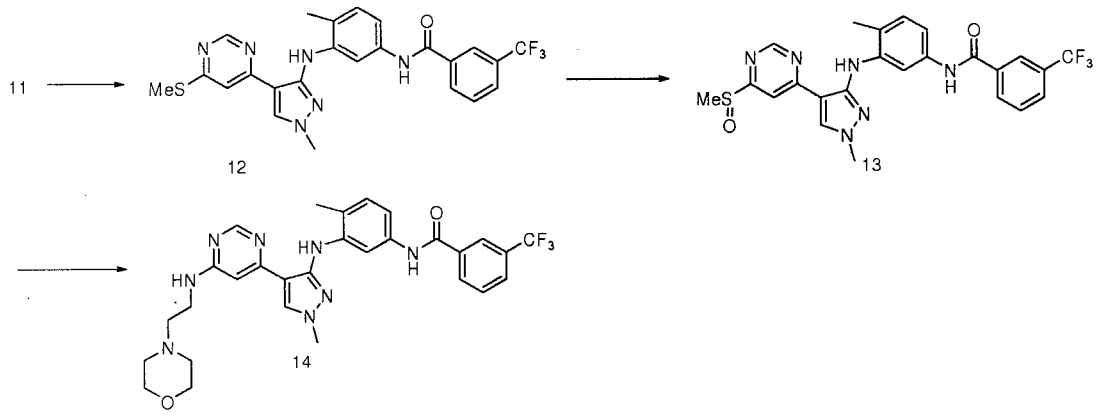
formula 1 con NaSMe en presencia de un solvente adecuado (ej., THF). Un compuesto de la Formula 3 puede ser preparado al reaccionar un compuesto de la Formula 2 e isocianato de metilo en presencia de un solvente (ej., DMSO, DMF y similares) utilizando una base apropiada (ej., hidruro de sodio (NaH)).

Un compuesto de la Formula 4 puede ser preparado mediante descarboxilación de un compuesto de la Formula 3 con NaCl en un solvente adecuado (ej., una mezcla de DMSO y agua) y en un rango de temperatura de entre 120 y 180°C aproximadamente puede tomar hasta 4 horas para terminar. Un compuesto de la Formula 4 puede ser convertido para proporcionar un compuesto de la Formula 5 con un reactivo adecuado de formación de eneamina (ej., dimetilacetal de N,N- dimetilformamida) y puede tomar hasta 24 horas para terminar. La reacción de la eneamina resultante 5 con una hidrazina apropiada rinde un compuesto de la Formula 6. Un compuesto de la Formula 7 puede ser preparado al reaccionar un compuesto de la Formula 6 con un haluro apropiado (ej., N- (3- bromo- 4- metil- fenil)- 3- trifluorometil- benzamida). La reacción avanza en presencia de un catalizador apropiado (ej., sal de Pd (II), o similares), un ligando apropiado (ej., Xantphos, o similares) y un solvente adecuado (ej., 1,4- dioxano, o similares), en un rango de temperatura entre 80 y 150°C aproximadamente y puede tomar hasta 20 horas aproximadamente para terminar. Un compuesto de la Formula 7 puede ser adicionalmente oxidado para proporcionar un compuesto de la Formula 8 con un agente oxidante apropiado (ej., ácido *m*- cloroperoxibenzóico (mCPBA), o similares) y puede tomar hasta 6 horas para terminar. Un compuesto de la Formula 9 puede ser preparado al reaccionar un compuesto de la Formula 8 con una amina o anilina apropiadas. La reacción es realizada en un rango de temperatura de 100- 150°C y puede tomar hasta 10 horas para terminar. Las condiciones de reacción para el desplazamiento de alquilamina involucra calentar un compuesto de la Formula 9 con 5- 10 equivalentes de amina en un solvente adecuado (ej. **DMSO, DMF,** o similares).

Esquema de Reacciones II



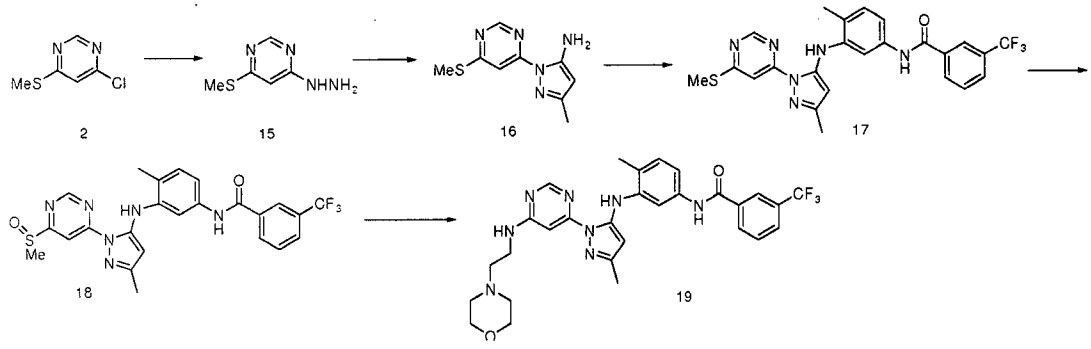
5 10 11 6



La reacción de la eneamina 5 con una hidrazina rinde un compuesto de fórmula 10. Un compuesto de la Formula 11 puede ser preparado al reaccionar un compuesto de la Formula 10 con reactivos alquilantes (ej., yoduro de metilo) en presencia de un solvente (ej., **DMSO, DMF** y similares) utilizando una base apropiada (ej., hidruro de sodio (NaH)).

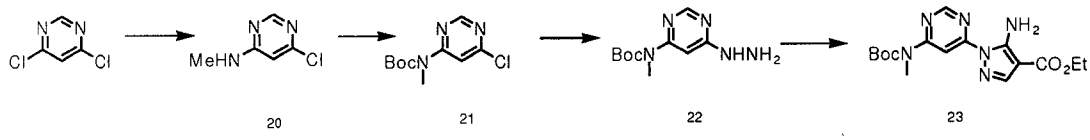
Un compuesto de la Formula 12 puede ser preparado al reaccionar un compuesto de formula 11 con un haluro apropiado (ej., N- (3- bromo- 4- metil- fenil)- 3- trifluorometil-benzamida). La reacción avanza en presencia de un catalizador apropiado (ej., sal de Pd (II), o similares), un ligando apropiado (ej., Xantphos, o similares) y un solvente adecuado (ej., 1,4-dioxano, o similares), en un rango de temperatura entre 80 y 150°C aproximadamente y puede tomar hasta sobre 20 horas para terminar. Un compuesto de la Formula 12 puede ser adicionalmente oxidado para proporcionar un compuesto de la Formula 13 con un agente oxidante apropiado (ej., ácido *m*- cloroperoxibenzóico (mCPBA), o similares) y puede tomar hasta 6 horas para terminar. Un compuesto de la Formula 14 puede ser preparado al reaccionar un compuesto de la Formula 13 con una amina o anilina apropiadas. La reacción es realizada en un rango de temperatura de 100- 150°C y puede tomar hasta 10 horas para terminar. La condiciones de reacción para desplazamiento de la alquilamina involucra calentar un compuesto de la Formula 13 con 5- 10 equivalentes de amina en un solvente adecuado (ej. **DMSO, DMF,** o similares).

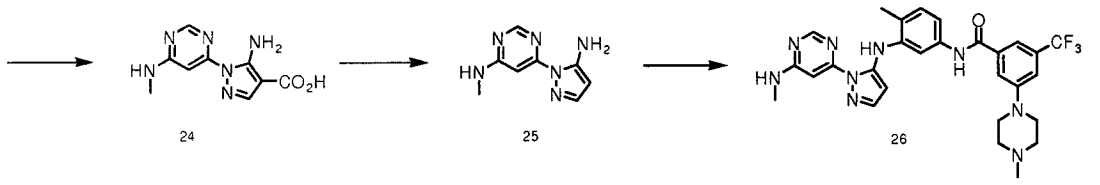
Esquema de Reacciones III



Un compuesto de la Formula 15 puede ser preparado al reaccionar un compuesto de formula 2 e hidrazina en presencia de un solvente (ej., etanol, DMSO, DMF y similares). La ciclización de un compuesto de la Formula 15 con un nitrilo apropiado (ej. 3-aminocrotononitrilo) rinde un compuesto de la Formula 16. Un compuesto de la Formula 17 puede ser preparado al reaccionar un compuesto de la Formula 16 con un haluro apropiado (ej., N- (3- brom$_{0-4}$- metil- fenil)- 3- trifluorometil- benzamida). La reacción avanza en presencia de una catalizador apropiado (ej., sal de Pd (II), o similares), un ligando apropiado (ej., Xantphos, o similares) y un solvente adecuado (ej., 1,4- dioxano, o similares), en un rango de temperatura entre 80 y 150°C aproximadamente y puede tomar hasta 20 horas aproximadamente para terminar. Un compuesto de la Formula 17 puede ser adicionalmente oxidado para proporcionar un compuesto de la Formula 18 con una agente oxidante apropiado (ej., ácido m-cloroperoxibenzóico (mCPBA), o similares) y puede tomar hasta 6 horas para terminar. Un compuesto de la Formula 19 puede ser preparado al reaccionar un compuesto de la Formula 18 con una amina o anilina apropiadas. La reacción es realizada en un rango de temperatura de 100-150°C y puede tomar hasta 10 horas para terminar. La condiciones de reacción para desplazamiento de la alquilamina involucran calentar un compuesto de la Formula 18 con 5- 10 equivalentes de amina en un solvente adecuado (ej. DMSO, DMF, o similares).

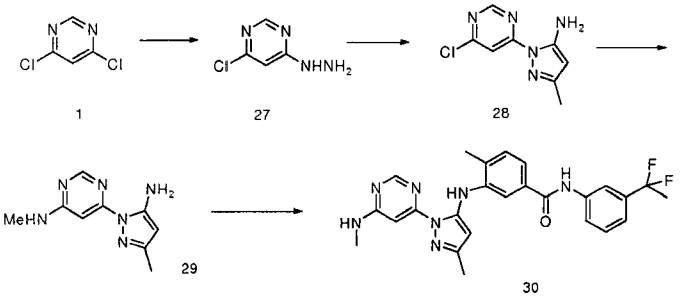
Esquema de Reacciones IV





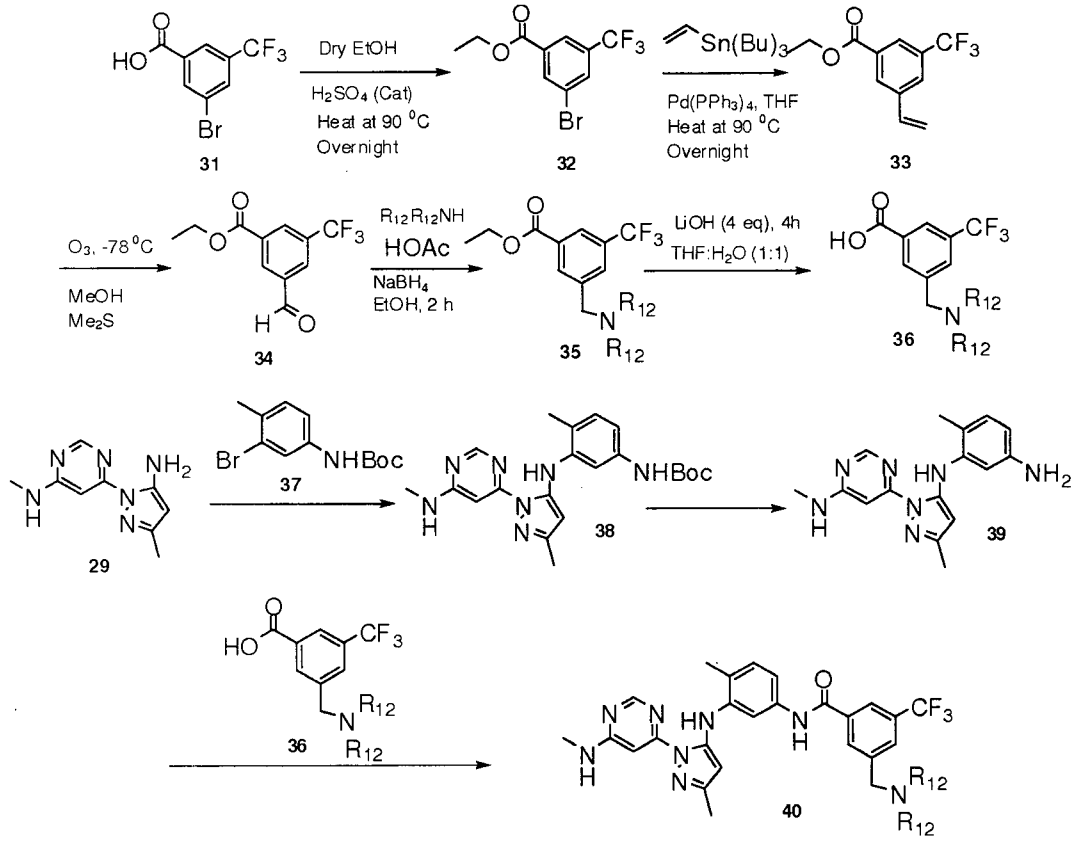
Un compuesto de la Formula 20 puede ser preparado al reaccionar 4,6- dicloro pirimidina con una amina apropiada (ej. metilamina) en presencia de un solvente adecuado (ej., etanol, THF y similares). Un compuesto de la Formula 21 puede ser preparado al reaccionar un compuesto de la Formula 20 y BOC2O en presencia de un solvente (ej., THF, DCM y similares) utilizando una base apropiada (ej., DMAP). Un compuesto de la Formula 22 puede ser preparado al reaccionar un compuesto de la Formula 21 e hidrazina en presencia de un solvente (ej., etanol, THF, DMF y similares). La ciclización de un compuesto de la Formula 22 con un nitrilo apropiado (ej. etil(etoximetileno) cianoacetato) rinde un compuesto de la Formula 23. La ciclización de un compuesto de la Formula 22 con un nitrilo apropiado (ej. etil(etoximetileno) cianoacetato) rinde un compuesto de la Formula 23. La hidrolisis del compuesto de la Formula 23 con una base apropiada (ej. NaOH) rinde un compuesto de la Formula 24. Un compuesto de la Formula 25 puede ser preparado mediante descarboxilación de un compuesto de la Formula 24 en un rango de temperatura entre 150 y 180°C aproximadamente puede tomar hasta 4 horas para terminar. Un compuesto de la Formula 26 puede ser preparado al reaccionar un compuesto de la Formula 25 con un haluro apropiado (ej., N- (3- brom$_{0-4}$- metil- fenil)- 3- (4- metil- piperazin- l- il)- 5- trifluorometil- benzamida). La reacción avanza en presencia de una catalizador apropiado (ej., Sal Pd (II), o similares), un ligando apropiado (ej., Xantphos, o similares) y un solvente adecuado (ej., 1,4- dioxano, o similares), en un rango de temperatura entre 80 y 150°C aproximadamente y puede tomar hasta sobre 20 horas para terminar.

Esquema de Reacciones V



Un compuesto de la Formula 27 puede ser preparado al reaccionar un compuesto de formula 1 e hidrazina en presencia de un solvente (ej., etanol, DMSO, DMF y similares). La ciclización de un compuesto de la Formula 27 con un nitrilo apropiado (ej. 3-aminocrotononitrilo) rinde un compuesto de la Formula 28. Un compuesto de la Formula 29 puede ser preparado al reaccionar un compuesto de la Formula 28 con una amina apropiada. La reacción es realizada en un rango de temperatura de 50- 100°C y puede tomar hasta 10 horas para terminar. Un compuesto de la Formula 30 puede ser preparado al reaccionar un compuesto de la Formula 29 con un haluro apropiado (ej., N- [3- (1,1- difluoro- etil)- fenil]- 3- yodo- 4- metil-benzamida). La reacción avanza en presencia de una catalizador apropiado (ej., Sal Pd (II), o similares), un ligando apropiado (ej., Xantphos, o similares) y un solvente adecuado (ej., 1,4-dioxano, o similares), en un rango de temperatura entre 80 y 150°C aproximadamente y puede tomar hasta 20 horas aproximadamente para terminar.

Esquema de Reacciones VI



En la cual R_{12} es como se define en el Resumen del invento. Un compuesto

de la Formula 33 puede ser preparado al reaccionar un compuesto de la Formula 32 y trialquil(vinilo) estannano en presencia de una catalizador apropiado (ej., complejo Pd(O) o Sal Pd (II), o similares), un fosfor- ligando apropiado (o similares), y un solvente (ej., 1,4- dioxano, THF o similares). La escisión del grupo vinilo utilizando condiciones bien conocidas en los campos (Ozonolisis, $OsO_4/NaIO_4$, o similares) proporciona el compuesto de la Formula 34. La aminación reductiva utilizando aminas primarias o secundarias en presencia de un reactivo reductor ($NaBH_4$, $Na(OAc)_3BH$, $Na(CN)\ bH_3$, o similares) y solvente apropiado (etanol, 1,2-dicloroetano, DMF, o similares) rinde el compuesto de la Formula 35. La saponificación del compuesto de la Formula 35 luego proporciona el ácido carboxílico de la Formula 36. La reacción del compuesto de la Formula 29 con el compuesto de la Formula 37 en presencia de un catalizador apropiado (ej., Sal Pd (II), o similares), un ligando apropiado (ej., Xantphos, o similares) y un solvente adecuado (ej., 1,4- dioxano, o similares), en un rango de temperatura entre 80 y 150°C aproximadamente, proporciona el compuesto de la Formula 38. La desprotección del grupo Boc bajo condiciones ácidas tal como ácido trifluoroacético /DCM rinde el compuesto de la Formula 39. La formación de enlaces de amina entre ácido carboxílico de la Formula 36 y la amina de la Formula 39 bajo las condiciones de reacción de acoplamiento de péptidos estándares (HATU/DIEA, EDCI/HOBT, o similares) rinde el compuesto de la Formula 40.

Un ejemplo detallado de la síntesis de un compuesto de la Formula I puede ser encontrado en los Ejemplos, *infra.*

Procesos Adicionales para Preparar los Compuestos del Invento

Un compuesto del invento se puede preparar como una sal de adición ácida farmacéuticamente aceptable al reaccionar la forma alcalina libre del compuesto con un ácido orgánico o inorgánico farmacéuticamente aceptable. Alternativamente, una sal de adición alcalina farmacéuticamente aceptable de un compuesto del invento se puede preparar al reaccionar la forma ácida libre del compuesto con una base orgánica o inorgánica farmacéuticamente aceptable. Alternativamente, las formas de sal de los compuestos del invento se pueden preparar utilizando sales de los materiales de inicio o intermedios.

Las formas ácidas o alcalinas libres de los compuestos del invento se pueden preparar a partir de formas de sal de adición alcalina o sal de adición ácida correspondientes,

respectivamente. Por ejemplo un compuesto del invento en una forma de sal de adición ácida se puede convertir en la base libre correspondiente al tratar con una base apropiada (ej., solución de hidróxido de amonio, hidróxido de sodio, y similares). Un compuesto del invento en una forma de sal de adición alcalina se puede convertir en el ácido libre correspondiente al tratar con un ácido apropiado (ej., ácido clorhídrico, etc.).

Los compuestos del invento en forma no oxidada se pueden preparar a partir de N-óxidos de compuestos del invento al tratar con un agente reductor (ej., azufre, dióxido de azufre, trifenilfosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fósforo, tribromuro, o similares) en un solvente orgánico inerte adecuado (ej. acetonitrilo, etanol, dioxano acuoso, o similares) a entre 0 y 80°C.

Derivados de profármacos de los compuestos del invento se pueden preparar mediante métodos conocidos por aquellos con experiencia común en el estado de la técnica (ej., para detalles adicionales ver Saulnier et al., (1994), Bioorganic y Medicinal Chemistry Letters, Vol. 4, p. 1985). Por ejemplo, se pueden preparar profármacos apropiados al reaccionar un compuesto no derivado del invento con un agente carbamilante apropiado (ej., 1,1-aciloxialquilcarbanocloridato, carbonato de para- nitrofenilo, o similares).

Los derivados protegidos de los compuestos del invento se pueden preparar mediante medios conocidos por aquellos con experiencia común en el estado de la técnica. Una descripción detallada de las técnicas aplicables a la creación de grupos protectores y su retiro se puede encontrar en T. W. Greene, "Grupos protectores en Química Orgánica", 3ra edición, John Wiley e Hijos, Inc., 1999.

Los compuestos del presente invento se pueden preparar de manera conveniente, o formar durante el proceso del invento, como solvatos (ej., hidratos). Hidratos de compuestos del presente invento se pueden preparar de manera conveniente mediante recristalización a partir de una mezcla solvente acuosa/orgánica, utilizando solventes orgánicos tal como dioxin, tetrahidrofurano o metanol.

Los compuestos del invento se pueden preparar como sus estereoisómeros individuales al reaccionar una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diastereoisómericos, separando los diastereómeros y recuperando los enantiomeros ópticamente puros. Mientras resolución de los enantiomeros se puede realizar utilizando derivados diastereoméricos covalentes de los compuestos del invento, se

prefieren complejos disociables (ej., sales diastereoméricas cristalinas). Los diastereómeros tienen diferentes propiedades físicas (ej., puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.) y se pueden separar de manera fácil al tomar ventaja de estas diferencias. Los diastereómeros se pueden separar mediante cromatografía, o preferiblemente, mediante técnicas de separación/resolución técnicas con base en diferencias en solubilidad. Luego el enantiómero ópticamente puro es recuperado, junto con el agente de resolución, mediante cualquier medio práctico que no resultara en racemización. Una descripción más detallada de las técnicas aplicables a la resolución de estereoisómeros de compuestos a partir de su mezcla racémica se puede encontrar en Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomeros, Racematos y Resoluciones", John Wiley e Hijos, Inc., 1981.

En resumen, los compuestos de la Formula I se pueden preparar mediante un proceso, el cual involucra:

(a) aquellos de los Esquemas de Reacción I a V, y

(b) Opcionalmente convertir un compuesto del invento en una sal farmacéuticamente aceptable;

(c) opcionalmente convertir una forma de sal de un compuesto del invento en una forma no de sal;

(d) opcionalmente convertir un forma no oxidada de un compuesto del invento en un N- óxido farmacéuticamente aceptable;

(e) opcionalmente convertir una Forma de N- óxido de un compuesto del invento a su forma no oxidada;

(f) opcionalmente resolver un isómero individual de un compuesto del invento a partir de una mezcla de isómeros;

(g) opcionalmente convertir un compuesto no derivado del invento en un derivado de profármaco farmacéuticamente aceptable; y

(h) opcionalmente convertir un derivado de profármaco de un compuesto del invento a su forma no derivada.

Puesto que la producción de materiales de inicio no es particularmente descrita, los compuestos son conocidos o se pueden preparar análogamente a métodos conocidos en el estado de la técnica o como se divulga en los Ejemplos a continuación.

Alguien con experiencia en el estado de la técnica apreciará que las anteriores transformaciones son solamente representativas de métodos para la preparación de los

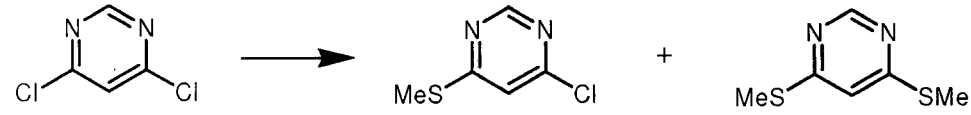
compuestos del presente invento, y que otros métodos bien conocidos se pueden utilizar de manera similar.

Ejemplos

El presente invento es ejemplificado adicionalmente, pero no está limitado, por los siguientes ejemplos que ilustran la preparación de compuestos de la Formula I según el invento.

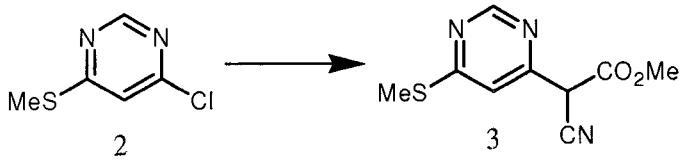
Ejemplo 1

N- (4- Metil- 3- {2- metil- 4- r6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida



1 2

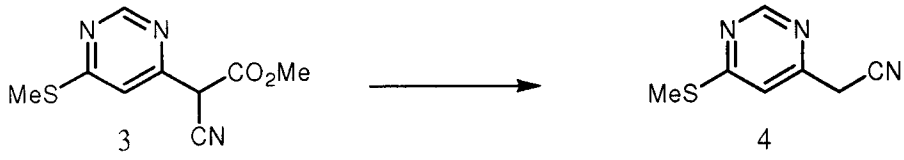
Una mezcla de 4,6- dicloro- pirimidina 1 (20.93 g, 140 mmol), tiometóxido de sodio (10.34 g, 147 mmol) en THF (100 mL) es agitada a temperatura ambiente, durante la noche. La mezcla de reacción es concentrada. El residuo es particionado entre acetato de etilo y salmuera. La capa orgánica es separada y lavada con salmuera, secada sobre Na_2SO_4. El producto crudo es purificado mediante recristalización a partir de hexanos (60 mL) para proporcionar 4- cloro- 6- metilsulfanil- pirimidina. El agua madre es concentrada y el residuo es purificado mediante cromatografía flash de gel de sílice eluyendo con acetato de etilo en hexanos de 0% a 10% para proporcionar 4- cloro- 6- metilsulfanil- pirimidina que contiene y una pequeña cantidad de subproducto 4,6- bis metiltio- pirimidina, el cual es fácilmente retirado en el próximo paso. ^1H NMR 400 MHz (CDC_{13}) 5 8.72 (5, 1H), 7.21 (5, 1H), 2.58 (s, 3H).



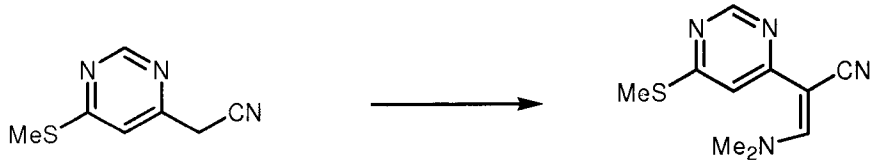
2 3

A la suspensión de NaH (2.19 g, 55 mmol, 60% en aceite) en DMSO (20 mL) se agrega isocianato de metilo (4.88 mL, 51 mmol) a 23°C (enfriado por agua helada si es necesario). Después que la evolución de hidrógeno ha terminado, se agrega 4- cloro- 6- metilsulfanil- pirimidina (3.56 g, 22 mmol). La reacción es calentada a 80°C durante 5 horas.

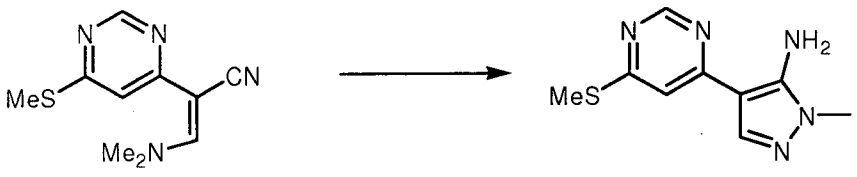
Luego la mezcla de reacción es enfriada a temperatura ambiente y apagada con NH_4Cl saturado enfriado con hielo (50 mL). El sólido es filtrado y lavado con agua. Se agrega 100 mL de hexanos al sólido y se calienta a 60°C durante 1 hora y luego se enfría a temperatura ambiente. El sólido es filtrado y lavado con hexanos para proporcionar éster metílico del ácido ciano- (6- metilsulfanil- pirimidin- 4- il)- acético. ^{1}H NMR 400 MHz (J6- DMSO) 5 8.42 *(d,* 1H), 6.64 (5, 1H), 3.71 (5, 3H), 2.55 (5, 3H). MS *m/z* 224.10 (M + 1).



Un tubito Smith (10- 20 mL) es cargado con éster metílico del ácido ciano- (6- metilsulfanil- pirimidin- 4- il)- acético (0.83 g, 3.72 mmol), NaCl (1.0 g), agua (1 mL) y DMSO. El tubito es sellado e irradiado a 160°C durante 50 minutos en un Sintetizador Smith. La mezcla de reacción es particionada entre acetato de etilo y salmuera, y luego se filtró a través de una almohadilla de Celite y lavó con acetato de etilo. La capa orgánica es separada y lavada con salmuera, secada sobre $Na2SO_4$, filtrada y concentrada. El producto crudo es purificado mediante cromatografía flash de gel de sílice eluyendo con acetato de etilo en hexanos de 10% a 100% para proporcionar (6- metilsulfanil- pirimidin- 4- il)- acetonitrilo: ^{1}H NMR 400 MHz (CDC_{13}) 5 8.93 (s, 1H), 7.47 (5, 1H), 4.20 (5, 2H), 2.56 (s, 3H); MS *m/z* 166.00 (M + 1).

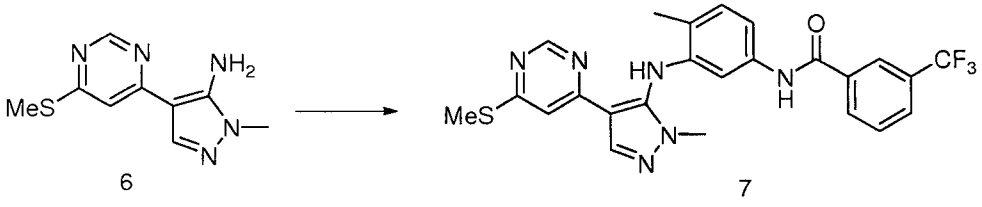


Se agrega tert- butoxi- bis (dimetilamino) metano (0.60 mL, 2.9 mmol.) a una mezcla de (6- metilsulfanil- pirimidin- 4- il)- acetonitrilo (0.397 g, 2.4 mmol) en DMF (10 mL) a 0°C. Después de 2 horas, la mezcla de reacción es concentrada, y el residuo se utiliza para la siguiente reacción sin purificación adicional.



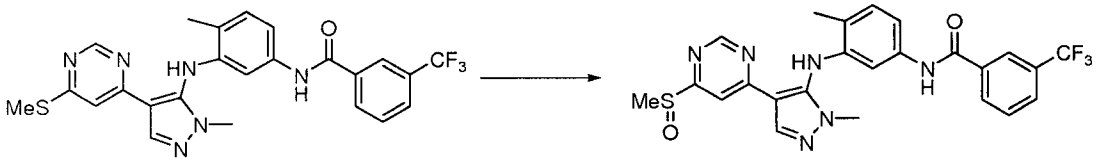
5 6

Una mezcla de crudo 5 e hidrazina de metilo (0.414 mL, 8.53 mmol) en etanol (15 ml) es calentada a 80°C durante 16 horas. La mezcla de reacción es enfriada a temperatura ambiente y concentrada. La mezcla de reacción es particionada entre acetato de etilo y salmuera. La capa orgánica es separada y lavada con salmuera, secada sobre Na_2SO_4, filtrada y concentrada. El producto crudo es purificado mediante cromatografía flash de gel de sílice eluyendo con acetato de etilo en hexanos desde 10% a 100% para proporcionar 2- metil- 4- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamina: ^{1}H NMR 400 MHz (J6- DMSO) 5 8.70 *(s,* 1H), 7.93 *(s,* 1H), 7.43 *(s,* 1H), 6.69 *(s, br* 2H), 3.57 (5, 3H), 2.53 *(s,* 3H); MS *m/z* 222.00 (M + 1).



6 7

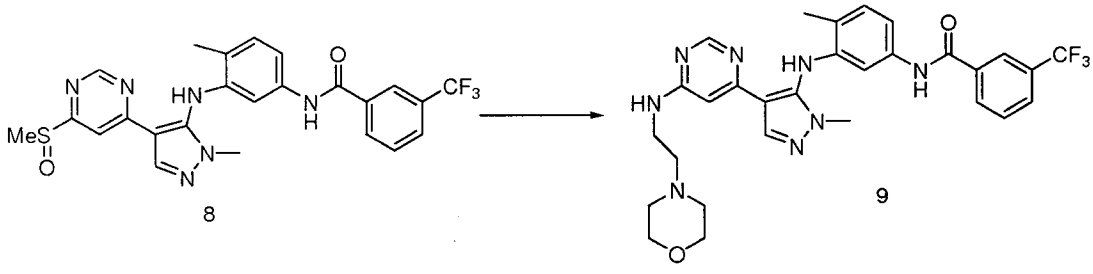
2- Metil- 4- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamina (120mg, 0.54mmol) es mezclada con N- (3- Bromo- 4- metil- fenil)- 3- trifluorometil- benzamida (290mg, 0.81mmol), acetato de paladio (25mg, 0.1 mmol), Xantphos (100 mg, 0.17mmol) y carbonato de cesio (530mg, 1.63mmol). Se agregó 10 mL de 1,4- dioxano anhidro bajo un ambiente de nitrógeno y la mezcla es sometida a irradiación de microondas hasta 150°C durante 1 hora. Luego la mezcla de reacción es enfriada a temperatura ambiente, tratada con 100 mL de THF, pasada a través de una columna de celite y concentrada. El producto crudo es purificado mediante Cromatografía ISCO eluyendo con acetato de etilo en hexanos desde 10% a 100% para proporcionar N- {4- Metil- 3- [2- metil- 4- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida: MS *m/z* 499.1 (M + 1).



7 8

Una suspensión de N- {4- Metil- 3- [2- metil- 4- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida (175mg, 0.35 mmol) en 40mL CH_2Cl_2 es tratada con ácido 3- cloloroperoxibenzóico (77% max, 150mg, 0.67mmol, 1.9eq) a 0°C. La mezcla de reacción es dejada calentar a temperatura ambiente con agitación durante 3 horas. Después que la oxidación está completa, la mezcla de reacción es apagada con solución de tiosulfato de sodio saturado 15mL y agitada vigorosamente durante 30 minutos, luego tratada con

100mL de diclorometano. La mezcla de reacción es particionada entre diclorometano y la capa acuosa. La capa orgánica es lavada con solución de $NaHCO_3$ saturado, agua, y salmuera secuencialmente, luego secada sobre $Na2SO_4$, concentrada para proporcionar N- {3- [4- (6- Metanosulfinil- pirimidin- 4- il)- 2- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida como sólido amarillo. El producto crudo se utiliza directamente en el próximo paso: MS *m/z* 515.1 (M + 1).

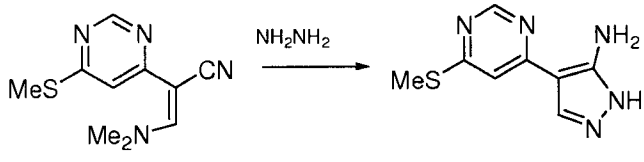


8 9

La mezcla de N- {3- [4- (6- Metanosulfinil- pirimidin- 4- il)- 2- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida (40mg, 0.078mmol) y 2- Morfolin- 4- il- etilamina (100 uL) en 2- propanol es calentada a 80 °C durante 3 horas. La mezcla de reacción es enfriada a temperatura ambiente y concentrada. Luego el producto crudo es tratado con 1mL de DMSO y purificado mediante LC/MS para proporcionar N- (4- Metil- 3- {2- metil- 4- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida.

Ejemplo 2

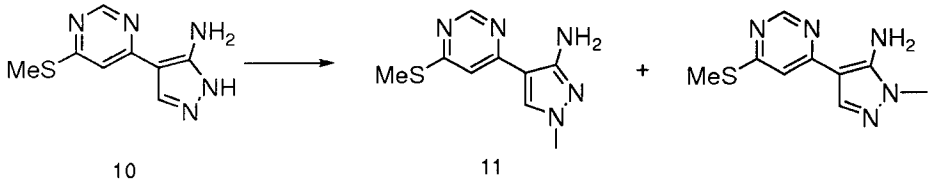
N- (4- Metil- 3- {1- metil- 4- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 1H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida



5 10

Se agrega tert- butoxibis(dimetilamino) metano (0.665 mL, 3.22 mmol.) a una mezcla de (6- metilsulfanil- pirimidin- 4- il)- acetonitrilo (0.484 g, 2.93 mmol) en DMF (10 mL) 0°C. Después de 2 horas, la mezcla de reacción es concentrada, y el residuo se utiliza para la siguiente reacción sin más purificación.

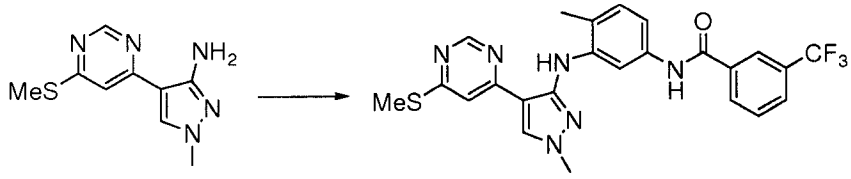
Una mezcla de la mezcla cruda anterior y monohidrato de hidrazina (0.426 mL, 8.78 mmol) en etanol (15 ml) es calentada a 80°C durante 3 horas. La mezcla de reacción es enfriada a temperatura ambiente y concentrada. La mezcla de reacción es particionada entre acetato de etilo y salmuera. La capa orgánica es separada y lavada con salmuera, secada sobre Na2SO4, filtrada y concentrada. El producto crudo es purificado mediante cromatografía flash de gel de sílice eluyendo con acetato de etilo en hexanos desde 10% a 100% para proporcionar 2- metil- 4- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamina: ^{1}H NMR 400 MHz (J6-DMSO) δ 8.70 (s, 1H), 7.92 *(bs,* 1H), 7.44 *(bs,* 1H), 6.45 *(bs,* 2H), 5.78 *(bs,* 1H), 2.53 (s, 3H); MS *m/z* 208.06 (M + 1).



10 11

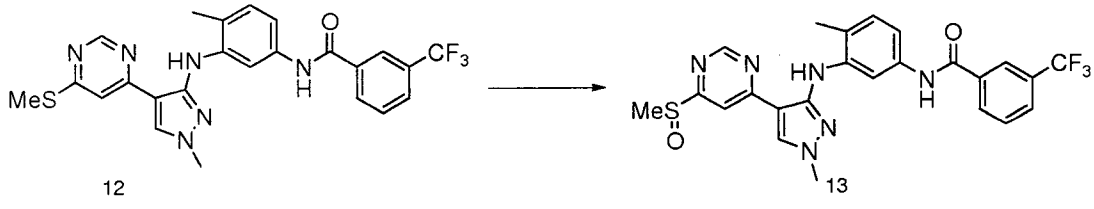
A la solución de 4- (6- Metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamina (245mg, 1.18 mmol) se agrega con solución de NaOMe (25 % por peso en MeOH, 425 μL, 1.53 mmol) por goteo. La mezcla de reacción es mantenida en agitación durante 30 minutos. Luego se agrega yodometano (110uL, 1.76 mmol) en la mezcla de reacción por goteo. Después de agitar durante la noche a temperatura ambiente, la mezcla de reacción es concentrada, tratada con 75 mL de acetato de etilo, y lavada con agua. La filtración retira el sólido sin disolver. El filtrado obtenido es separado, y la capa orgánica recolectada es secada sobre sulfato de sodio, y

concentrada. El producto crudo es purificado mediante cromatografía ISCO eluyendo con acetato de etilo en hexanos desde 25% a 100% para proporcionar l- Metil- 4- (6- metilsulfanil- pirimidin- 4- il)- lH- pirazol- 3- ilamina: ^{1}H NMR 400 MHz (J6- DMSO) δ 8.73 *(s,* 1H), 8.27 (5, 1H), 7.44 (5, 1H), 5.81 (5, 1H), 3.65 *(s,* 3H), 2.53 *(s,* 3H); MS *m/z* 222.07 (M + 1).



11 12

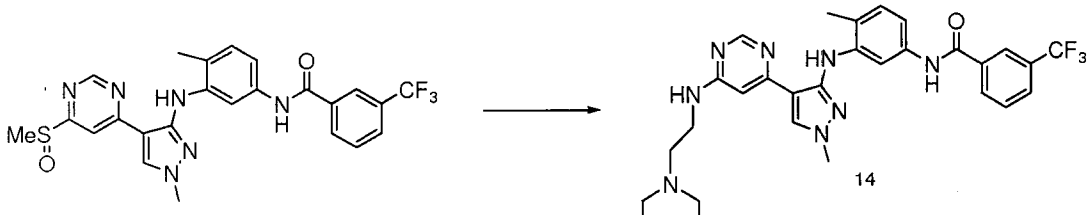
Metil- 4- (6- metilsulfanil- pirimidin- 4- il)- lH- pirazol- 3- ilamina (61mg, 0.27mmol) es mezclada con N- (3- Bromo- 4- metil- fenil)- 3- trifluorometil- benzamida (161mg, 0.45mmol), acetato de paladio (20mg, 0.089mmol), Xantphos (78mg, 0.135mmol) y carbonato de cesio (280mg, 0.86mmol). Se agrega 2 mL 1,4- dioxano anhidro bajo ambiente de nitrógeno y la mezcla es sometida a irradiación de microondas a 150°C durante 45 minutos. Luego la mezcla de reacción es enfriada a temperatura ambiente, tratada con 100 mL de THF, pasada a través de una columna de celite y concentrada. El producto crudo es purificado mediante cromatografía ISCO eluyendo con acetato de etilo en hexanos desde 10% a 100% para proporcionar N- {4- Metil- 3- [l- metil- 4- (6- metilsulfanil- pirimidin- 4- il)- lH- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida.



12 13

La suspensión de N- {4- Metil- 3- [l- metil- 4- (6- metilsulfanil- pirimidin- 4- il)- lH- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida ($_{12}$8mg, 0.26 mmol) en 25 mL CH_2Cl_2 es tratada con ácido 3- cloloroperoxibenzóico (77% max, 86mg, 0.38mmol) a 0 °C. La mezcla de reacción es dejada calentar a temperatura ambiente y mantenida en agitación durante 3 horas. Después que la oxidación está completa, la mezcla de reacción es apagada con solución de tiosulfato de sodio saturado 10 mL y agitada vigorosamente durante 30 minutos, luego tratada con 75 mL de diclorometano. La mezcla de reacción es particionada entre diclorometano y capa acuosa. La capa orgánica es lavada con solución de $NaHCO_3$ saturado,

agua, y salmuera secuencialmente, luego secada sobre Na_2SO_4, concentrada para proporcionar N- {3- [4- (6- Metanosulfinil- pirimidin- 4- il)- l- metil- lH- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida como sólido amarillo. El producto crudo es directamente utilizado en el próximo paso.

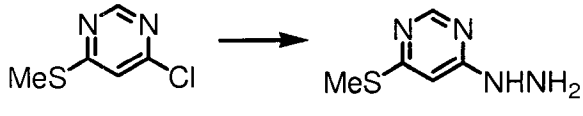


13 14

La mezcla de N- {3- [4- (6- Metanosulfinil- pirimidin- 4- il)- l- metil- lH- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida (30mg, 0.058 mmol) y 2- Morfolin- 4- il- etilamina (100 uL) en 2- propanol es calentada a 80 °C para 3 horas. La mezcla de reacción es enfriada a temperatura ambiente y condensada. Luego el producto crudo es tratado con 1 mL DMSO y purificado mediante LC/MS para proporcionar N- (4- Metil- 3- { l- metil- 4- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida.

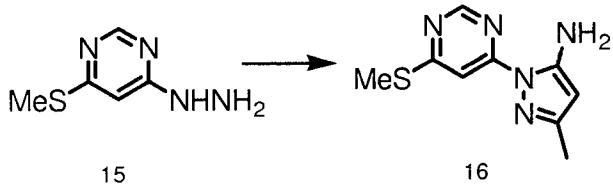
Ejemplo 3

N- (4- Metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino - fenil)- 3- trifluorometil- benzamida



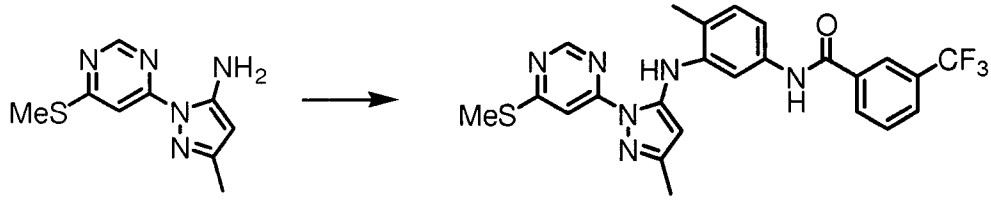
2 15

Una mezcla de 4- Cloro- 6- metilsulfanil- pirimidina (1,1g, 6.85mmol), monohidrato de hidrazina (1.2g, 23.5mmol), y 2- propanol (10 mL) es calentada a 90 °C durante 4 horas. Luego la mezcla de reacción es enfriada a temperatura ambiente, concentrada, triturada con agua, y filtrada. El sólido sin disolver es lavado con agua, secado con aire para proporcionar (6- Metilsulfanil- pirimidin- 4- il)- hidrazina como sólido amarillo claro: ^{1}H NMR 400 MHz *(d6-* DMSO) δ 8.29 (s, 1H), 8.16 (s, 1H), 6.55 (s, 1H), 4.34 (s, 2H), 2.43 (s, 3H); MS *m/z* 157.05 (M+l).

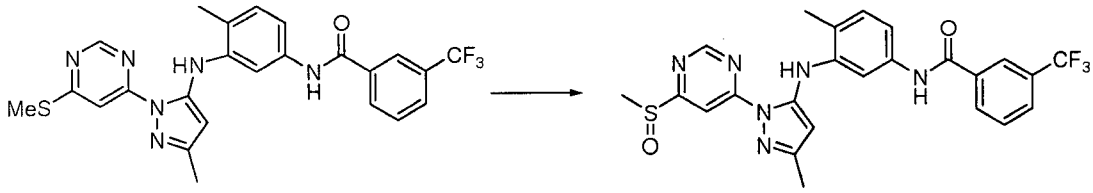


15 16

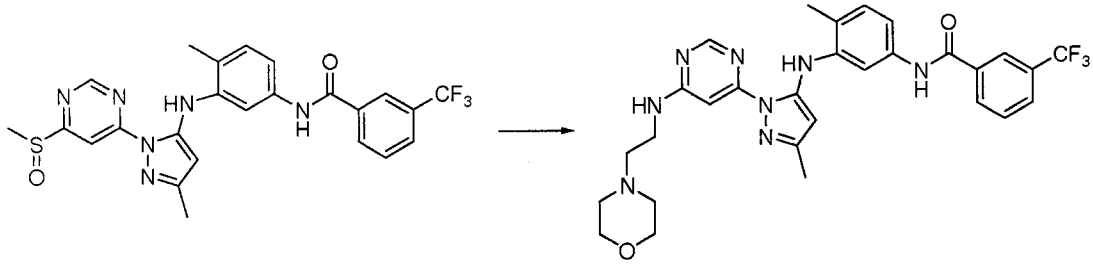
La mezcla de (6- Metilsulfanil- pirimidin- 4- il)- hidrazina (1.0g, 6.4 mmol), 3- imino-butironitrilo (1,1g, 12.8 mmol), y etanol (30mL) es calentada a 85°C durante la noche. Luego la mezcla de reacción es enfriada a temperatura ambiente, condensada, y tratada con 75mL de acetato de etilo. La mezcla de reacción es particionada entre acetato de etilo y capa acuosa. La capa orgánica es secada sobre Na_2SO_4 y concentrada. El producto crudo es purificado mediante cromatografía ISCO eluyendo con acetato de etilo en hexanos desde 10% a 80% para proporcionar 5- Metil- 2- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamina: ^{1}H NMR 400 MHz (J6- DMSO) 5 8.72 (5, 1H), 7.53 *(s,* 1H), 6.90 *(s,* 1H), 5.26 *(s,* 1H), 2.57(s, 3H), 2.08(5, 3H); MS *m/z* 222.07 (M + 1).



5- Metil- 2- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamina (90mg, 0.40mmol) es mezclada con N- (3- $Brom_{0-4}$- metil- fenil)- 3- trifluorometil- benzamida (228mg, 0.64mmol), acetato de paladio (20mg, 0.089mmol), Xantphos (75mg, 0.13mmol) y carbonato de cesio (420mg, 1.28mmol). Se agregó 4 mL de 1,4- dioxano anhidro bajo un ambiente de nitrógeno y la mezcla es sometida a irradiación de microondas a 150°C durante 30 minutos. Luego la mezcla de reacción es enfriada a temperatura ambiente, tratada con 100 mL de THF, pasada a través de una columna de celite y concentrada. El producto crudo es purificado mediante cromatografía ISCO eluyendo con acetato de etilo en hexanos desde 0% a 40% para proporcionar N- {4- Metil- 3- [5- metil- 2- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida: ^{1}H NMR 400 MHz (J6- DMSO) δ 10.65 *(s,* 1H), 10.46 (5, 1H), 8.89 *(s,* 1H), 8.30- 8.25 *(m,* 2H), 7.98 *(d, J*= 7.5 Hz, 1H), 7.89 *(s,* 1H), 7.80 *(t, J* = 7.5 Hz, 1H), 7.67 (5, 1H), 7.40 *(d, J* = 7.5 Hz, 1H), 7.25 *(d, J*= 8.2 Hz, 1H), $6._{12}$ (5, 1H), 2.61 (5, 3H), 2.34 (5, 3H), 2.25 (s, 3H); MS *m/z* 499.14 (M + 1).



La suspensión de N- {4- Metil- 3- [5- metil- 2- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida (240mg, 0.48mmol) en 25 mL CH_2Cl_2 es tratada con ácido 3- clororoperoxibenzóico (77% max, 162mg, 0.72mmol, 1.5 eq) a 0°C. La mezcla de reacción es dejada calentar a temperatura ambiente con agitación durante 3 horas. Después que la oxidación está completa, la mezcla de reacción es apagada con solución de tiosulfato de sodio saturado 10 mL y agitada vigorosamente durante 30 minutos, luego tratada con 75 mL de diclorometano. La mezcla de reacción es particionada entre diclorometano y capa acuosa. La capa orgánica es lavada con solución de $NaHCO_3$ saturado, agua, y salmuera secuencialmente, luego secada sobre Na_2SO_4, concentrada para proporcionar N- {3- [2- (6- Metanosulfinil- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida como un sólido verde. El producto crudo es directamente utilizado en el próximo paso. MS *m/z* 515.1 (M + 1).

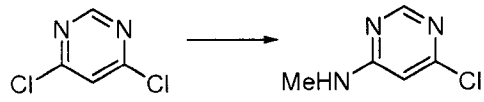


La mezcla de N- {3- [2- (6- Metanosulfinil- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida (20mg, 0.04mmol) y 2- Morfolin- 4- il- etilamina (100 uL) en 2- propanol es calentada a 80 °C durante 3 horas. La mezcla de reacción es enfriada a temperatura ambiente y condensada. Luego el producto crudo es tratado con 1 mL de DMSO y purificado mediante LC/MS para proporcionar N- (4- Metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida.

Ejemplo 4

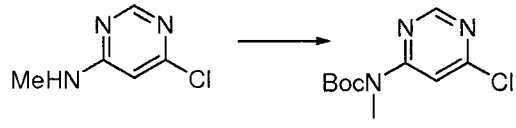
N- {4- Metil- 3- r2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil]- 3- (4-

metil- piperazin- 1- il)- 5- trifluorometil- benzamida



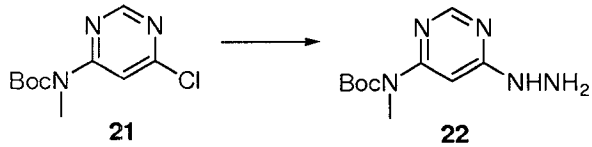
20

Una mezcla de 4,6- dicloro- pirimidina(3.53g, 23.7mmol) y metilamina (33% por peso en etanol, 10ml, 80mmol) en etanol es mantenida en agitación durante la noche a temperatura ambiente. La mezcla de reacción es concentrada, triturada con agua y filtrada. El producto crudo es lavado con agua, una pequeña cantidad de etanol y éter etílico secuencialmente, y secado con aire para proporcionar (6- Cloro- pirimidin- 4- il)- metil- amina como un polvo blanco: ^{1}H NMR 400 MHz (J6- DMSO) δ 8.36- 8.16 *(m,* 1H), 7.69 (5, 1H), 6.50 (5, 1H), 2.90- 2.68 *(m,* 3H); MS *m/z* 144.00 (M + 1).



20 21

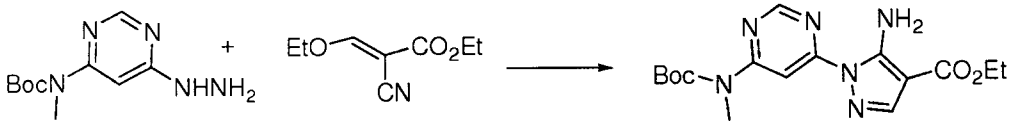
A una mezcla de (6- cloro- pirimidin- 4- il)- metil- amina (10g, 69.7mmol), trietilamina (15mL, 106.7mmol), y dimetilaminopiridina (8.5g, 69.5mmol) en 100mL de diclorometano se agrega dicarbonate de *di- t- butilo* (18.75g, 85.9mmol) por porciones. La mezcla de reacción es mantenida en agitación a temperatura ambiente durante 4 horas y concentrada. La producto crudo resultante es tratado con agua y filtrado. El sólido obtenido es secado al vacío para proporcionar éster tert- butílico del ácido (6- Cloro- pirimidin- 4- il)- metil- carbámico: ^{1}H NMR 400 MHz (J6- DMSO) 5 8.80 (5, 1H), 8.04 (5, 1H), 3.37 (5, 3H), 1.52 (5, 9H); MS *m/z* 244.10 (M+l).



21 **22**

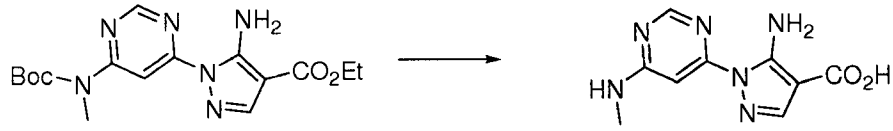
Una mezcla de éster tert- butílico del ácido (6- Cloro- pirimidin- 4- il)- metil- carbámico (l0g, 41.1mmol), monohidrato de hidrazina (6.5g, 130.0mmol), y 2- propanol (50mL) es calentada a 90 °C durante 4 horas. Luego la mezcla de reacción es enfriada a temperatura ambiente, y concentrada. La producto crudo resultante es tratado con una mezcla de agua (80mL)

y etanol (15 mL), calentado durante 30 minutos, y lentamente enfriado a temperatura ambiente. Se forma un precipitado blanco. Después de la filtración, el sólido sin disolver es lavado con agua, secado al vacío durante la noche para proporcionar éster tert- butílico del ácido (6- Hidrazino- pirimidin- 4- il)- metil- carbámico como polvo blanco en forma de aguja: ^{1}H NMR 400 MHz (J6- DMSO) 5 8.23 (s, 1H), 8.19 (s, 1H), 7.14 (s, 1H), 4.29 (s, 2H), 3.23 (s, 3H), 1.49 (s, 9H); MS *m/z* 240.10 (M + 1).



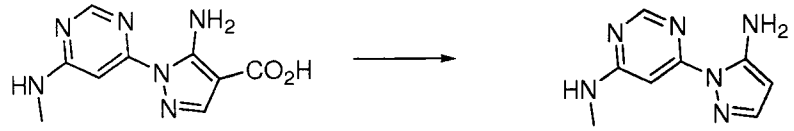
22 **23**

Una mezcla de éster tert- butílico del ácido (6- hidrazino- pirimidin- 4- il)- metil- carbámico (4.0g, 16.7mmol), éster etílico del ácido 2- ciano- 3- etoxi- acrílico (3.02g, 17.5mmol) y etanol (25mL) es calentada a reflujo durante 4 horas. Luego la mezcla de reacción es concentrada y triturada con agua (l0mL). Formas precipitadas blancas. Después de la filtración, el sólido sin disolver es adicionalmente lavado con agua, luego secado con aire para proporcionar éster etílico del ácido 5- amino- l- [6- (tert- butoxicarbonil- metil- amino)- pirimidin- 4- il]- lH- pirazol- 4- carboxílico como polvo blanco.



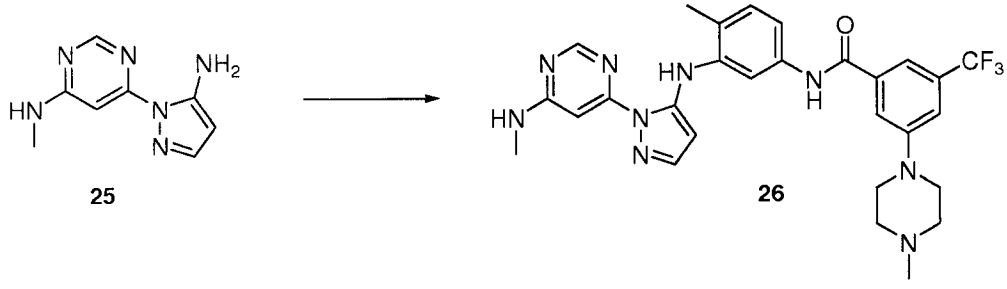
23 **24**

Una mezcla de éster etílico del ácido 5- amino- l- [6- (tert- butoxicarbonil- metil- amino)- pirimidin- 4- il]- lH- pirazol- 4- carboxílico (5.5 g, 15.2mmol), hidróxido de litio (1.82g, 75.8 mmol) disuelta en una mezcla de 1,4- dioxano (20mL) y agua (5 mL) es calentada a 85°C durante 8 horas. Luego la mezcla de reacción es neutralizada con solución acuosa de HCl 2M hasta pH~4- 5 produciendo la formación de un precipitado blanco. Después de la filtración, el sólido sin disolver es lavado con una pequeña cantidad de agua, secado con aire para proporcionar ácido 5- amino- l- [6- (tert- butoxicarbonil- metil- amino)- pirimidin- 4- il]- lH- pirazol- 4- carboxílico como polvo blanco: ^{1}H NMR 400 MHz (J6- DMSO) δ 8.41 (5, 1H), 8.00- 7.40 *(m,* 4H), 6.86- 6.58 *(m,* 1H), 2.86 (5, 3H); MS *m/z* 235.10 (M + 1).



24 25

El ácido 5- amino- 1- [6- (tert- butoxicarbonil- metil- amino)- pirimidin- 4- il]- 1H- pirazol- 4- carboxílico (230mg, 0.98mmol) es calentado a 160 °C durante 1.5 horas sobre una placa caliente en forma de polvo. El producto crudo es purificado mediante cromatografía ISCO eluyendo con acetato de etilo en hexanos desde 20% a 100% para proporcionar [6- (5- Amino- pirazol- 1- il)- pirimidin- 4- il]- metil- amina: ^{1}H NMR 400 MHz (J6- DMSO) δ 8.33 *(s,* 1H), 7.53 *(s,* 1H), 7.35 *(s,* 1H), 7.00- 6.60 *(m,* 3H), 5.34 (5, 1H), 2.83 *(bs,* 3H); MS *m/z* 191.10 (M + 1).

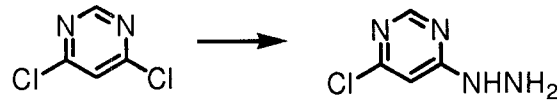


25 26

[6- (5- Amino- pirazol- 1- il)- pirimidin- 4- il]- metil- amina (200mg, 1.05mmol) es mezclada con N- (3- brom$_{0-4}$- metil- fenil)- 3- (4- metil- piperazin- 1- il)- 5- trifluorometil- benzamida (640mg, 1.40mmol), acetato de paladio (60mg, 0.27mmol), Xantphos (235mg, 0.41mmol) y carbonato de cesio (1.03g, 3.15mmol). Se agregó10 mL de 1,4- dioxano anhidro bajo ambiente de nitrógeno y la mezcla se sometió a irradiación de microondas a 160°C durante 25 minutos. La mezcla de reacción es tratada con 150 mL de THF, pasada a través de una columna de celite y condensada. El producto crudo es purificado mediante cromatografía ISCO eluyendo con THF y metanol (v/v =1:1) en cloruro de metileno desde 0% a 10% para proporcionar N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- (4- metil- piperazin- 1- il)- 5- trifluorometil- benzamida.

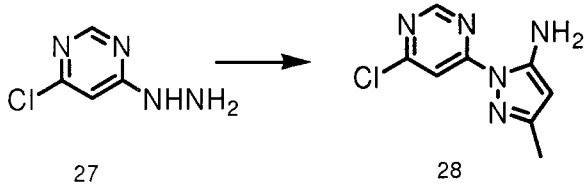
Ejemplo 5

N- [5- (1- Fluoro- 1- metil- etil)- piridin- 3- il]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida



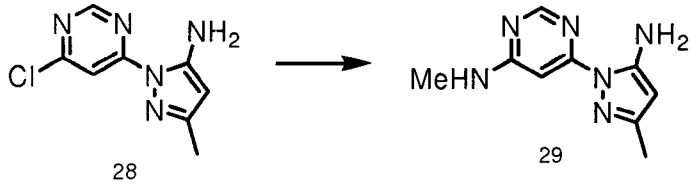
1 27

Una mezcla de 4,6- dicloro- pirimidina (18.68 g, 125 mmol), monohidrato de hidrazina (18.28 mL, 376 mmol), y 2- propanol (300 mL) se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción fue concentrada, triturada con agua, y filtrada. El sólido fue lavado con agua, secado con aire para proporcionar (6- cloro- pirimidin- 4- il)- hidrazina (16.97 g, Rendimiento 94%): ^{1}H NMR 400 MHz (J6- DMSO) δ 8.83 *(s,* 1H), 8.17 (5, 1H), 6.76 (5, 1H), 4.50 (5, 2H); MS *m/z* 145.02 (M + 1).



27 28

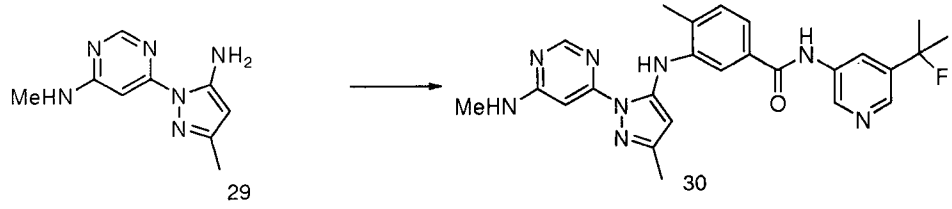
La mezcla de (6- cloro- pirimidin- 4- il)- hidrazina (16.97 g, 117 mmol), 3- imino- butironitrilo (28.88 g, 352 mmol), y 2- propanol (500 mL) se calentó a 85°C durante 5 h. La mezcla de reacción luego se enfrió a temperatura ambiente, se condensó, y recristalizó a partir de etanol/agua (1:1, 400 mL). El sólido fue filtrado y lavado con agua (200 mL), luego etanol/agua (1 : 1, 100 mL), secado para proporcionar el producto deseado 20 .66 g. Un producto adicional (0.9 g) fue aislado a partir del filtrado después de sentar durante la noche a temperatura ambiente. MS *m/z* 210.05 (M + 1).



28 29

5- Metil- 2- (6- cloro- pirimidin- 4- il)- 2H- pirazol- 3- ilamina (2.09 g, 10 mmol) fue mezclada con metilamina (40 % en agua, 9 mL) y 2- propanol (30 mL). La mezcla fue calentada a 50 °C en un tubo sellado. Después de 4 h, la mezcla de reacción fue enfriada a temperatura ambiente y condensada, triturada con agua, y filtrada. El sólido fue lavado con agua, secado con aire para proporcionar [6- (5- amino- 3- metil- pirazol- 1- il)- pirimidin- 4- il]- metil- amina (2.08 g, Rendimiento 97%): ^{1}H NMR 400 MHz (J6- DMSO) δ 8.80 *(s,* 1H), 7.44 (5, 1H),

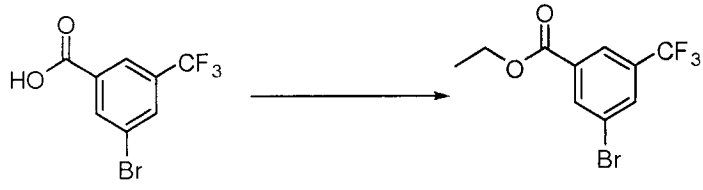
6.82 - 6.74 *(m,* 3H), 5.19 (s, 1H), 2.83 (s, 3H), 2.06 (s, 3H); MS *m/z* 210.64 (M + 1).



Una suspensión de [6- (5- amino- 3- metil- pirazol- l- il)- pirimidin- 4- il]- metil- amina (17 mg, 0.083 mmol), *N*- [5- (l- fluoro- l- metil- etil)- piridin- 3- il]- 3- yodo- 4- metil- benzamida (41 mg, 0.104 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), Xantphos (9 mg, 0.0166 mmol) y Cs_2CO_3 (54 mg, 0.166 mmol) en 1,4- dioxano anhidro (2 mL) en un tubito de presión fue degasificada por una corriente de argón y sellada. La reacción fue agitada a 150 °C durante 1 hora. LCMS mostró terminación de la reacción. Una solución de sal de sodio de ácido dietil ditiocarbómico al 5% (3 mL) se agregó a la reacción. Se recolectó un precipitado amarillo claro por filtración, se lavó con agua y secó. La crudo fue purificado mediante columna (SiO_2, EtOAc/hexanos: 30 a 100%) para proporcionar un sólido blanco (25 mg, 64%): m/z 475.2 (M+l).

Ejemplo 426

3- ((isopropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1 H- pirazol- 5 - ilamino) fenil)- 5- (trifluorometil) benzamida

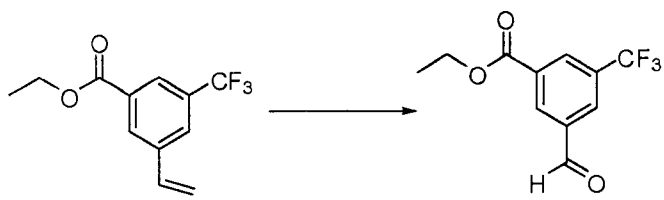


Se disolvió 100g (371 .71 mmol) de ácido 3- bromo- 5- (trifluorometil) benzoico 31 en etanol seco (300 mL) y se agregó por goteo19 mL de H_2SO_4 concentrado (Catalítico) durante un periodo de 15 minutos a temperatura ambiente. La mezcla de reacción se agitó a 90°C durante la noche. Una alícuota es extraída y verificada vía LC/MS y un pico grande de producto es observado y no se detectó material de inicio. La mezcla de reacción es vertida en agua helada (200 mL) y es extraída con acetato de etilo (3 X 100 mL). Las capas orgánicas son combinadas y secadas sobre sulfato de magnesio y es suficientemente pura para ser llevada al próximo paso sin

más purificación. El producto es 3- bromo- 5- (trifluorometil)- benzoato de etilo 32. MS: *mlz* [M + H+]) 296.80, ^{1}HNMR: 8.36 (s, 1H), 8.24, (s, 1H), 7.95, (s, 1H), 4.4$_1$- $_4$.47 (q, 2H, 7=7.21 Hz), 1.42- 1.45 (t, 3H, 7 = 7.21 Hz).

32 **33**

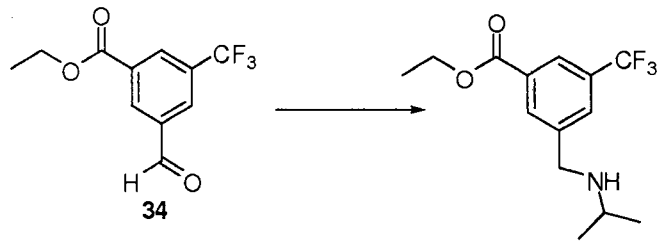
Se disolvió 50g de 3- bromo- 5- (trifluorometil) benzoato de etilo 32 en THF seco (100 mL), y se agregó tributil vinil estaño (56.85g, 185.14 mmol, 1.09 eq) seguido por paladio de tetrakistrifenilfosphina (O) (2.5g, 2.16 mmol, 0.013eq). La reacción se calentó a 90 °C durante 18 horas. El día siguiente la mezcla de reacción fue probada vía LC/MS y solamente se detectó el pico de producto sin cualquier rastro de materiales de inicio. La mezcla de reacción se filtró sobre celite para retirar el paladio y luego el solvente extra se retiró al vacío. Luego el compuesto deseado se aisló vía cromatografía en columna flash utilizando hexano puro seguido por 10 % EtoAc/Hex) para proporcionar 3- (trifluorometil)- 5- vinilbenzoato de etilo 33. MS: *mlz* [M + H+]) 245.10, ^{1}HNMR8.26(s, 1H), 8.19 (s, 1H), 7.82 (s, 1H), 6.76- 6.80 (dd, 7 = 4, 16 Hz, 1H), 5.91- 5.95 (dd, 7 = 4, 16Hz, 1H), 5.45- 5.48 (dd, 7= 4, 16Hz), 4.4$_1$- $_4$.47 (q, 2H, 7 = 7.21 Hz), 1.42- 1.62 (t, 3H, 7 = 7.21 Hz).



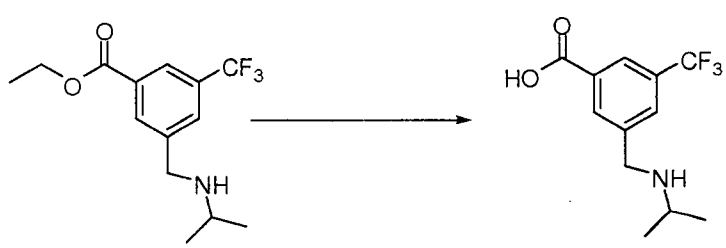
33 **34**

Se disolvió 25.39 g (103.96 mmol) de 3- (trifluorometil)- 5- vinilbenzoato de etilo 33 en MeOH seco (200 mL) y el recipiente de reacción se enfrió a - 78 °C. Luego O_3 se burbujeó a través durante 1.5 horas hasta que la mezcla de reacción se tornó azul oscuro. Luego el ozono es apagado y se burbujeó nitrógeno a través de la mezcla de reacción para retirar el ozono extra de la solución. Se agregó 9.6 g de sulfuro de dimetilo (155.95 mmol, 1.5 eq) y la mezcla de reacción se agitó a - 78 °C durante 2 horas seguido por una temperatura ambiente durante otra

hora. Todos los solventes son retirados y 3- formil- 5- (trifluorometil) benzoato de etilo 34 es aislado vía cromatografía en columna flash (5- 10 % EtOAc/Hex). MS: *mlz* [M + H+]) 247.18, ^{1}H NMR 10.16 (s, 1H), 8.73 (s, 1H), 8.56, (s, 1H), 8.35 (s, 1H), 4.46- 4.51(q, 2H, *J* = 7.21 Hz), 1.45- 1.49 (t, 3H, *J*= 7.21 Hz).

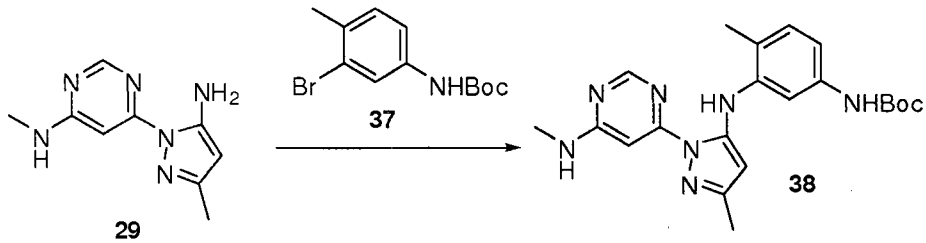


Se disolvió 1g (4.06 mmol, 1 eq) de 3- formil- 5- (trifluorometil) benzoato 34 en EtOH seco (20 mL). A este frasco de reacción se agregó 287mg de isopropilamina (4.87 mmol, 1.2 eq) y ácido acético (5 gotas). Esta mezcla de reacción es calentada a 50 °C durante 2 horas bajo condición sellada. Luego la mezcla de reacción se enfrió a 0 °C y se agregó borohidruro de sodio (184 mg, 4.87 mmol, 1.2 eq) en una porción. El recipiente de reacción es sellado una vez más y la mezcla es agitada a 0 °C durante media hora seguido por agitación a temperatura ambiente durante 2 horas más. La mezcla de reacción es verificada mediante LC/MS y un único pico de producto es encontrado sin ningún rastro de materiales de inicio. La mezcla de reacción es vertida en solución helada de $NaHO_3$ y extraída con acetato de etilo (3 X 20 mL). Las capas orgánicas son combinadas y secadas sobre sulfato de magnesio. Después de purificación utilizando una cromatografía en columna flash (5- 20 % acetato de etilo/Hex) el compuesto puro 3- ((isopropilamino)- metil)- 5- (trifluorometil) benzoato de etilo es aislado como un aceite amarillo claro. MS: *mlz* [M + H+]) 290.20. ^{1}H NMR: 8.10 (m, 2H), 7.74 (s, 1H), 4.3$_1$- $_4$.37 (q, 2H, *J*= 7.20 Hz), 3.88 (s, 2H), 2.75- 2.82 (m, 1H), 1.33- 1.38 (t, 3H, *J* = 7.20 Hz), 1.03- 1.05 (m,6H).

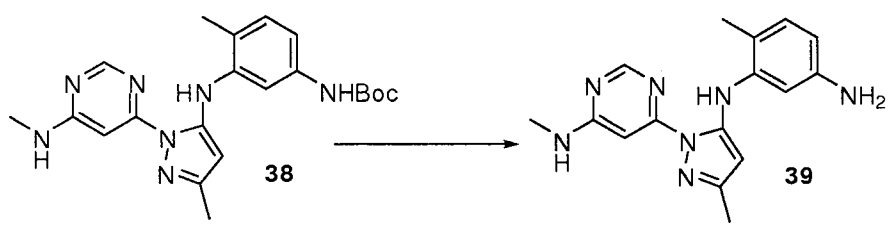


Se disolvió 3- ((isopropilamino) metil)- 5- (trifluorometil) benzoato de etilo (1.01g, 3.49

mmol, 1 eq) en THF/H_20 (1:1) 10 mL y se agregó LiOH 0.39g (16.32 mmol, 4.6 eq). La mezcla se agitó a temperatura ambiente durante 4 horas y luego se verificó vía LC/MS para un pico de material de inicio cero. El solvente orgánico es retirado y algo más de agua se agregó al recipiente de reacción. La mezcla de reacción es enfriada y se agregó por goteo solución de HCl 1M en éter hasta que el pH está entre 4 y 5. Las sales de cloruro de litio comienzaron a precipitarse fuera de la solución. Los solventes orgánicos extra son retirados y el precipitado es transferido a tubitos pequeños y liofilizado. MS: *mlz* [M + H+]) 262.20, ^{X}H NMR: 8.45 (s, 1H), 8.27 (s, 1H), 8.15 (s, 1H), 4.26 (s, 2H), 3.25- 3.38 (m, 2H), 1.33- 1.34 (m, 2H).

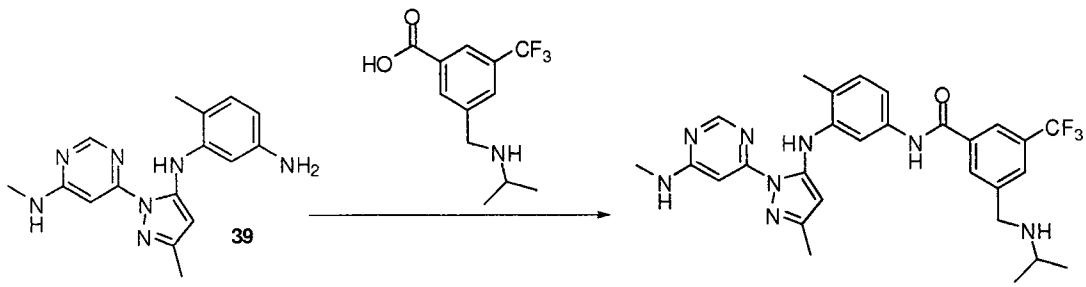


A un tubo de alta presión se agregó 6- (5- amino- 3- metil- lH- pirazol- 1- il)- N- metilpirimidin- 4- amina 29 (2.0 g, 9.8 mmol), éster tert- butílico del ácido 3- bromo- 4- metilfenil carbámico 37 (2.4 g, 10.8 mmol), $Pd(OAc)_2$ ($_{13}$2 mg, 0.59 mmol), Cs_2C0_3 (3.5 g, 10.8 mmol), 4,5- bis(difenilfosfino)- 9,9- dimetilxanteno (340 mg, 0.59 mmol) y 1,4- dioxano (30 mL). La mezcla es lavada a chorro con N_2 a 0°C durante pocos minutos, luego se calentó 120 °C durante 2 días. La mezcla es vertida en agua y extraída con EtOAc. La capa orgánica es separada, secada con $MgSO_4$, luego concentrada *al vacío.* El residuo es purificado mediante cromatografía flash [gel de sílice, hexano:EtOAc/5:5] para proporcionar tert- butil 4- metil- 3- (3- metil- l- (6- (metilamino)- pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenilcarbamato **38.**



Se disolvió Tert- butil 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenilcarbamato 38 (2.0 g) en un solvente mixto de TFA:DCM/1:1 (20 mL). La mezcla se agitó a temperatura ambiente durante 4 horas, luego se concentró *al vacío.* El

residuo se disolvió en EtOAc y se lavó con NaHCO3 acuoso. La capa orgánica es separada, secada con $MgSO_4$, luego concentrada *al vacío* para proporcionar 6- metil- N1- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- il) benceno- l,3- diamina **39.**

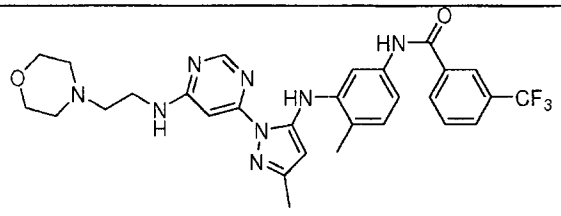
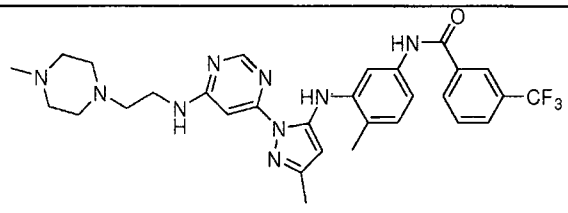
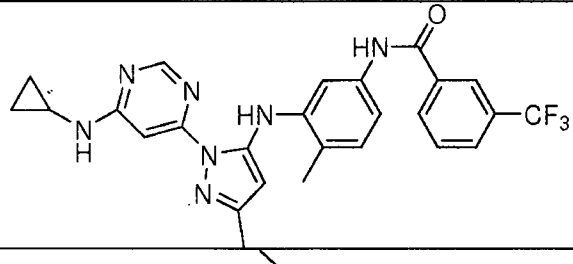
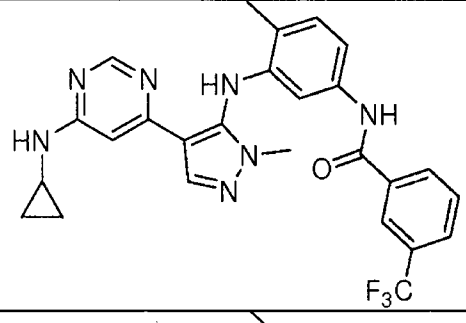
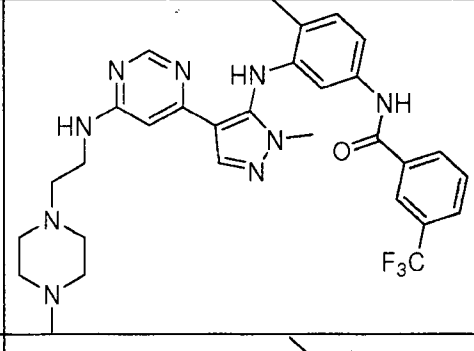
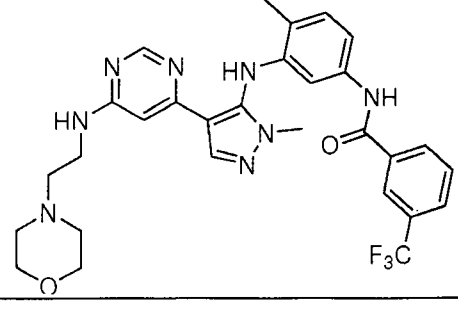


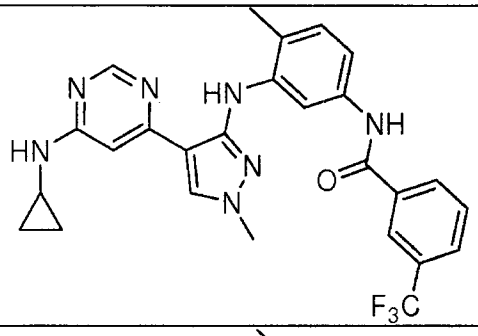
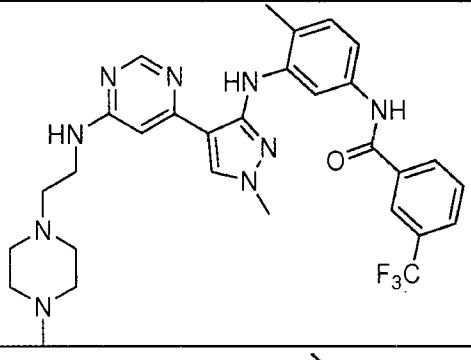
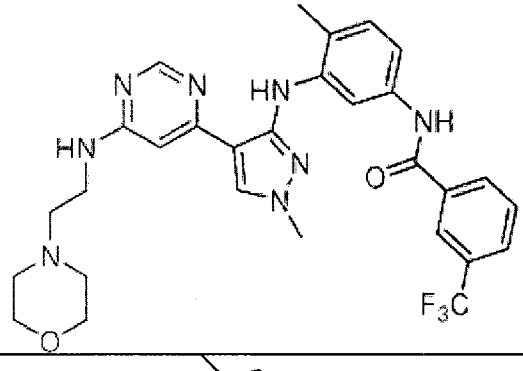
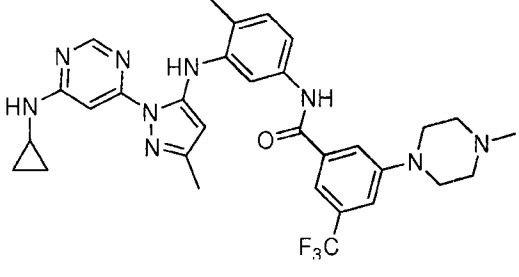
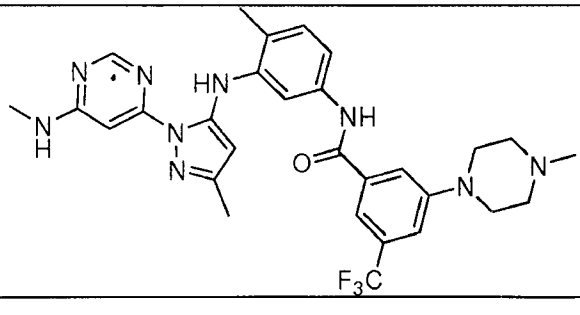
Se disolvió 6- metil- N1- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- il) benceno- l,3- diamina 39 (360 mg, 1.16 mmol, 1 eq) en DMF seco (10 mL), seguido por ácido 3- ((isopropilamino) metil)- 5- (trifluorometil) benzoico (0.504 mg, 1.02 mmol, 0.9 eq), HATU (663 mg, 1.74 mmol, 1.5 eq), y DIEA (0.5 mL, 3.49 mmol, 3 eq). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas aproximadamente hasta que la reacción estuvo completa como se evidenció por el pico de producto LC/MS. Luego la mezcla de reacción se apago mediante solución de $NaHCO_3$ y se extrajo con acetato de etilo. Las capas orgánicas son combinadas y secadas sobre sulfato de magnesio. Los solventes son retirados al vacío y el residuo es purificado mediante cromatografía en columna flash para proporcionar 3- ((isopropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida. MS: *mlz* [M + H+]) 553.20, ^{X}H NMR: 11.07 (s, 1H), 10.61 (s, 1H), 9.17 (bs, 1H), 8.58 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 7.95 (s, 1H), 7.69 (s, 1H), 7.39 (m, 1H), 7.24 (m, 1H), 6.88 (s, 1H), 6.16 (s, 1H), 4.36 (m, 2H), 3.34- 3.48 (m, 1H), 2.87 (m, 3H), 2.49(m, 3H), 2.22 (m, 3H), 1.33- 1.34 (m,6H).

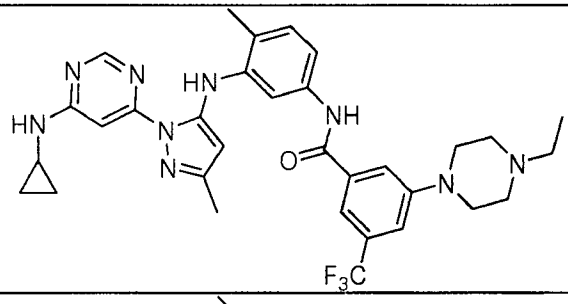
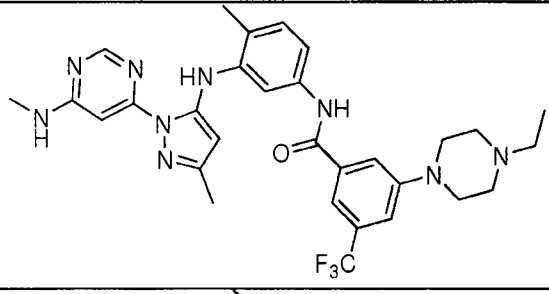
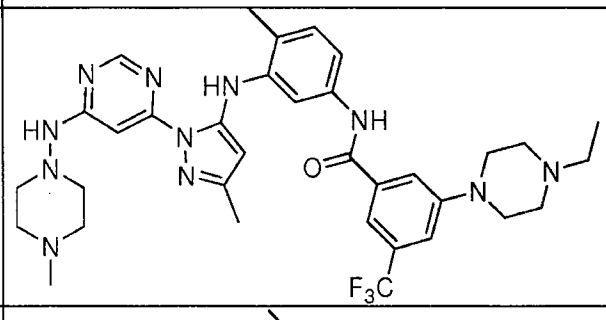
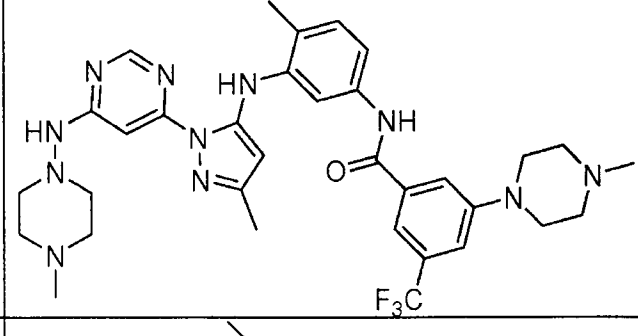
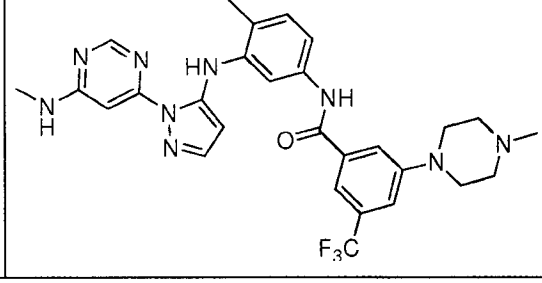
Al repetir los procedimientos descritos en los ejemplos anteriores, utilizando materiales de inicio apropiados, se obtuvieron los siguientes compuestos de la Fórmula I, como identifican en la Tabla 1.

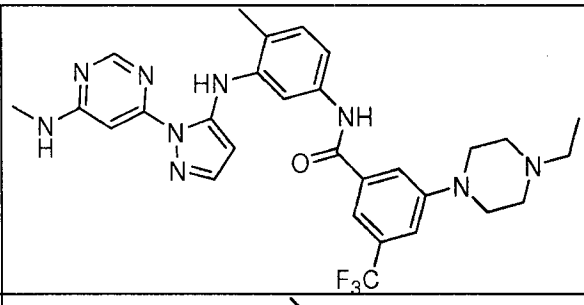
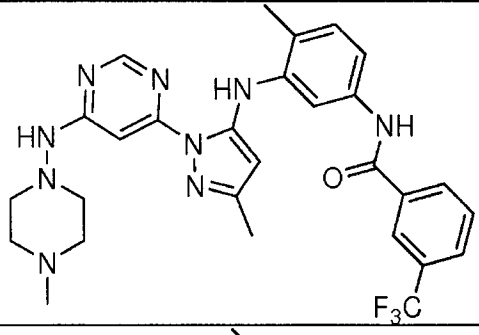
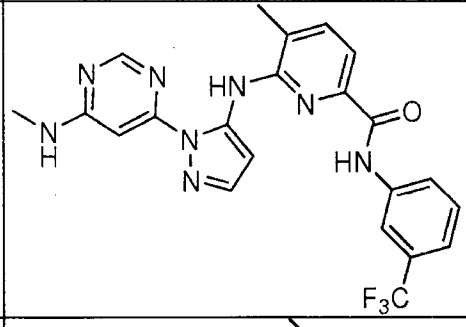
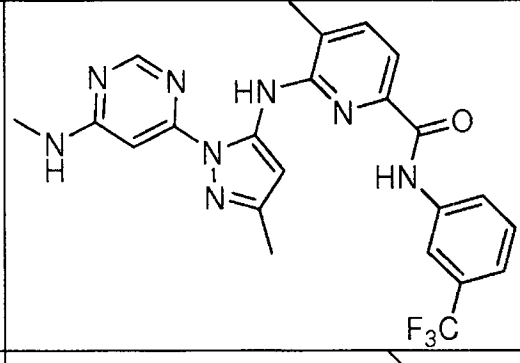
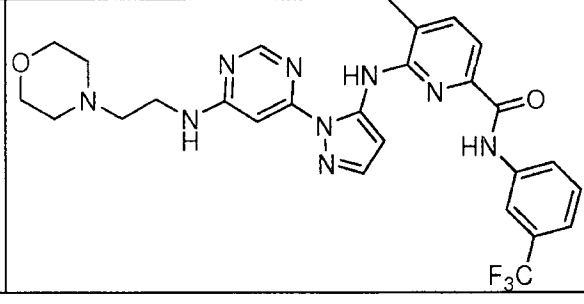
Tabla 1

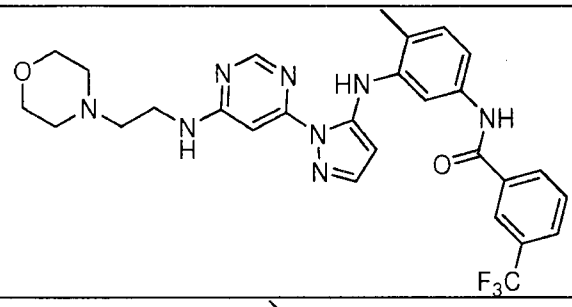
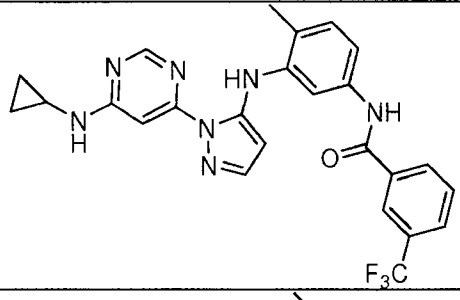
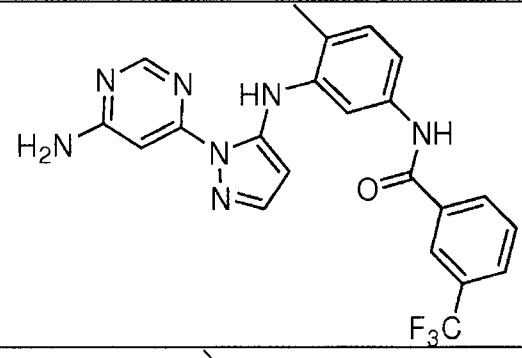
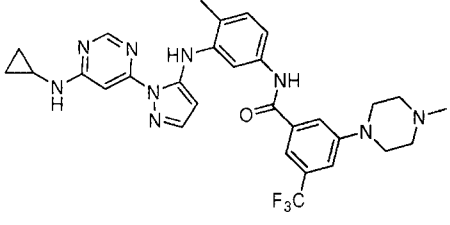
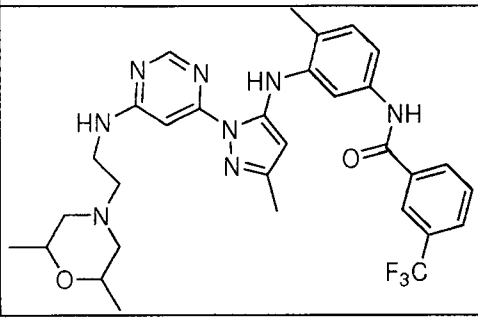
Número de Compuesto	Estructura	Datos Físicos ^{1}H NMR 400 MHz or 600 MHz (DMSO-d_6) y/o MS (m/z)

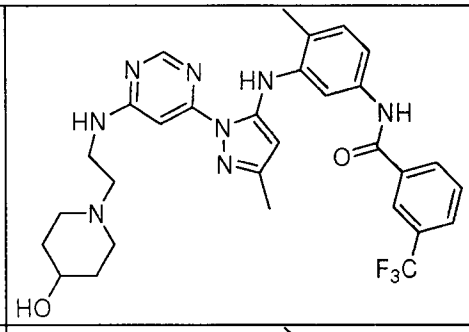
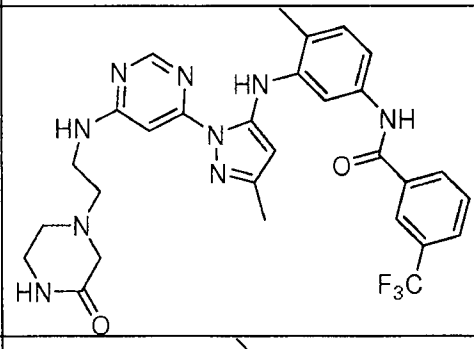
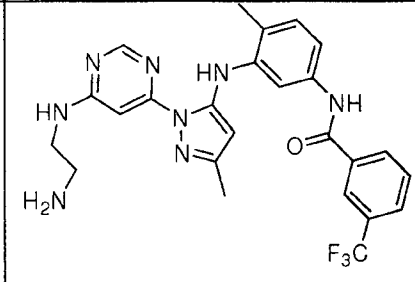
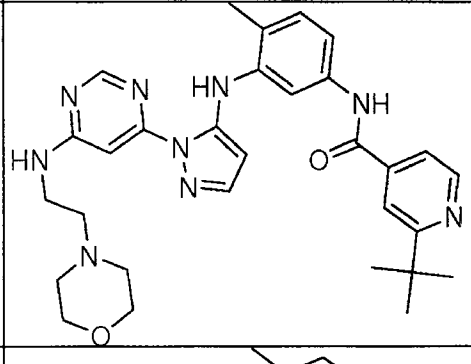
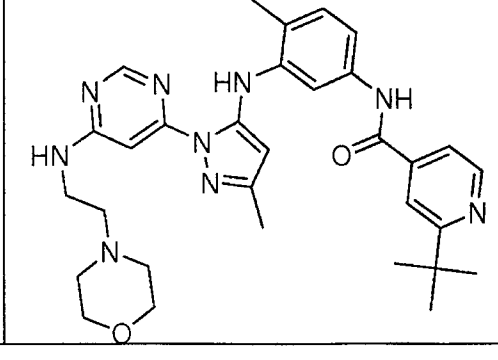
5		MS *m/z* 581.3 (M + 1)
6		MS *m/z* 594.3 (M + 1)
7		MS *m/z* 508.2 (M + 1)
8		MS *m/z* 508.2 (M + 1)
9		MS *m/z* 594.3 (M + 1)
10		MS *m/z* 581.3 (M + 1)

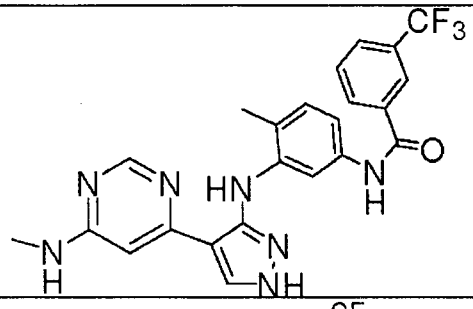
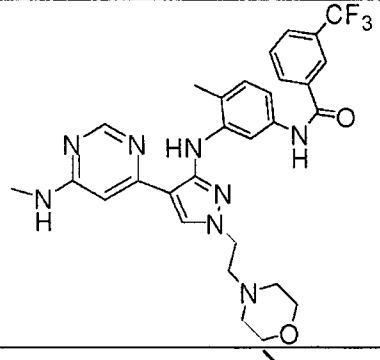
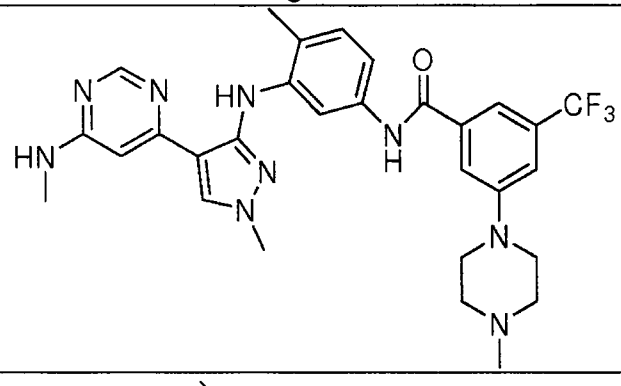
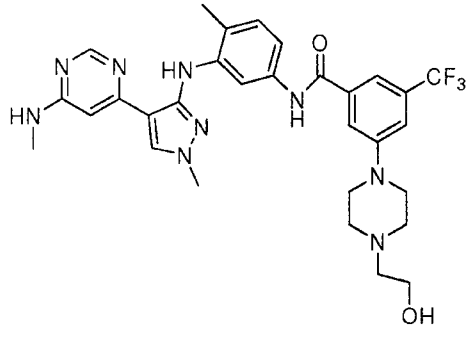
11		MS *m/z* 508.2 (M + 1)
12		MS *m/z* 594.3 (M + 1)
13		MS *m/z* 581.3 (M + 1)
14		MS *m/z* 606.3 (M + 1)
15		MS *m/z* 580.3 (M + 1)

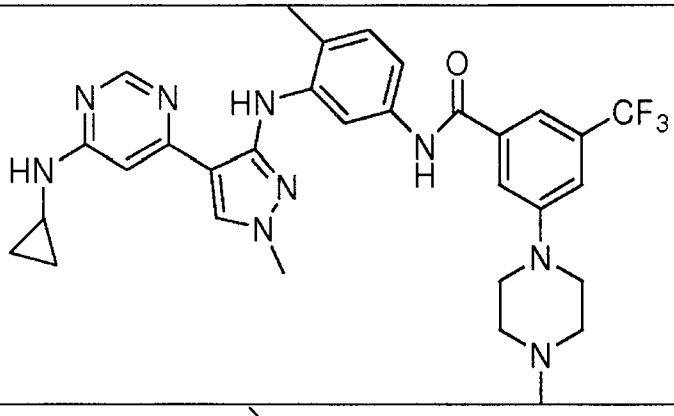
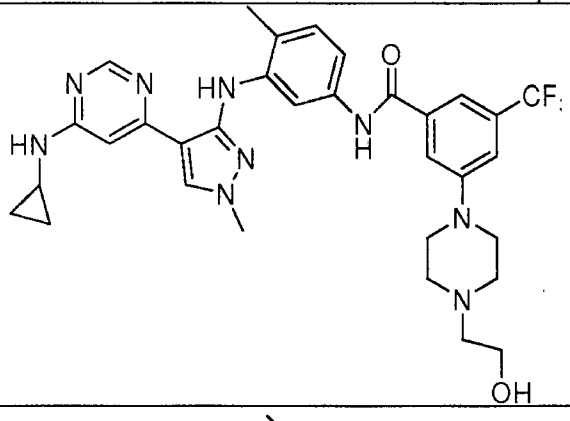
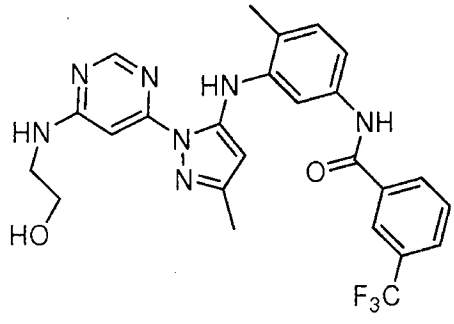
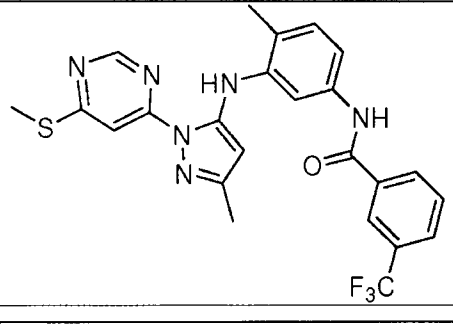
16		MS *m/z* 620.3 (M + 1)
17		MS *m/z* 594.3 (M + 1)
18		MS *m/z* 678.4 (M + 1)
19		MS *m/z* 664.3 (M + 1)
20		MS *m/z* 566.3 (M + 1)

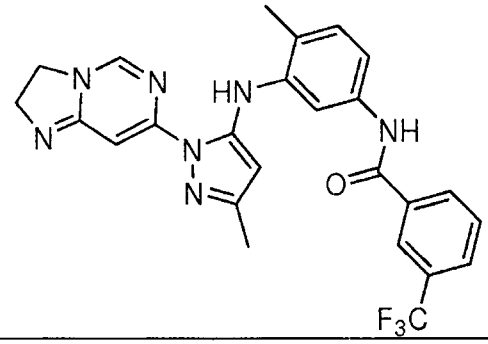
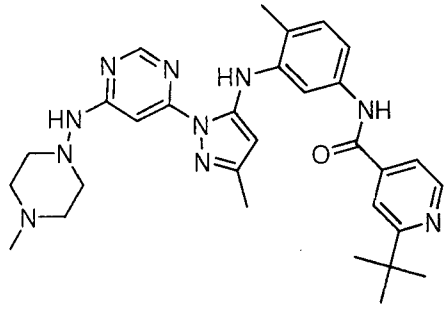
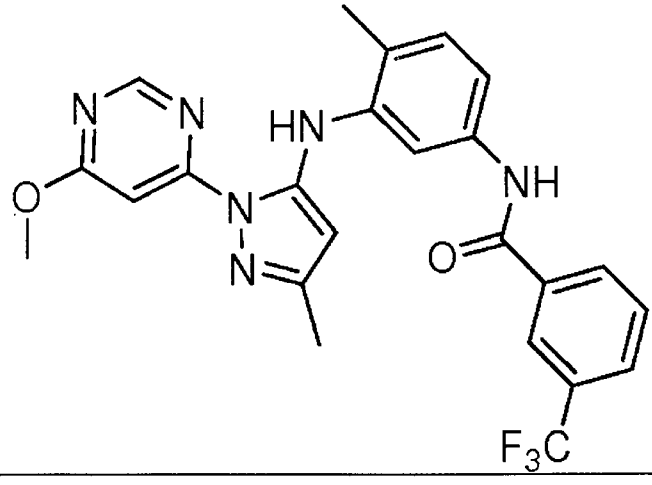
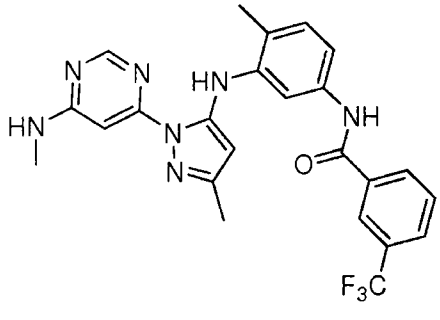
21		MS *m/z* 580.3 (M + 1)
22		MS *m/z* 566.3 (M + 1)
23		MS *m/z* 469.2 (M + 1)
24		MS *m/z* 483.2 (M + 1)
25		MS *m/z* 568.2 (M + 1)

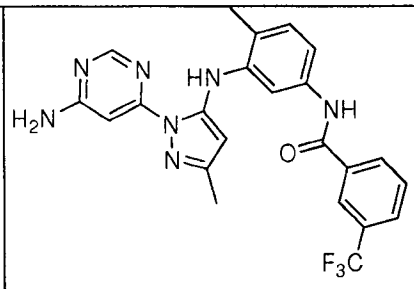
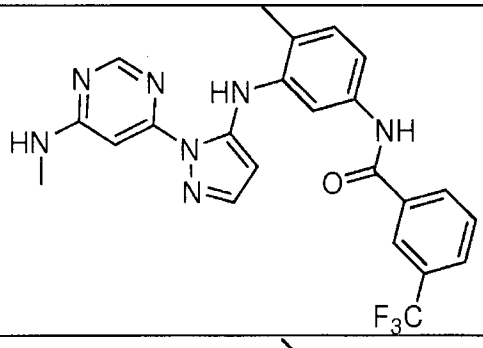
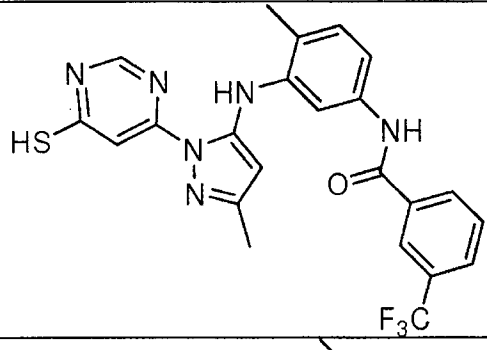
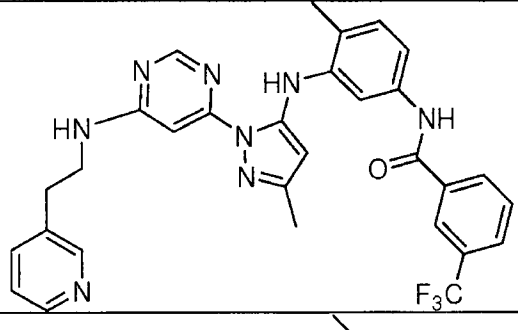
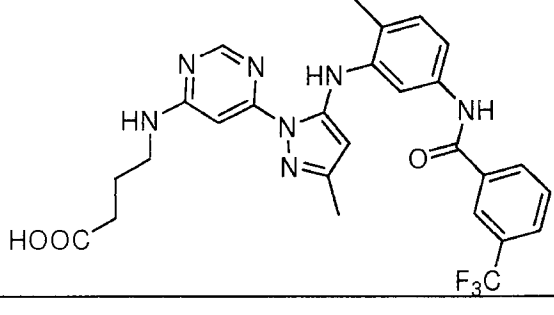
26		MS *m/z* *561.2* (M + 1)
27		MS *m/z* 494.2 (M + 1)
28		MS *m/z* 454.2 (M + 1)
29		MS *m/z* 592.3 (M + 1)
30		MS *m/z* 609.3 (M + 1)

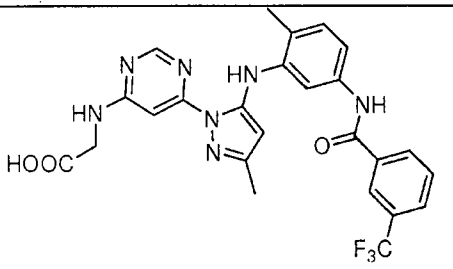
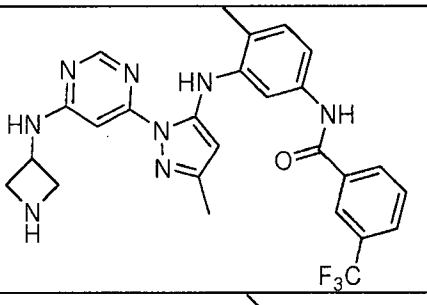
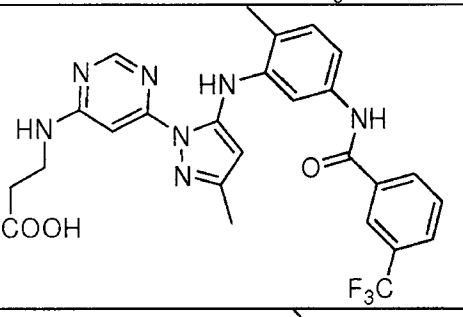
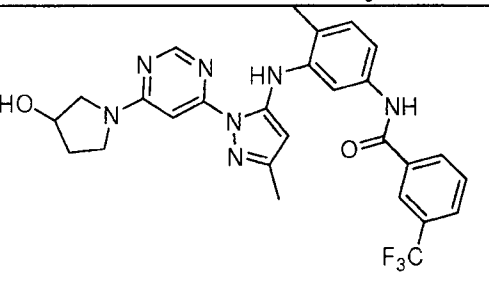
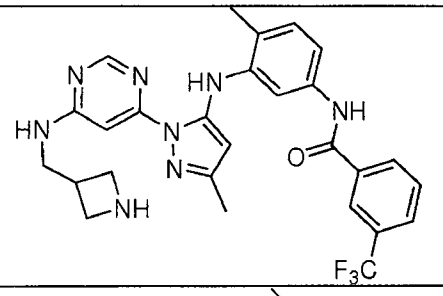
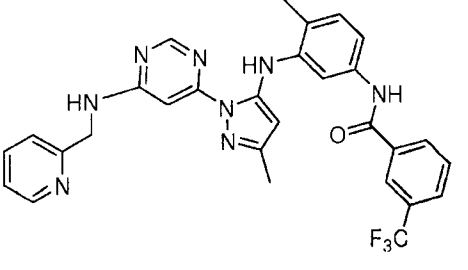
31		MS *m/z* 595.3 (M + 1)
32		MS *m/z* 594.3 (M + 1)
33		MS *m/z* 511.2 (M + 1)
34		MS *m/z* 511.2 (M + 1)
35		MS *m/z* 570.3 (M + 1)

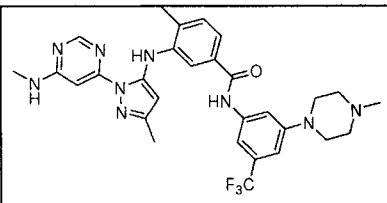
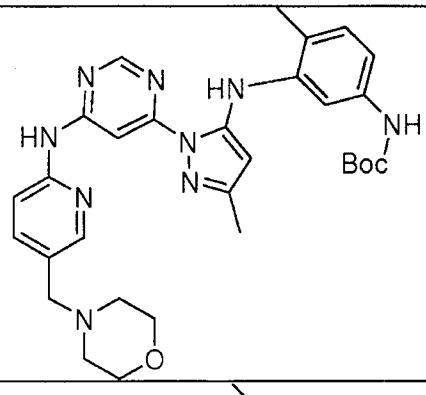
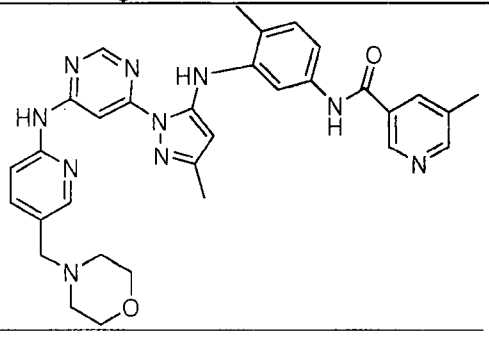
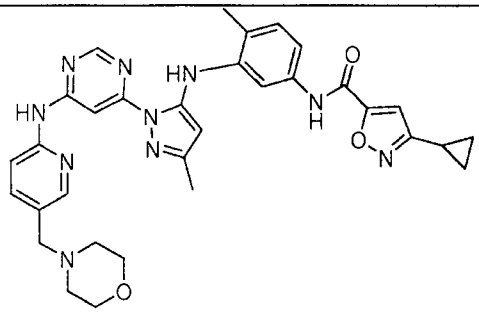
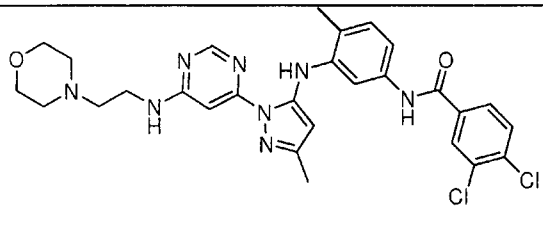
36		MS *m/z* 468.2 (M + 1)
37		MS *m/z* 581.3 (M + 1)
38		MS *m/z* 580.3 (M + 1)
39		MS *m/z* 610.3 (M + 1)

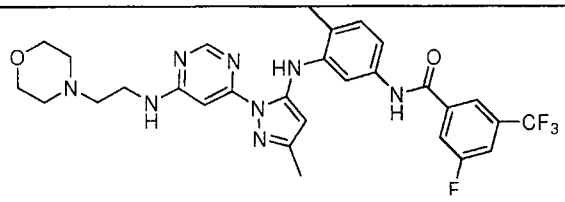
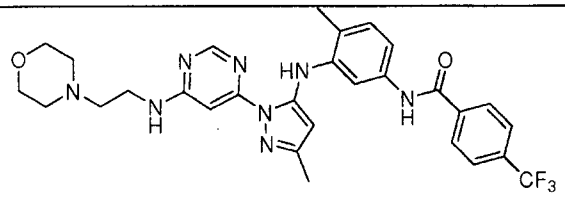
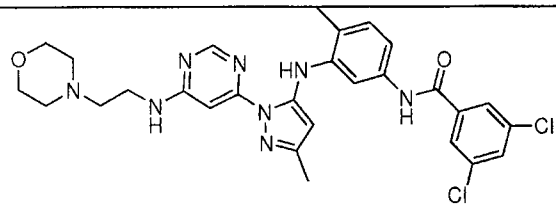
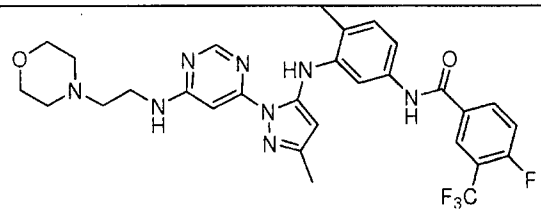
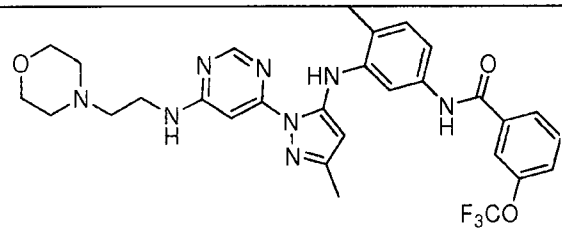
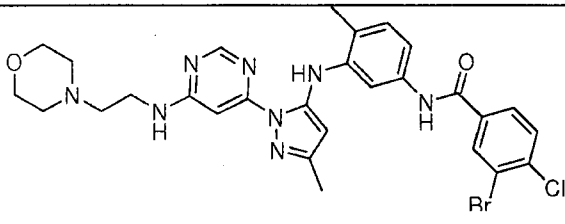
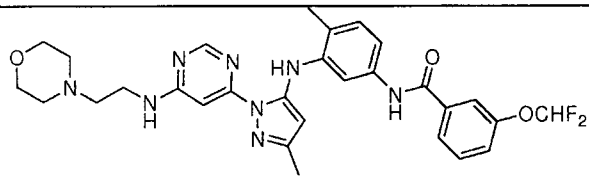
40		MS *m/z* 606.3 (M + 1)
41		MS *m/z* 636.3 (M + 1)
42		MS *m/z* 512.2 (M + 1)
43		MS *m/z* 499.1 (M + 1)

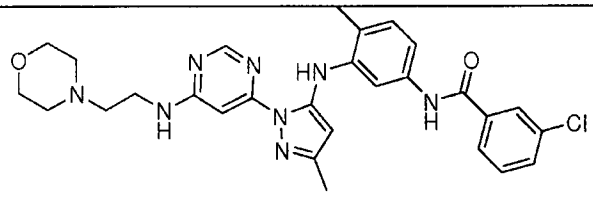
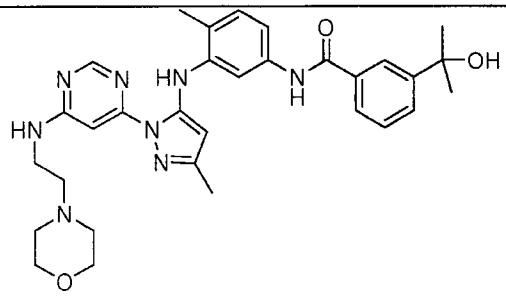
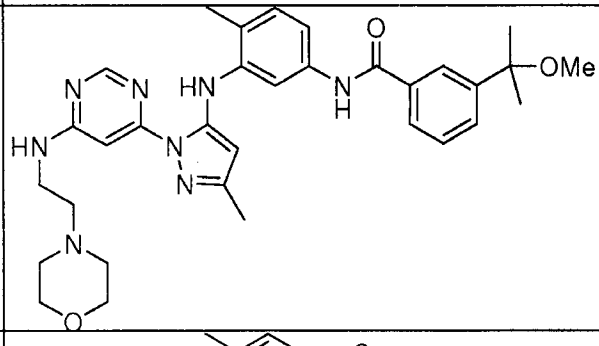
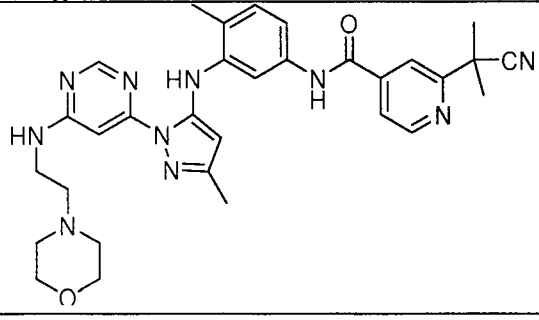
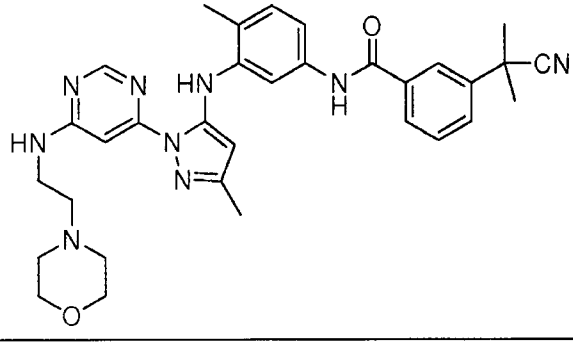
44		MS *m/z* 494.2 (M + 1)
45		MS *m/z* 555.3 (M + 1)
46		MS *m/z* 483.2 (M + 1)
47		MS *m/z* 482.2 (M + 1)

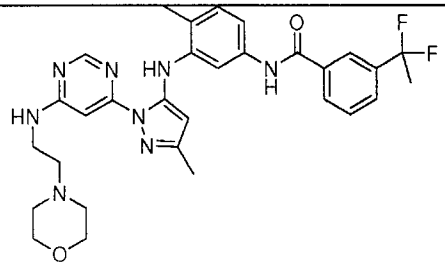
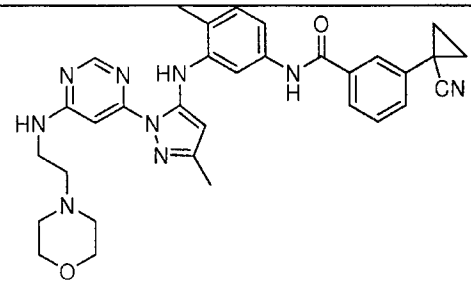
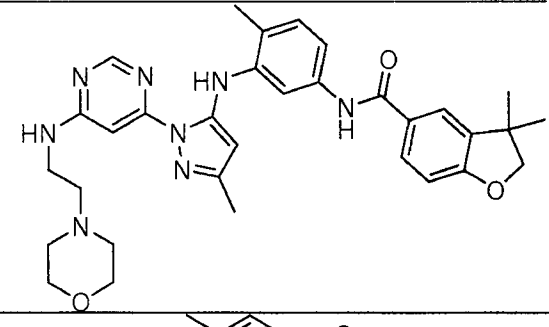
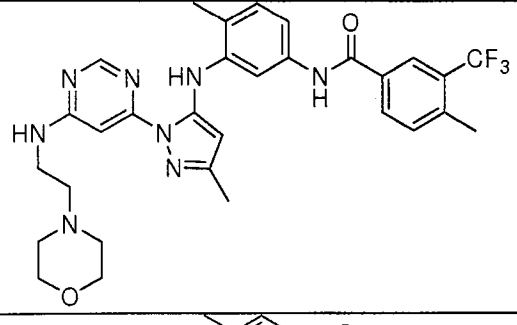
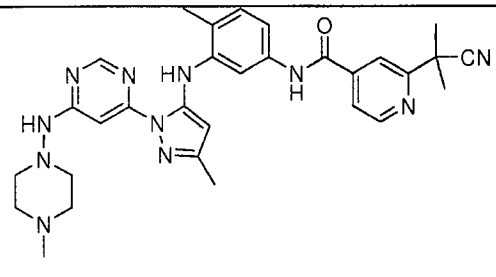
48		MS *m/z* 468.2 (M + 1)
49		MS *m/z* 468.2 (M + 1)
50		MS *m/z* 484.1 (M + 1)
51		MS *m/z* 573.2 (M + 1)
52		MS *m/z* 554.2 (M + 1)

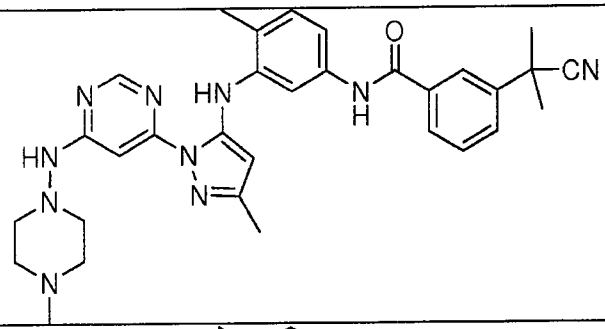
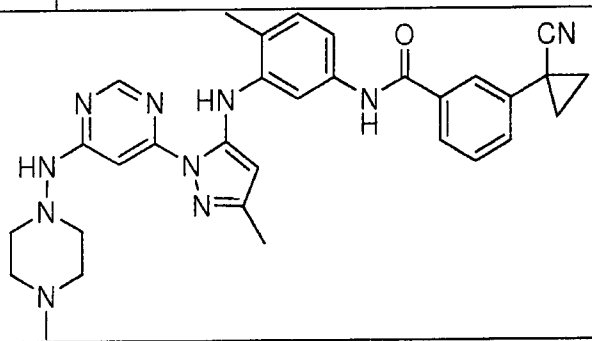
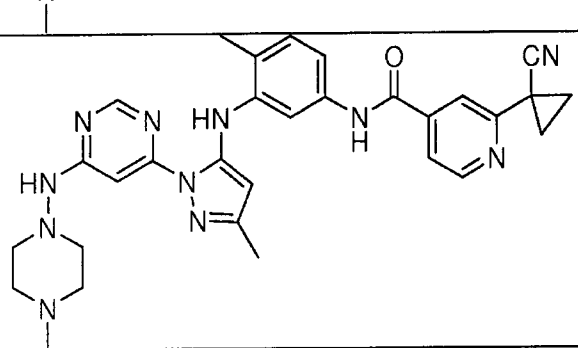
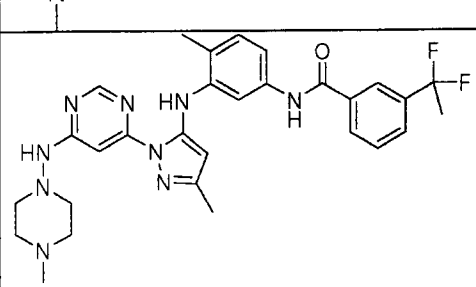
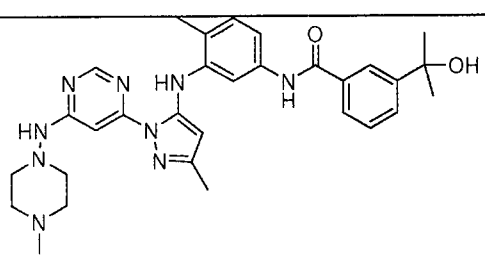
53		MS *m/z* 556.2 (M + 1)
54		MS *m/z* 523.2 (M + 1)
55		MS *m/z* 540.2 (M + 1)
56		MS *m/z* 538.2 (M + 1)
57		MS *m/z* 537.2 (M + 1)
58		MS *m/z* 559.2 (M + 1)

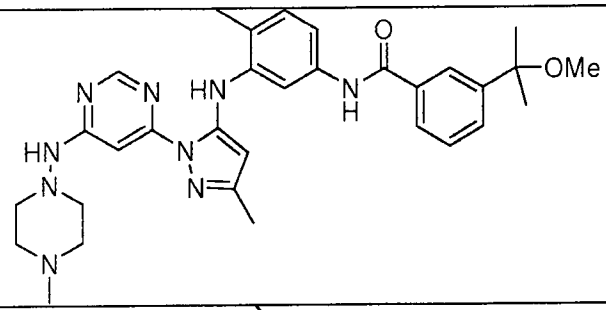
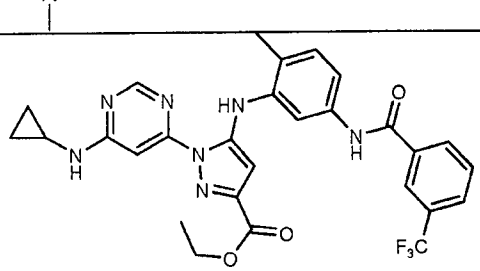
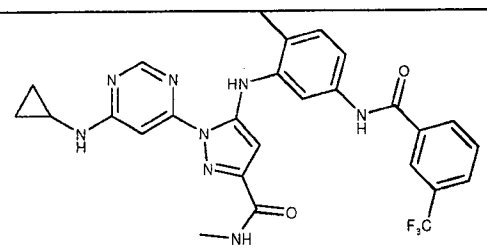
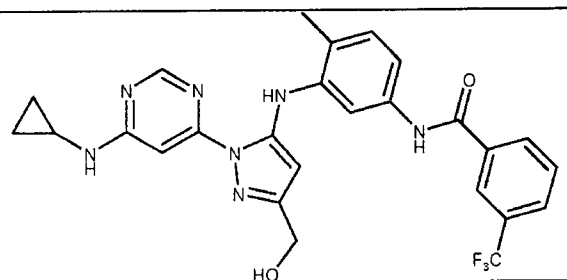
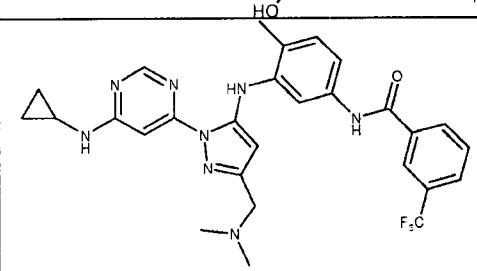
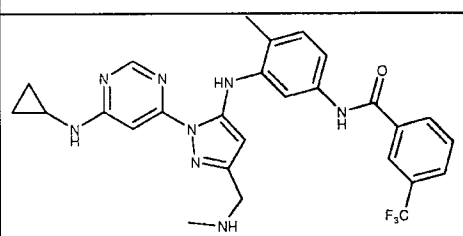
59		MS *m/z* 580.3 (M + 1)
60		MS *m/z* 572.3 (M + 1)
61		MS *m/z* 591.3 (M + 1)
62		MS *m/z* 607.3 (M + 1)
63		MS *m/z* 581.2 (M + 1)

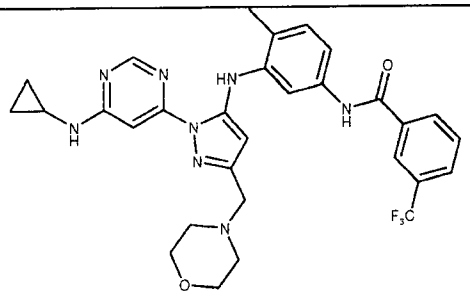
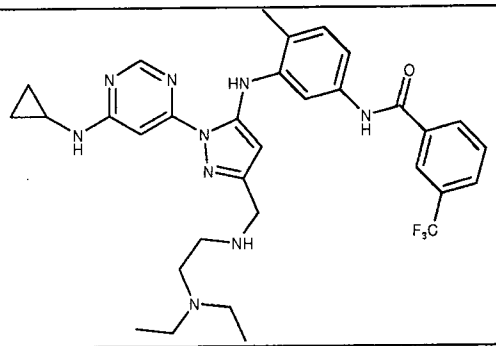
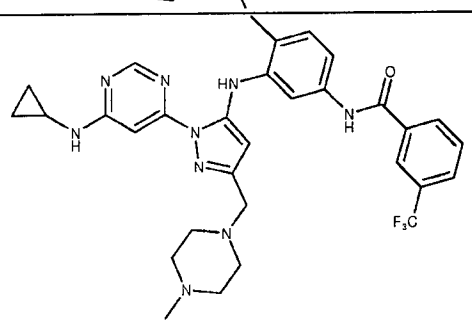
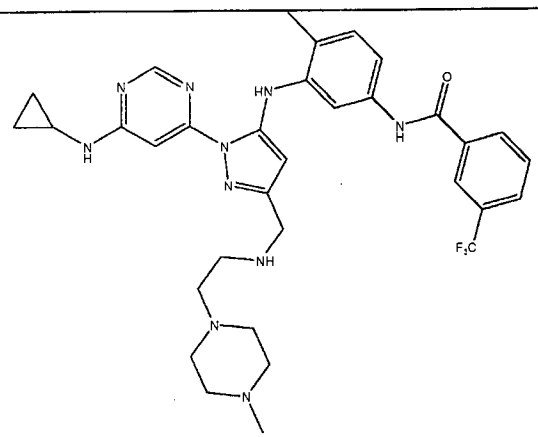
64		MS *m/z* 599.2 (M + 1)
65		MS *m/z* 581.3 (M + 1)
66		MS *m/z* 581.2 (M + 1)
67		MS *m/z* 599.2 (M + 1)
68		MS *m/z* 597.3 (M + 1)
69		MS *m/z* 625.1 (M + 1)
70		MS *m/z* 579.3 (M + 1)

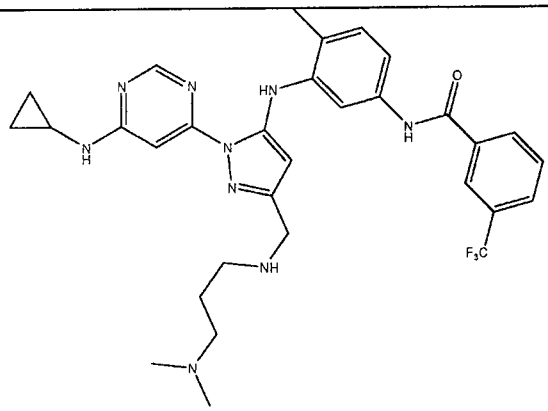
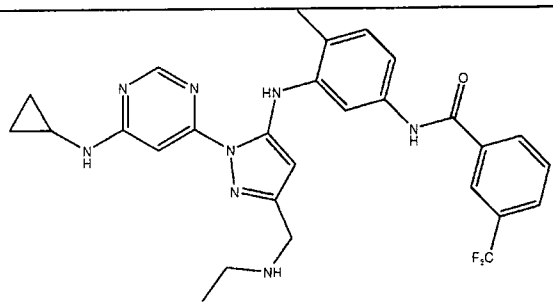
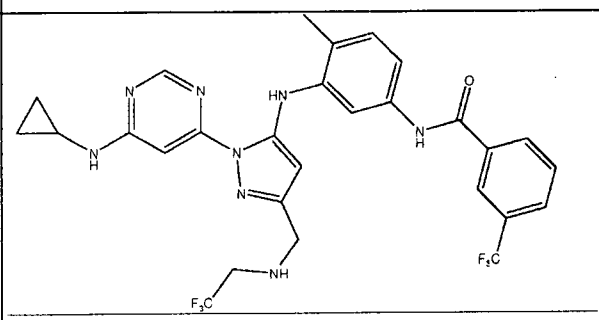
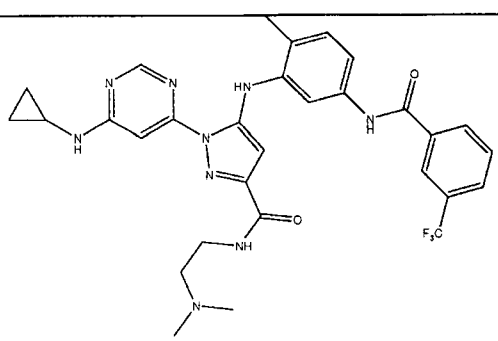
71		MS *m/z* 547.2 (M + 1)
72		MS *m/z* 571.3 (M + 1)
73		MS *m/z* 585.3 (M + 1)
74		MS *m/z* 581.3 (M + 1)
75		MS *m/z* 580.3 (M + 1)

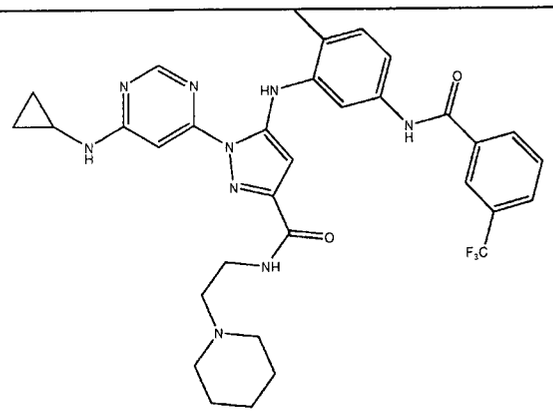
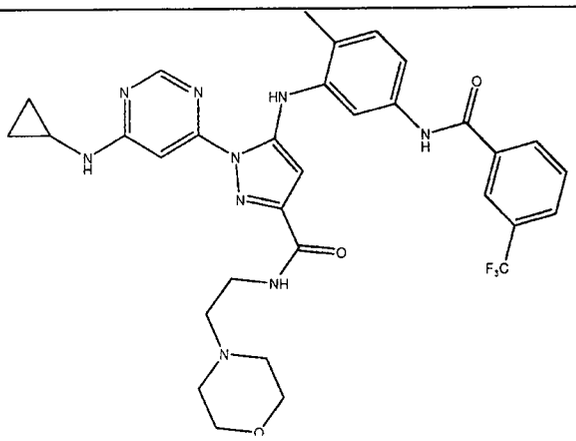
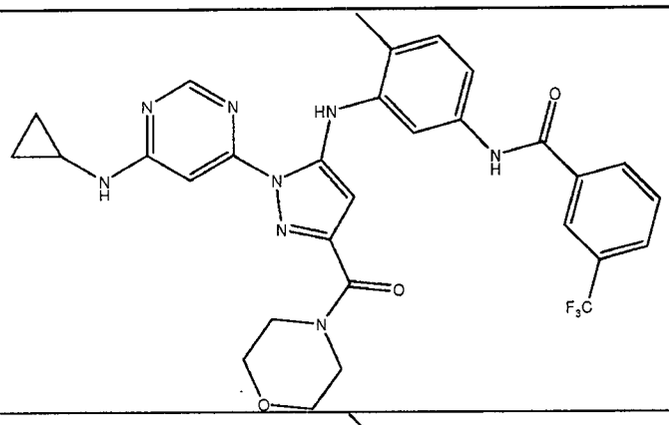
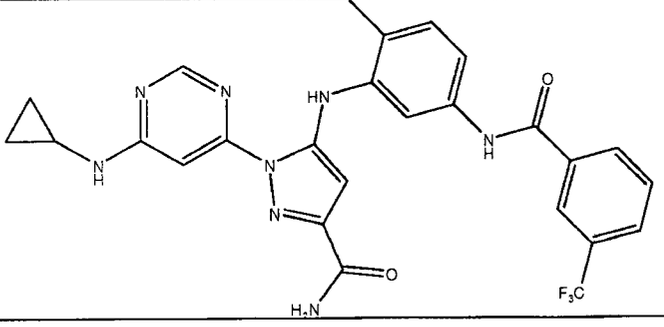
76		MS *m/z* 577.3 (M + 1)
77		MS *m/z* 578.3 (M + 1)
78		MS *m/z* 583.3 (M + 1)
79		MS *m/z* 595.3 (M + 1)
80		MS *m/z* 566.3 (M + 1)

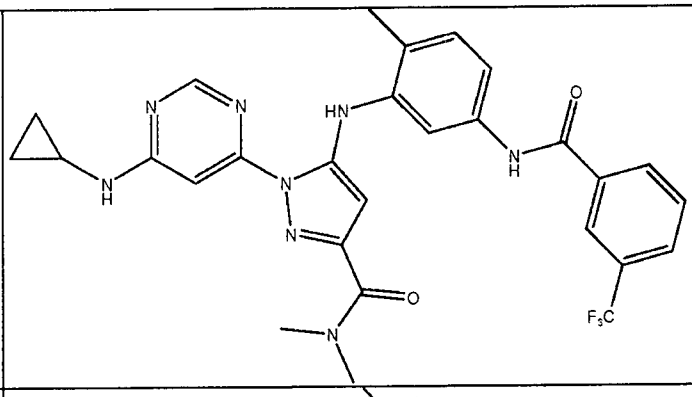
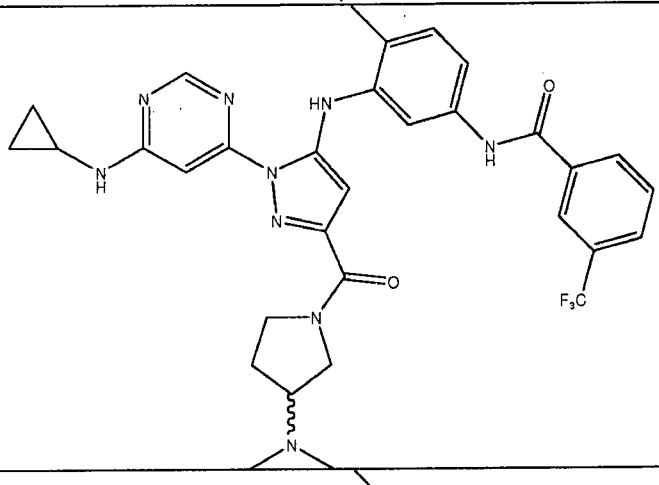
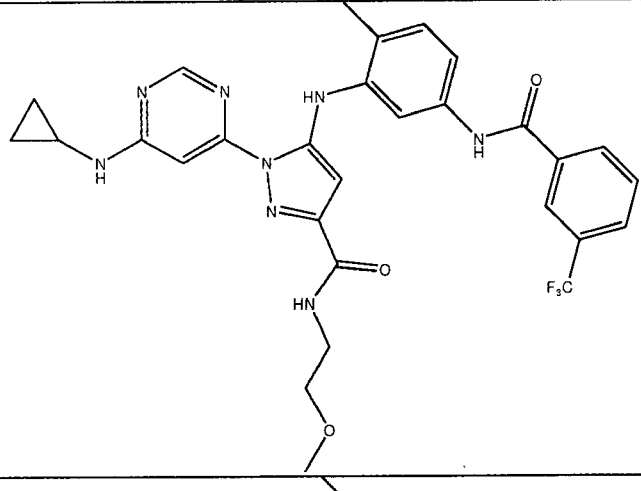
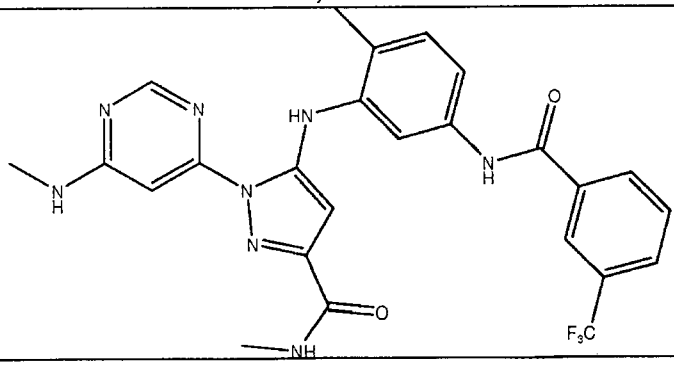
81		MS *m/z* 565.3 (M + 1)
82		MS *m/z* 563.3 (M + 1)
83		MS *m/z* 564.3 (M + 1)
84		MS *m/z* 562.3 (M + 1)
85		MS *m/z* 556.3 (M + 1)

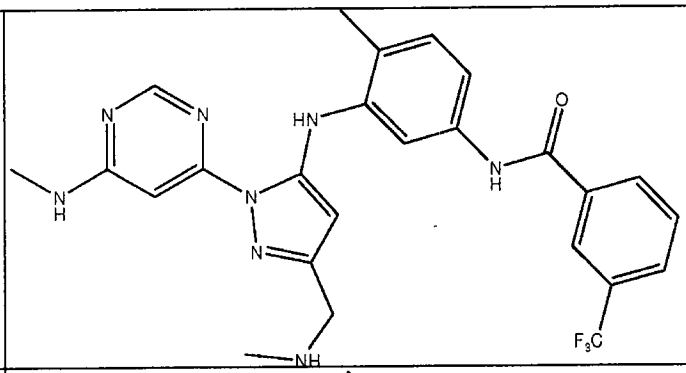
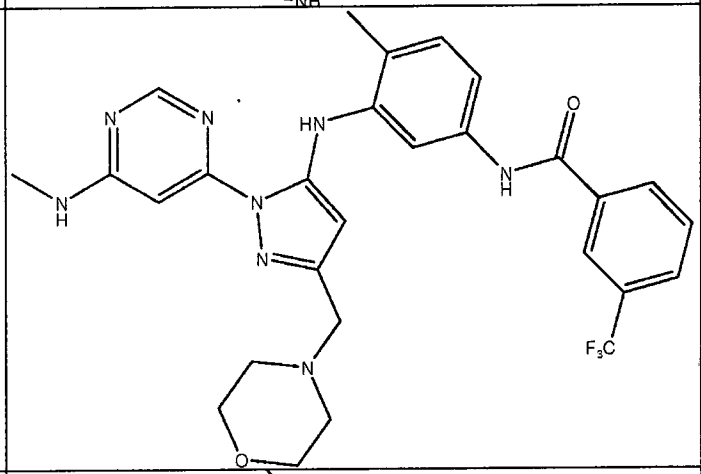
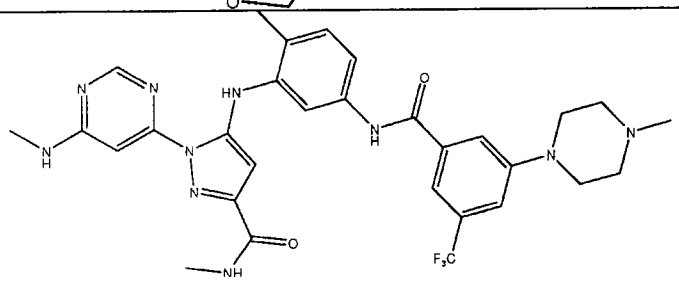
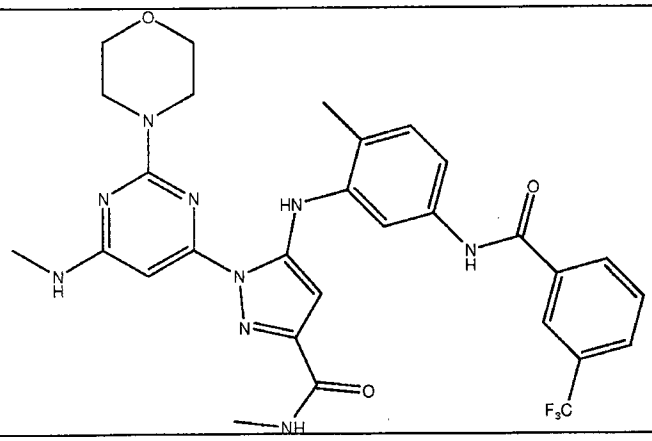
86		MS *m/z* 570.3 (M + 1)
87		MS *m/z* 566.2 (M + 1)
88		MS *m/z* 551.2 (M + 1)
89		MS *m/z* 524.2 (M + 1)
90		MS *m/z* 551.2 (M + 1)
91		MS *m/z* 537.2 (M + 1)

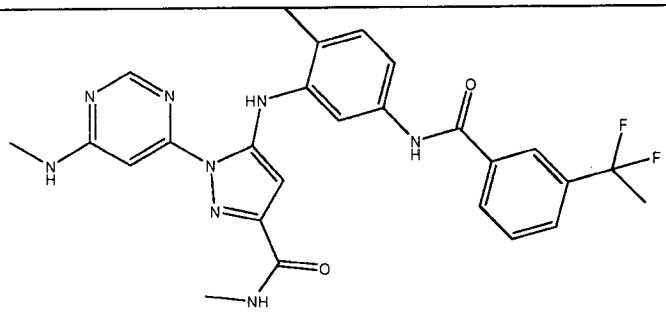
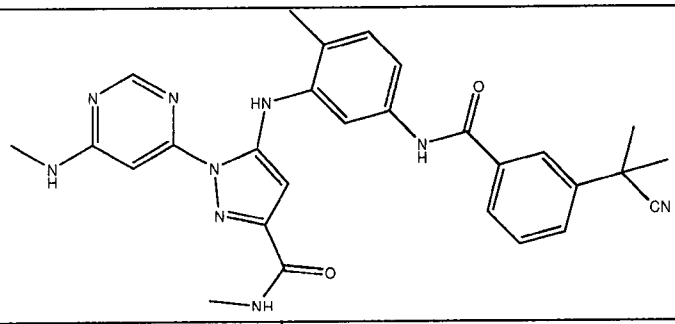
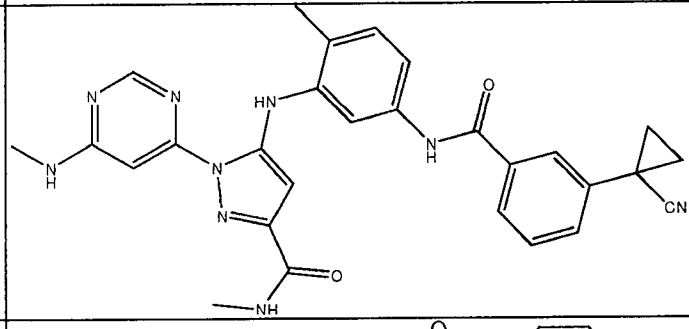
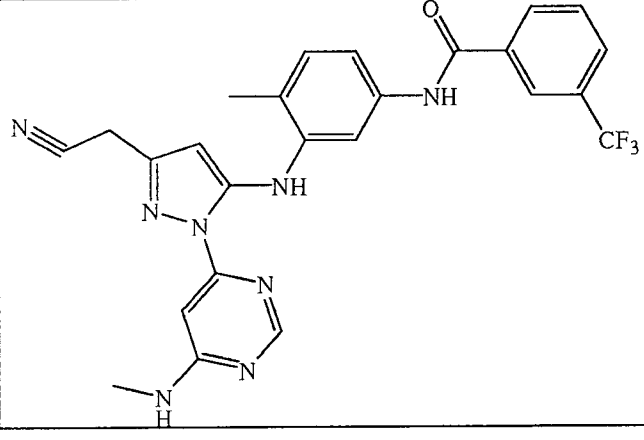
92		MS *m/z* 593.3 (M + 1)
93		MS *m/z* 622.3 (M + 1)
94		MS *m/z* 606.3 (M + 1)
95		MS *m/z* 649.3 (M + 1)

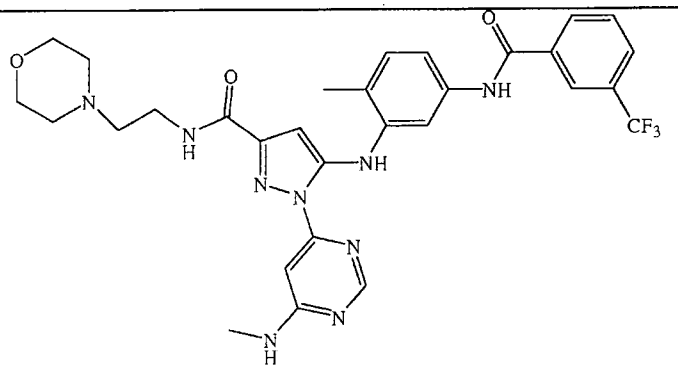
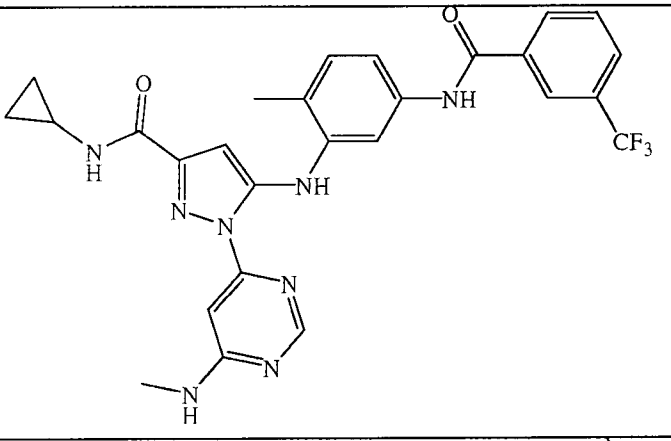
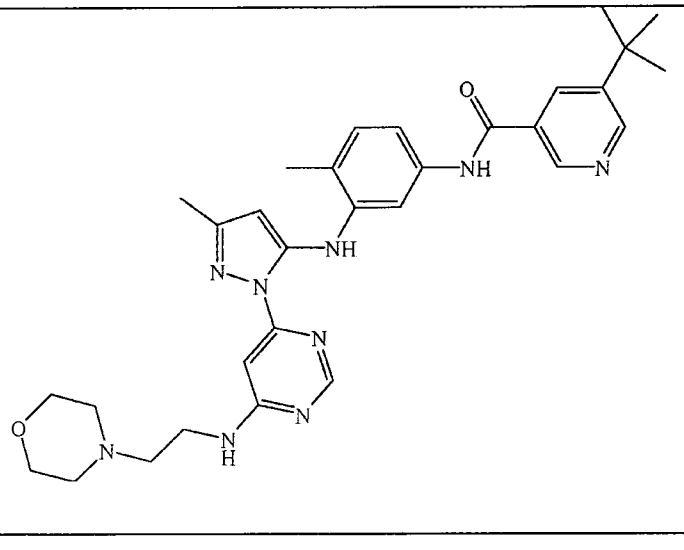
96		MS *m/z* 608.3 (M + 1)
97		MS *m/z* 551.2 (M + 1)
98		MS *m/z* 605.2 (M + 1)
99		MS *m/z* 608.3 (M + 1)

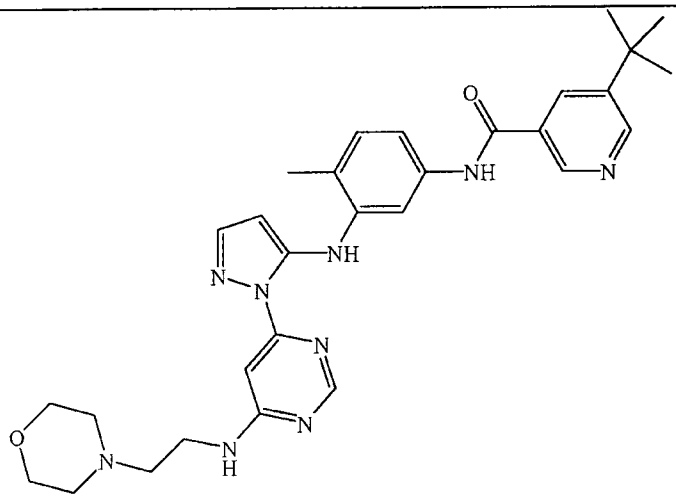
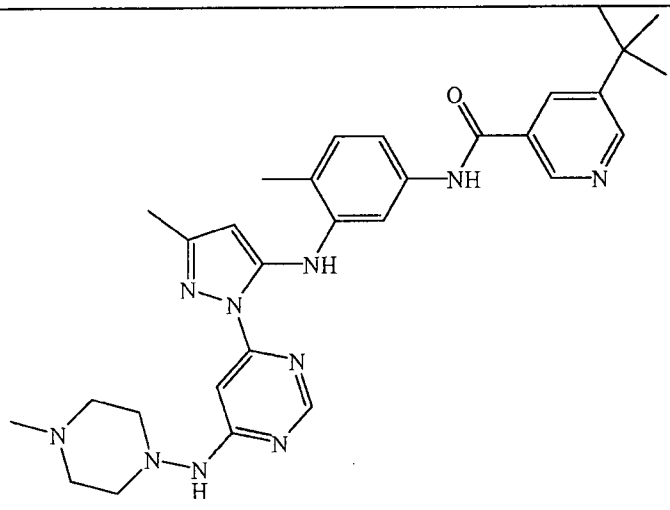
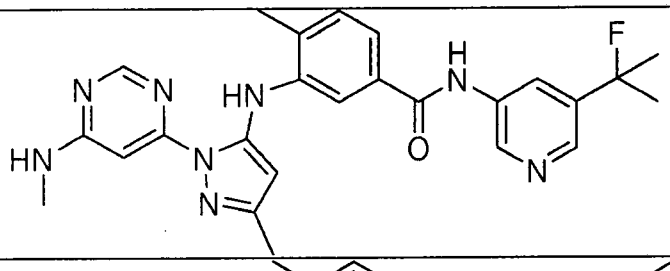
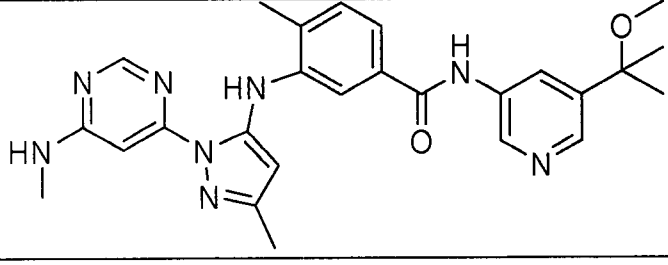
100		MS *m/z* 648.3 (M + 1)
101		MS *m/z* 650.3 (M + 1)
102		MS *m/z* *601.2* (M + 1)
103		MS *m/z* 537.2 (M + 1)

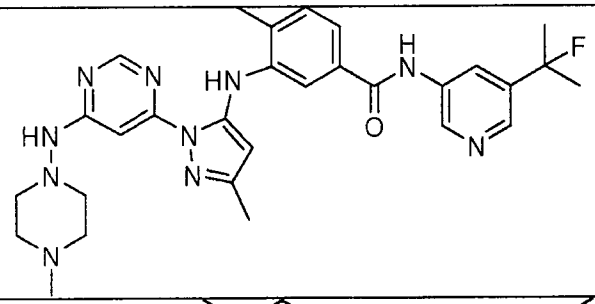
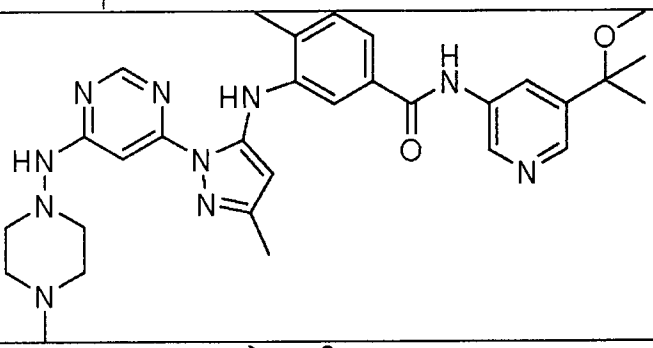
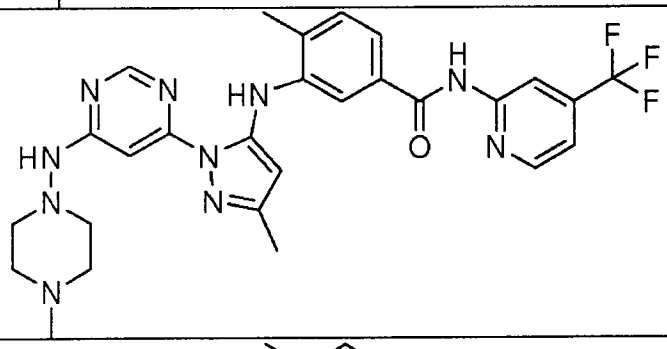
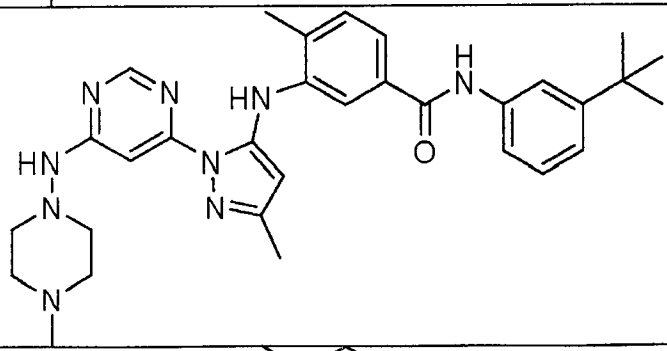
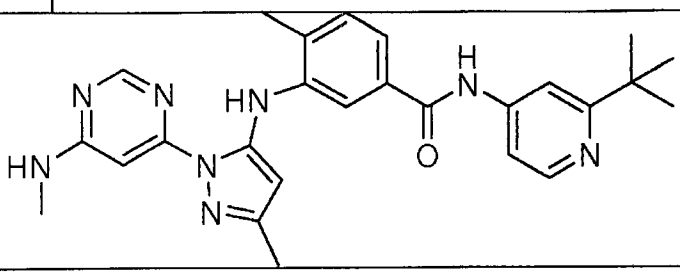
104		MS *m/z* 562.2 (M + 1)
105		MS *m/z* 634.3 (M + 1)
106		MS *m/z* 595.3 (M + 1)
107		MS *m/z* 525.3 (M + 1)

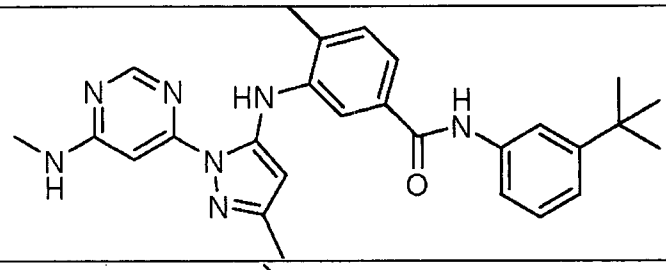
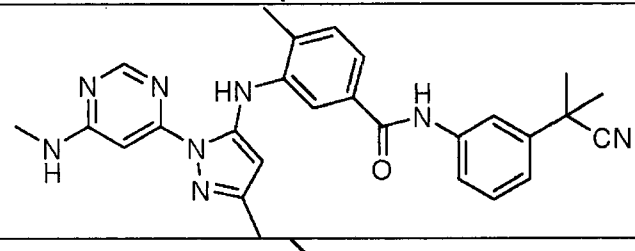
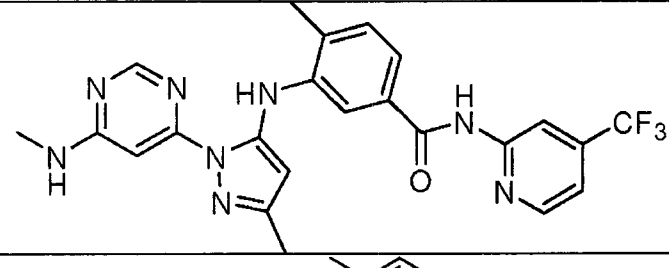
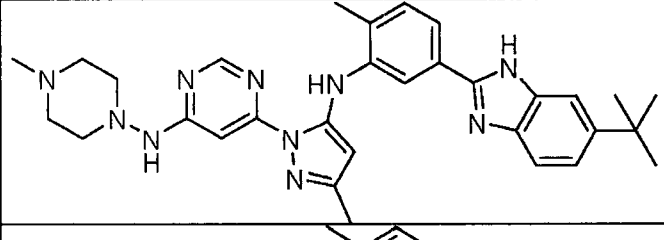
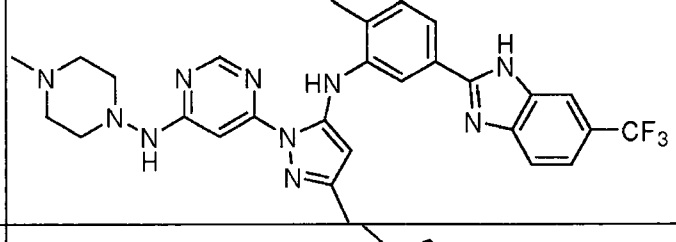
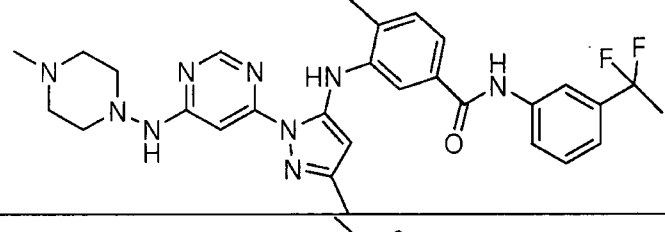
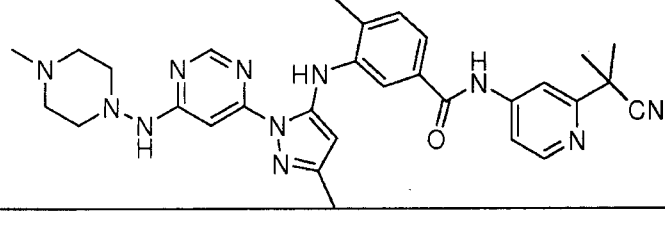
108		MS *m/z* 511.2 (M + 1)
109		MS *m/z* *561.2* (M + 1)
110		MS *m/z* 623.3 (M + 1)
111		MS *m/z* 610.2 (M + 1)

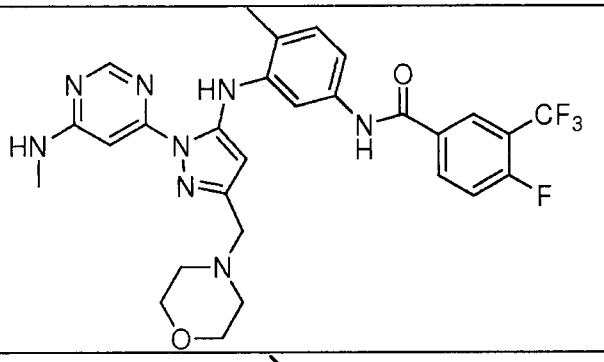
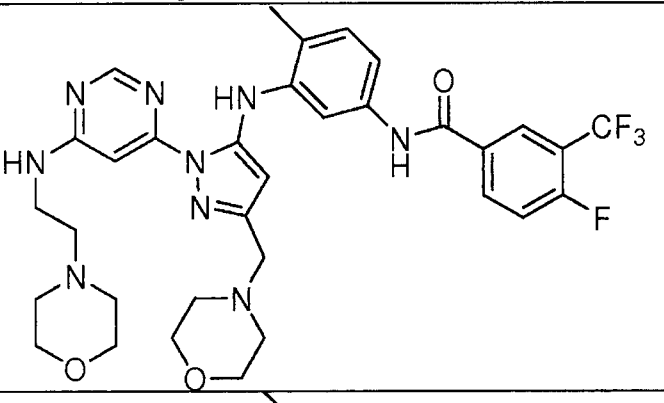
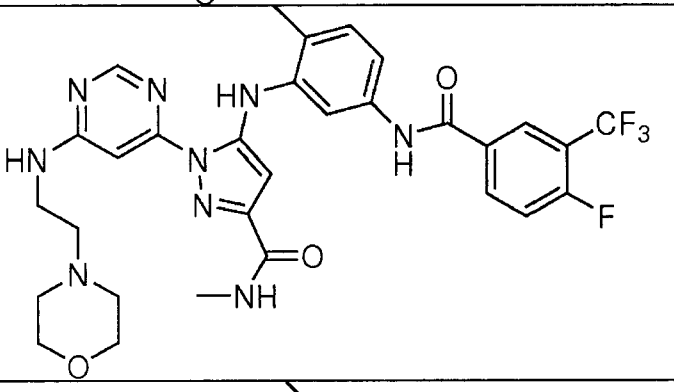
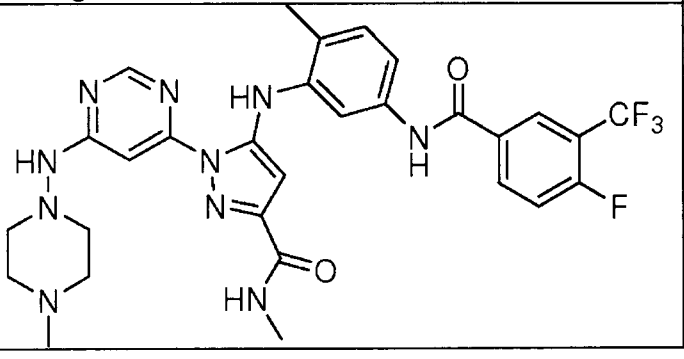
112		MS *m/z* 521.2 (M + 1)
113		MS *m/z* 524.2 (M + 1)
114		MS *m/z* 507.2 (M + 1)
115		MS *m/z* 522.2 (M + 1)

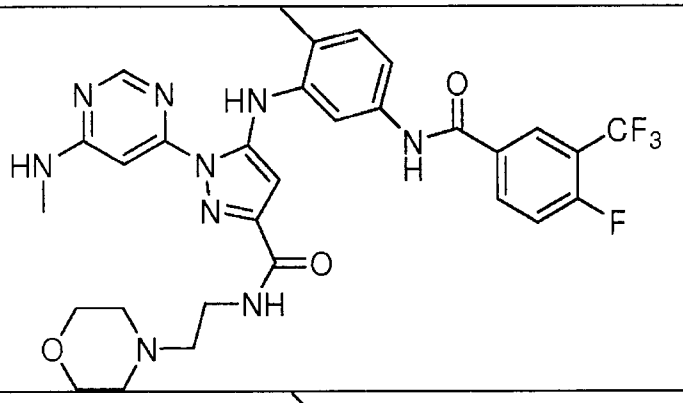
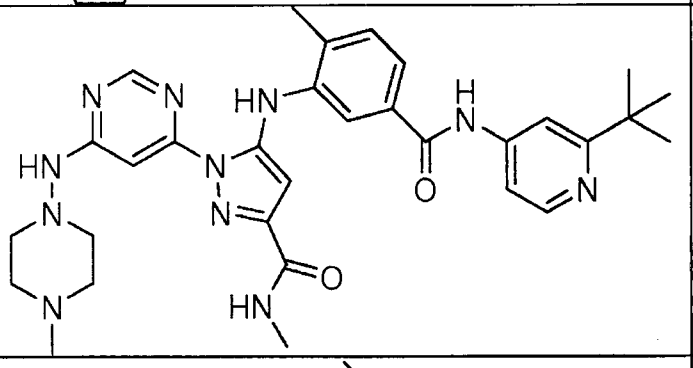
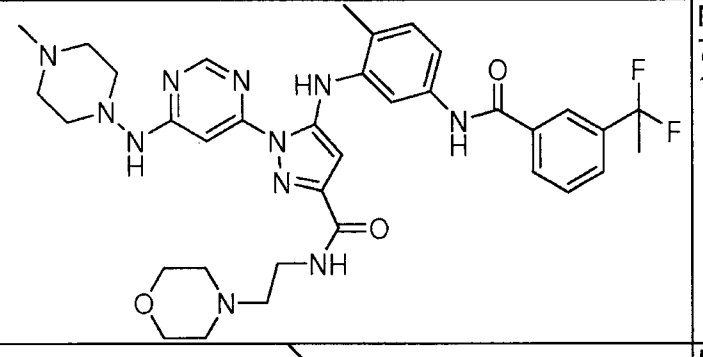
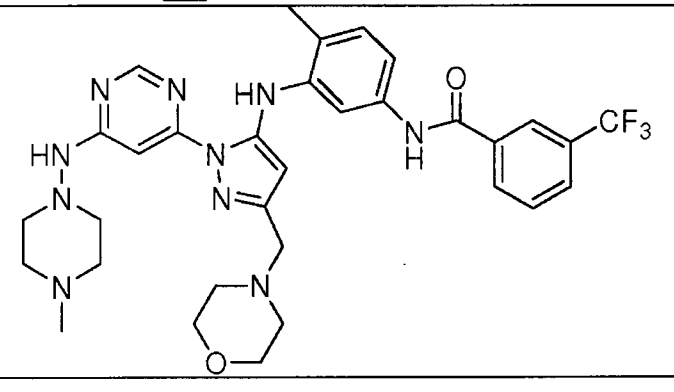
116		MS *m/z* *62M* (M + 1)
117		MS *m/z* 551.2 (M + 1)
118		MS *m/z* 570.3 (M + 1)

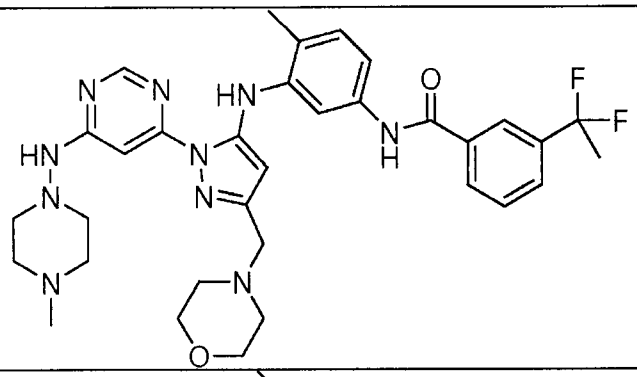
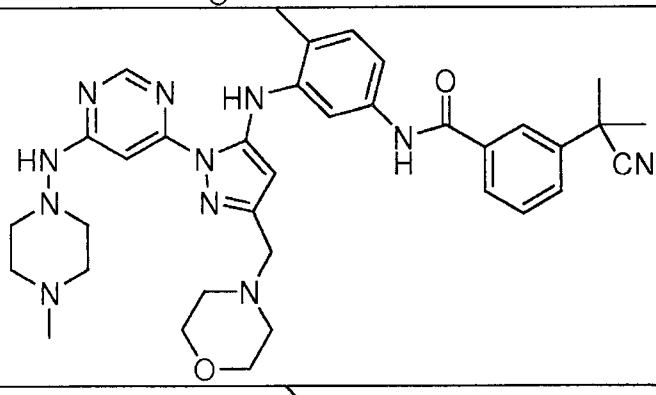
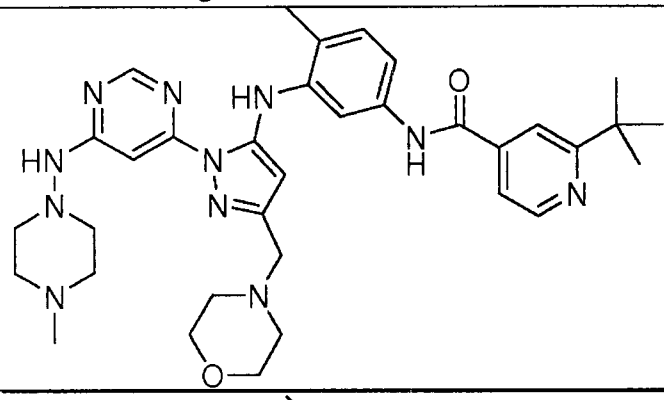
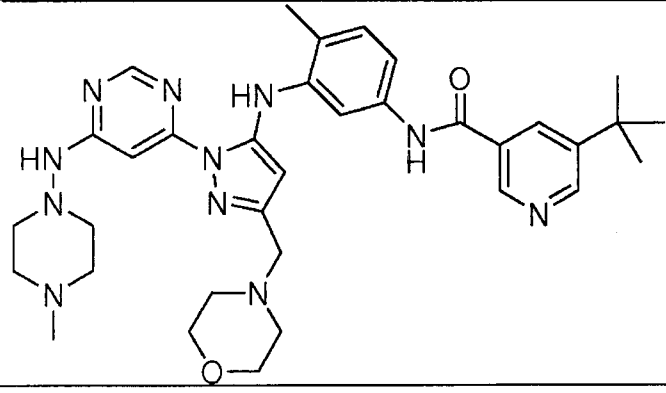
119		MS *m/z* 556.3 (M + 1)
120		MS *m/z* 555.3 (M + 1)
121		MS *m/z* 475.2 (M + 1)
122		MS *m/z* 487.3 (M + 1)

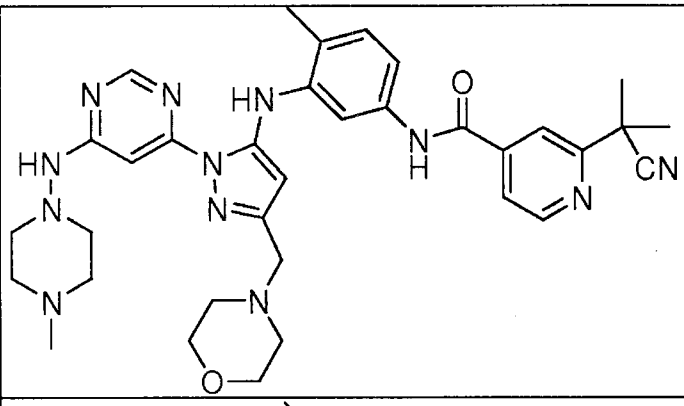
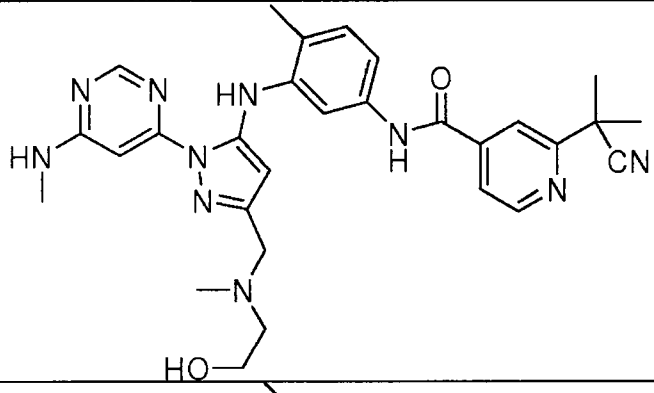
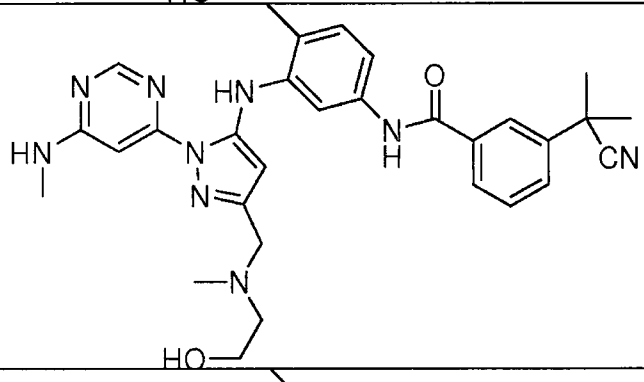
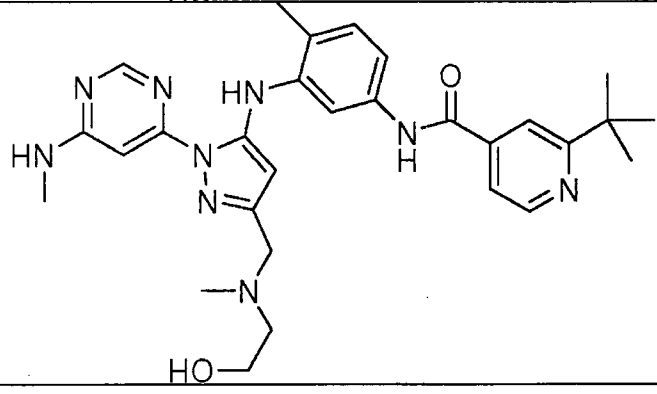
123		MS *m/z* 559.3 (M + 1)
124		MS *m/z* 571.3 (M + 1)
125		MS *m/z* 567.3 (M + 1)
126		MS *m/z* 554.3 (M + 1)
127		MS *m/z* 471.3 (M + 1)

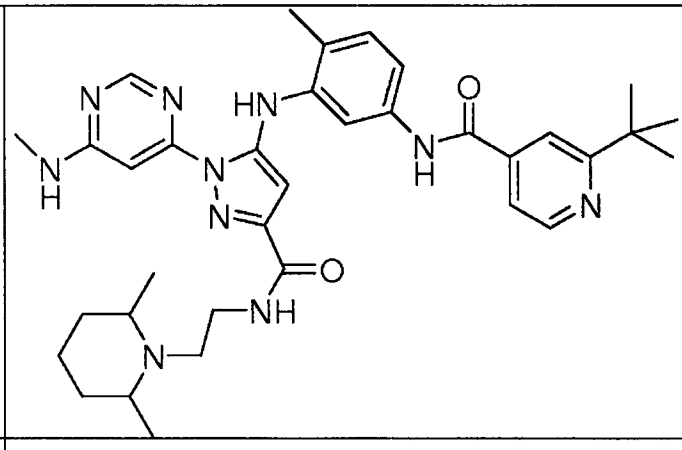
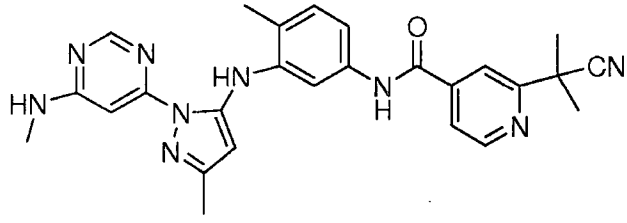
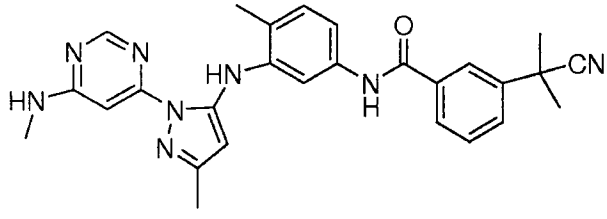
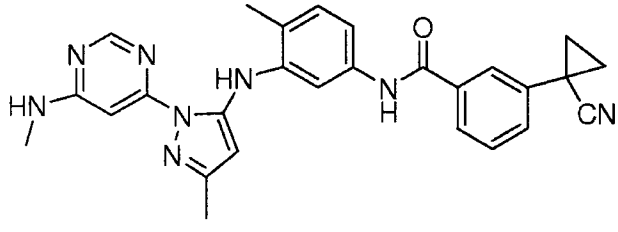
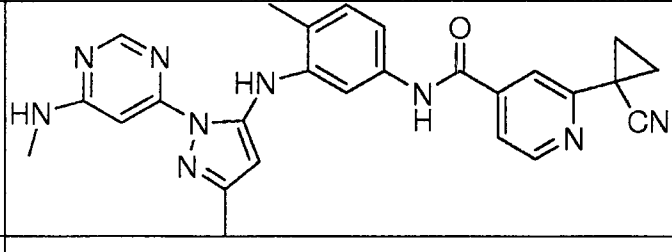
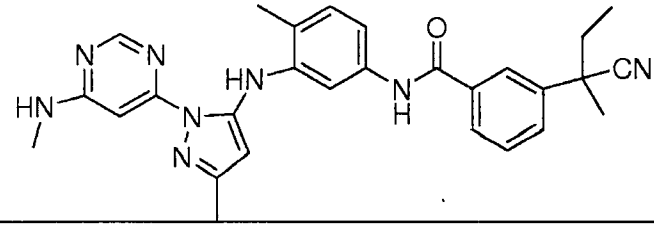
128		MS *m/z* 470.3 (M + 1)
129		MS *m/z* 481.3 (M + 1)
130		MS *m/z* 483.3 (M + 1)
131		MS *m/z* 551.3 (M + 1)
132		MS *m/z* 563.3 (M + 1)
133		MS *m/z* 562.3 (M + 1)
134		MS *m/z* 566.3 (M + 1)

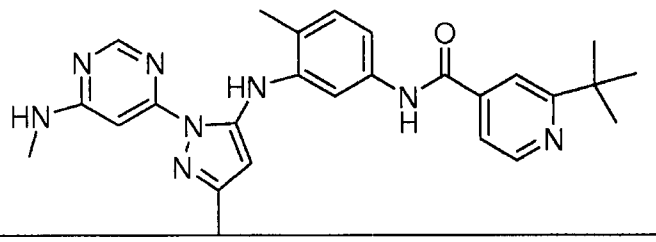
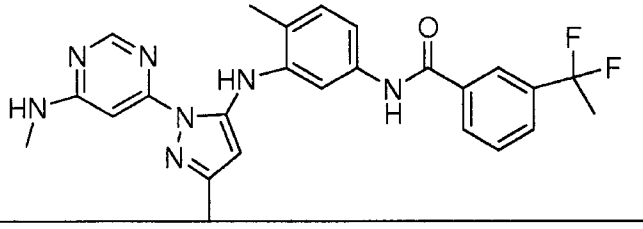
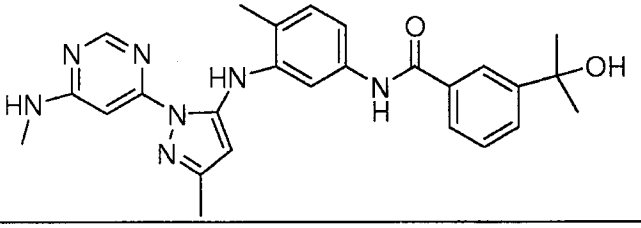
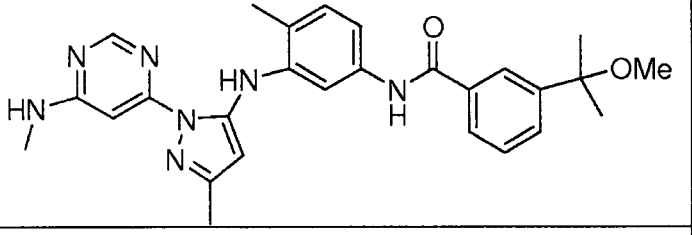
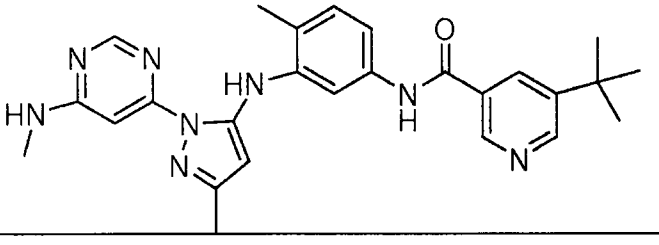
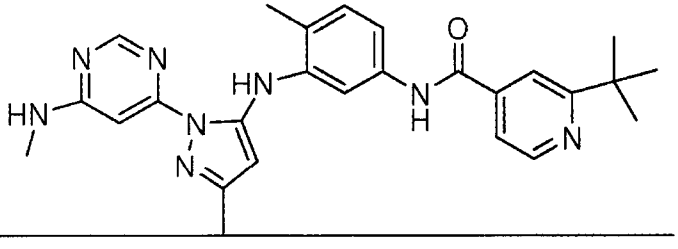
135		MS *m/z* 585.3 (M + 1)
136		MS *m/z* 684.3 (M + 1)
137		MS *m/z* 642.3 (M + 1)
138		MS *m/z* 627.3 (M + 1)

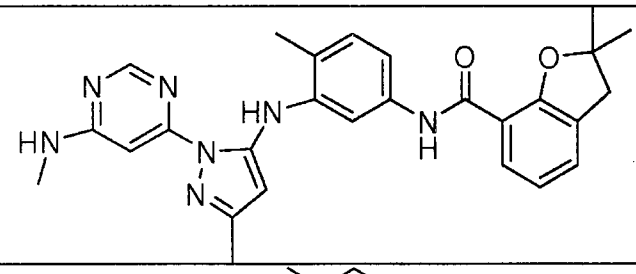
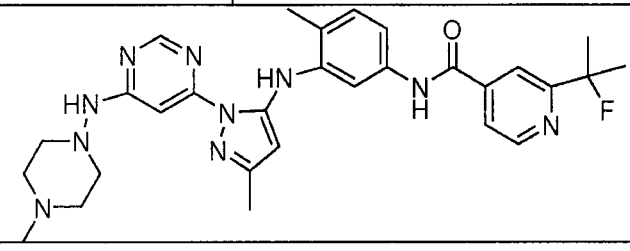
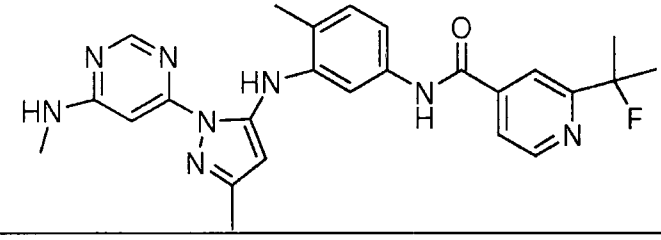
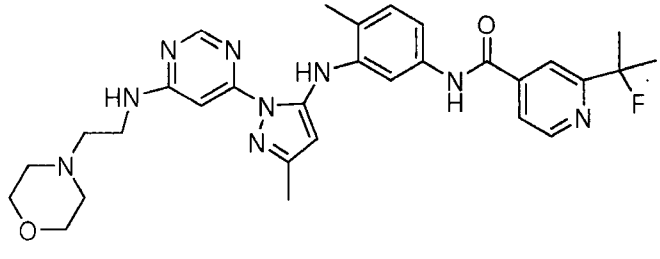
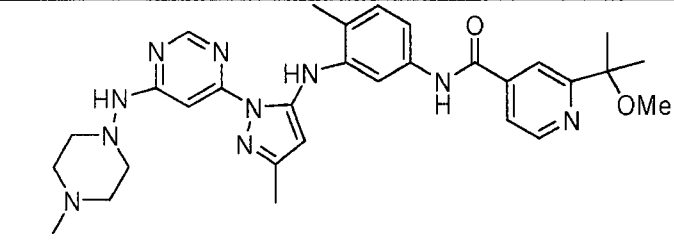
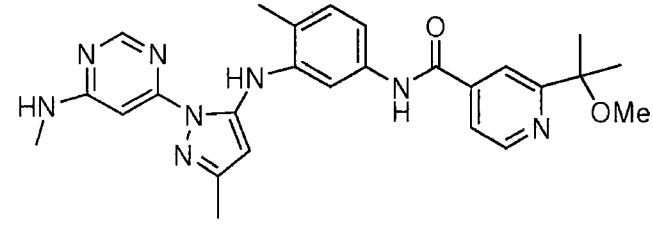
139		MS *m/z* 642.3 (M + 1)
140		MS *m/z* 598.3 (M + 1)
141		MS *m/z* 704.3 (M + 1)
142		MS *m/z* 651.3 (M + 1)

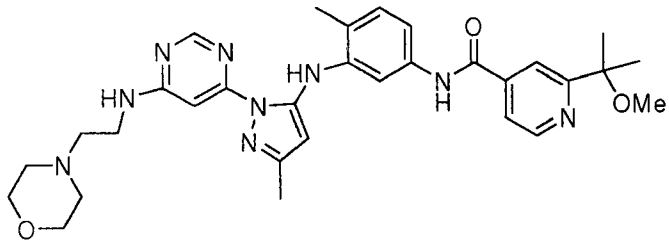
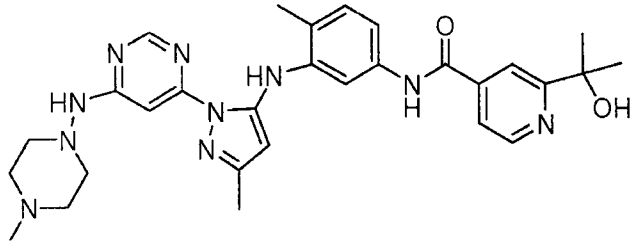
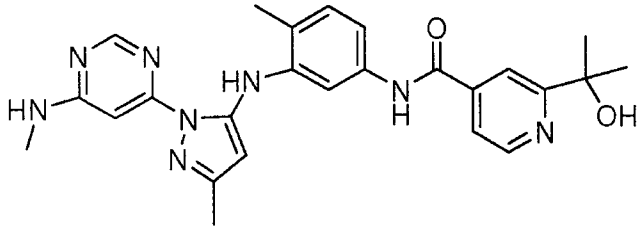
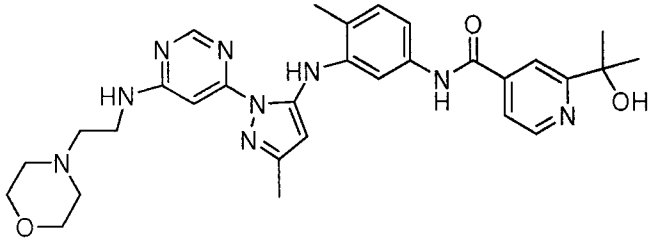
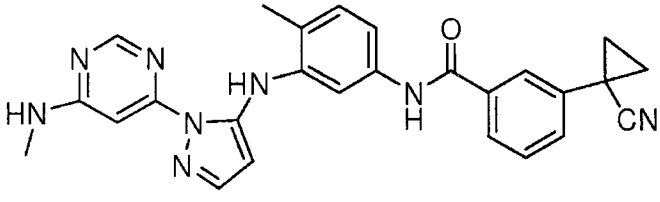
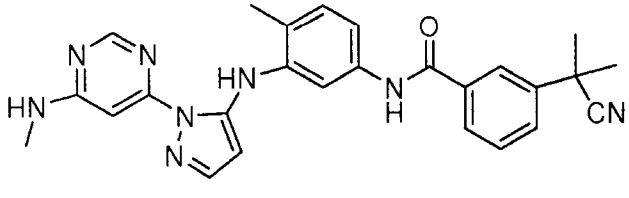
143		MS *m/z* 647.3 (M + 1)
144		MS *m/z* 650.3 (M + 1)
145		MS *m/z* 640.3 (M + 1)
146		MS *m/z* 640.3 (M + 1)

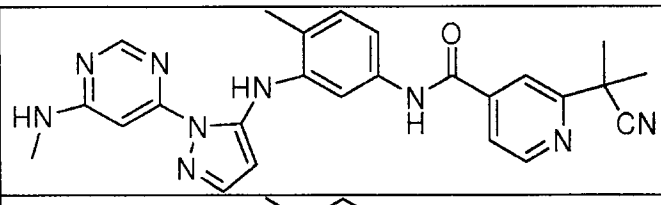
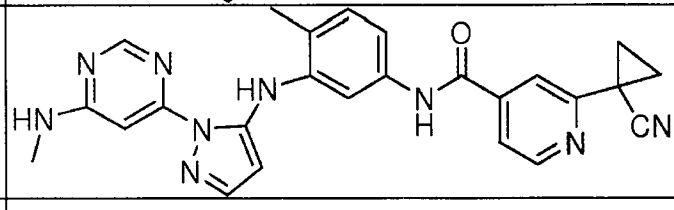
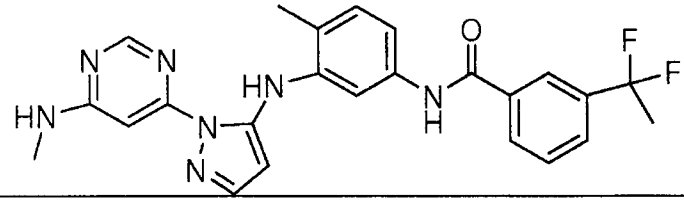
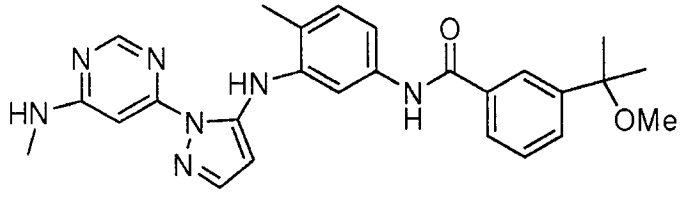
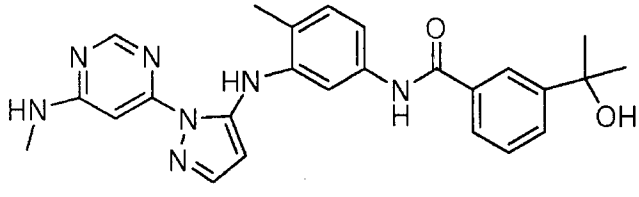
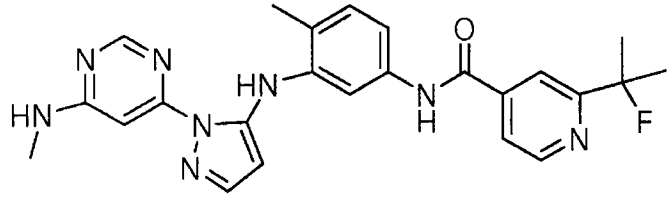
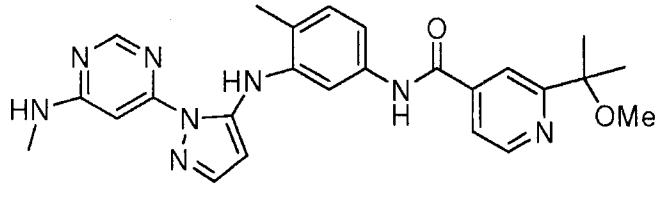
147		MS *m/z* 651.3 (M + 1)
148		MS *m/z* 555.3 (M + 1)
149		MS *m/z* 554.3 (M + 1)
150		MS *m/z* 544.3 (M + 1)

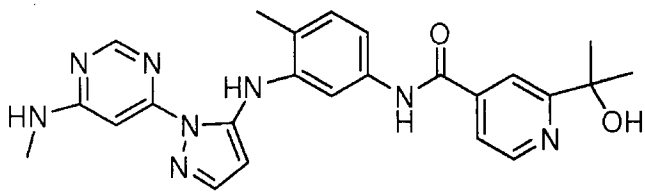
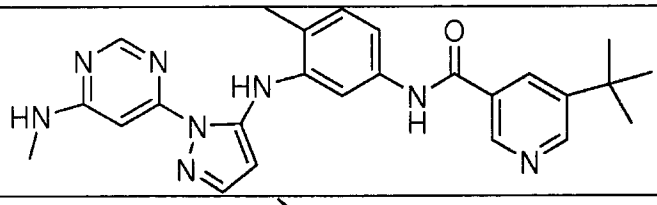
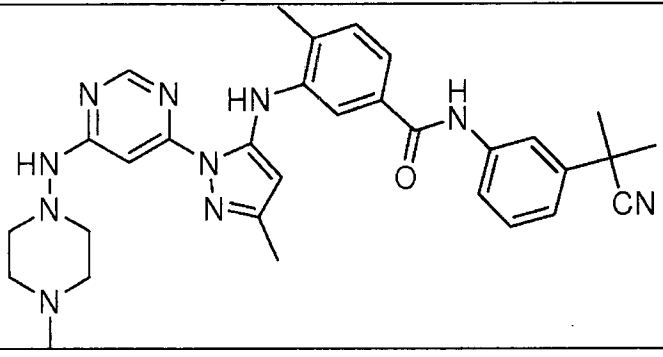
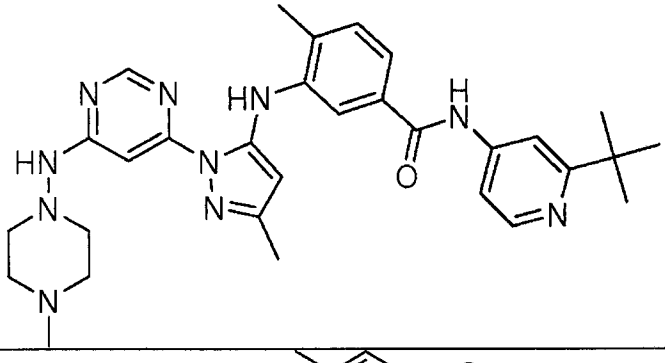
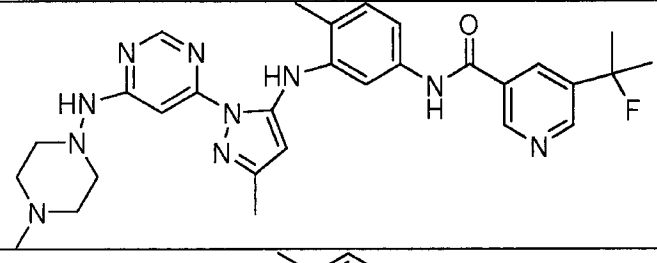
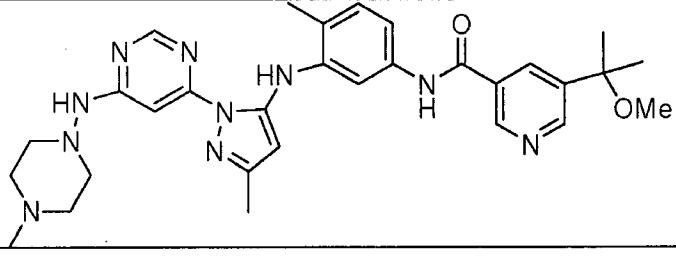
151		MS *m/z* 639.3 (M + 1)
152		MS *m/z* 482.2 (M + 1)
153		MS *m/z* 481.2 (M + 1)
154		MS *m/z* 479.2(M + 1)
155		MS *m/z* 480.2 (M + 1)
156		MS *m/z* 495.3 (M + 1)

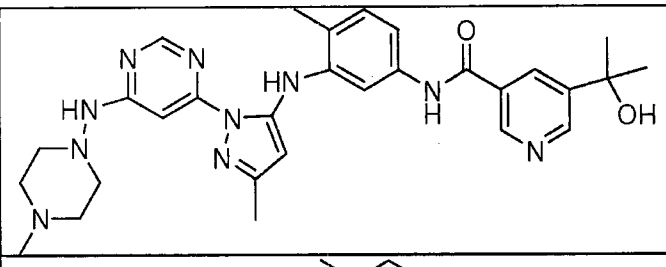
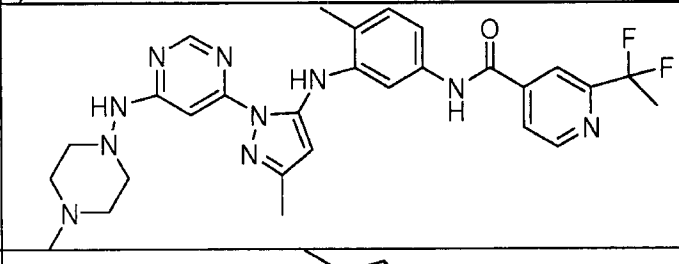
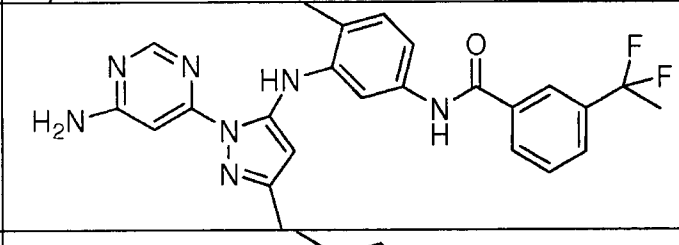
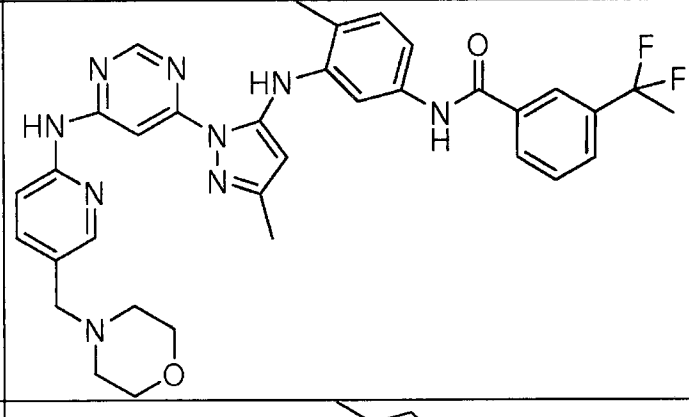
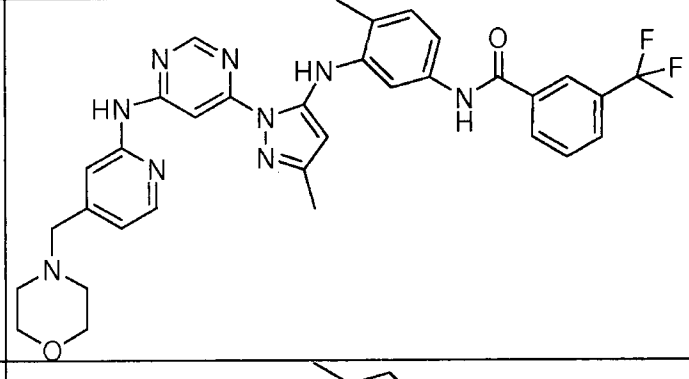
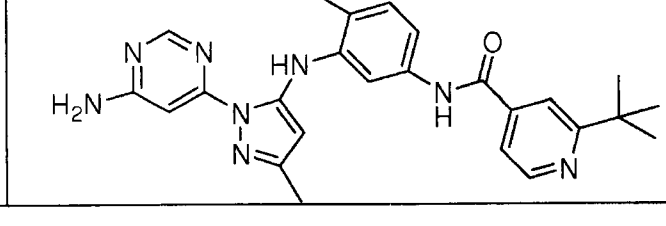
157		MS *m/z* 471.3 (M + 1)
158		MS *m/z* 478.2 (M + 1)
159		MS *m/z* 472.2 (M + 1)
160		MS *m/z* 486.3 (M + 1)
161		MS *m/z* 471.3 (M + 1)
162		MS *m/z* 471.3 (M + 1)

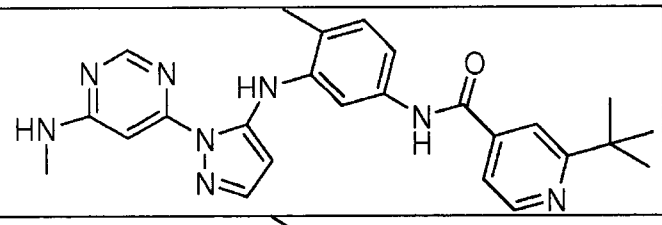
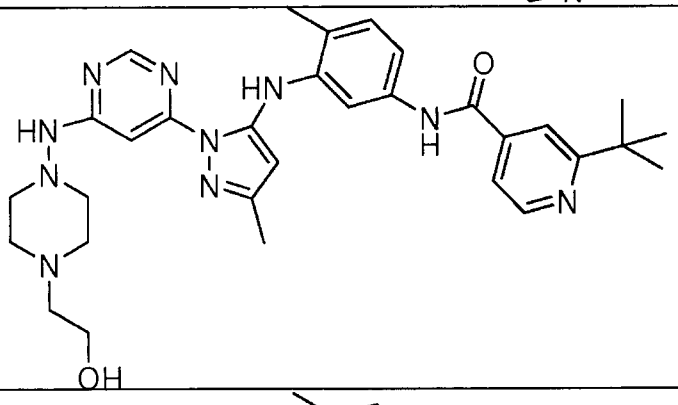
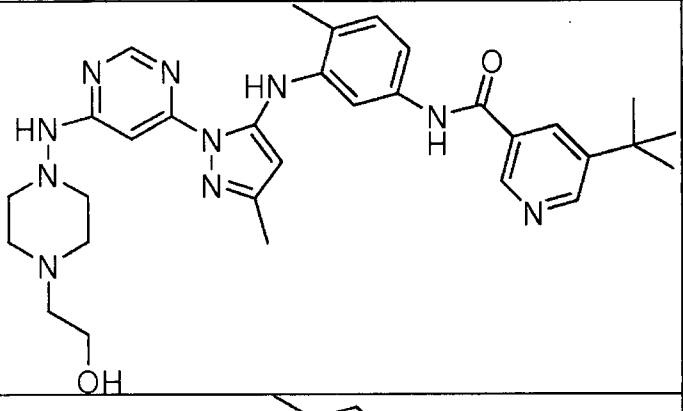
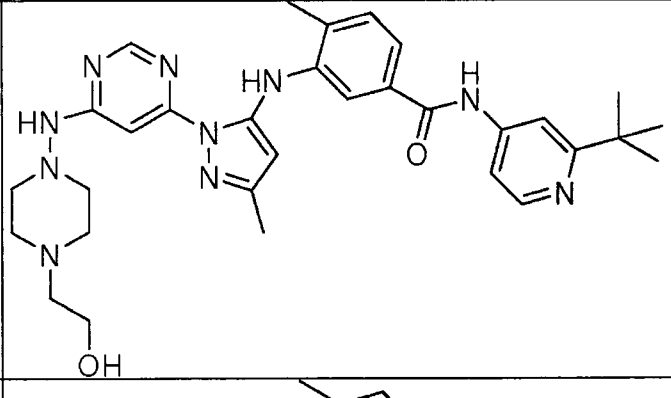
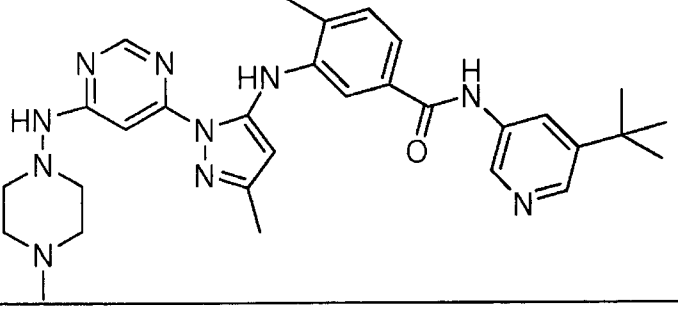
163		MS *m/z* 484.2 (M + 1)
164		MS *m/z* 559.3 (M + 1)
165		MS *m/z* 475.2 (M + 1)
166		MS *m/z* 574.3 (M + 1)
167		MS *m/z* 571.3 (M + 1)
168		MS *m/z* 487.3 (M + 1)

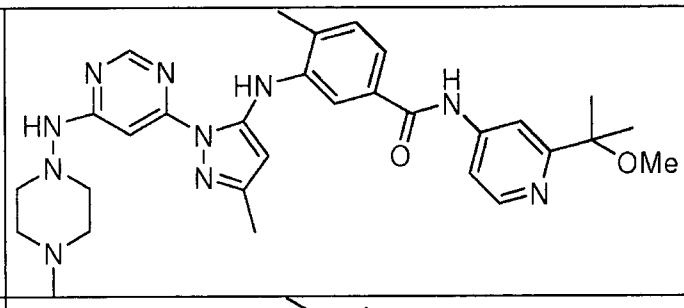
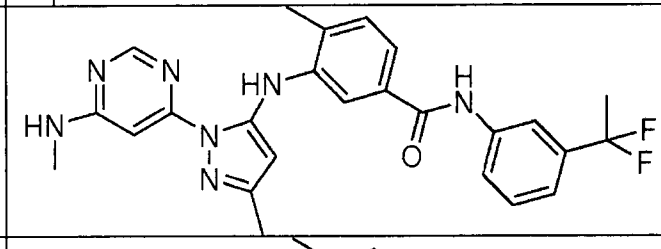
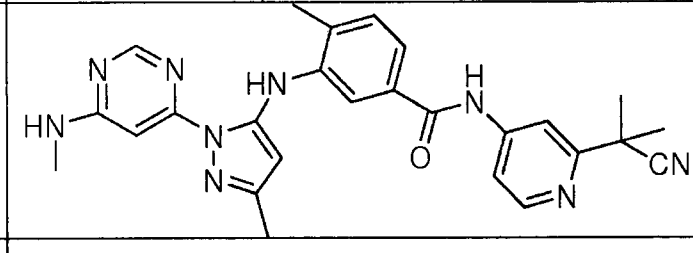
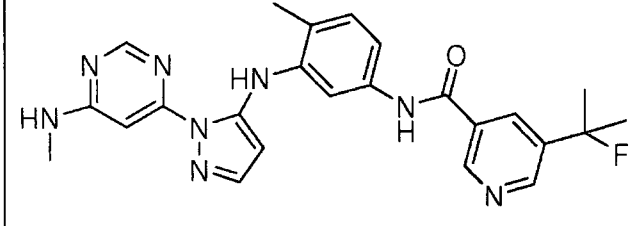
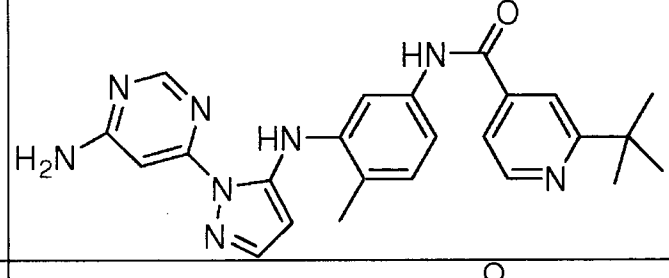
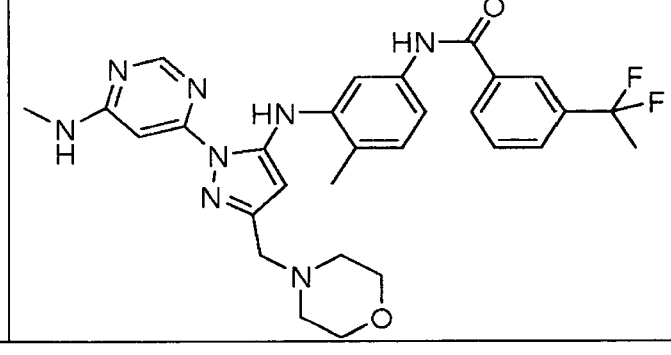
169		MS *m/z* 586.3 (M + 1)
170		MS *m/z* 557.3 (M + 1)
171		MS *m/z* 473.2 (M + 1)
172		MS *m/z* 572.3 (M + 1)
173		MS *m/z* 465.2 (M + 1)
174		MS *m/z* *A61.2* (M + 1)

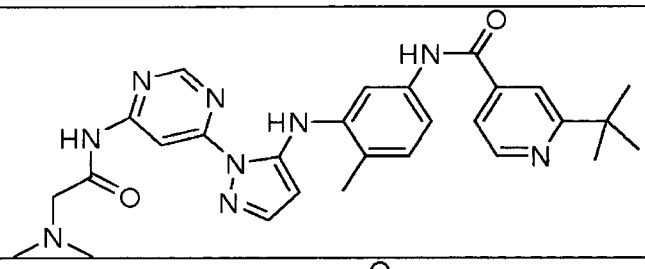
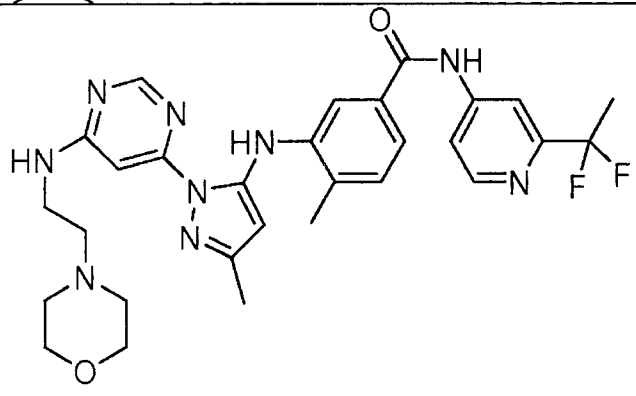
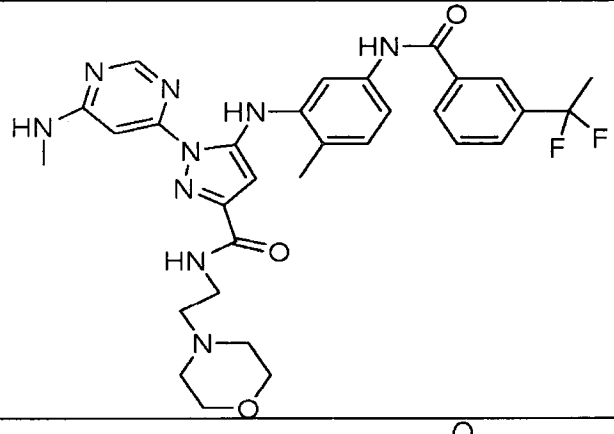
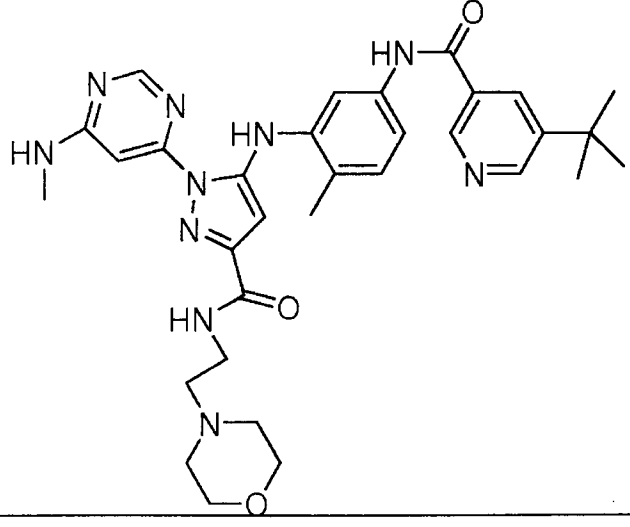
175		MS *m/z* 468.2 (M + 1)
176		MS *m/z* 466.2 (M + 1)
177		MS *m/z* 464.2 (M + 1)
178		MS *m/z* 472.2 (M + 1)
179		MS *m/z* 458.2 (M + 1)
180		MS *m/z* 461.2 (M + 1)
181		MS *m/z* 473.2 (M + 1)

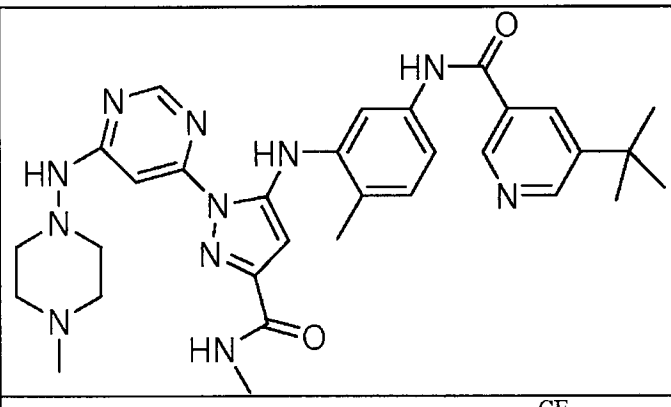
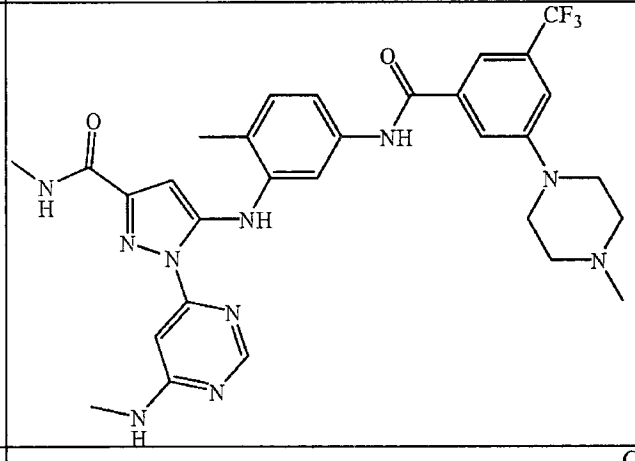
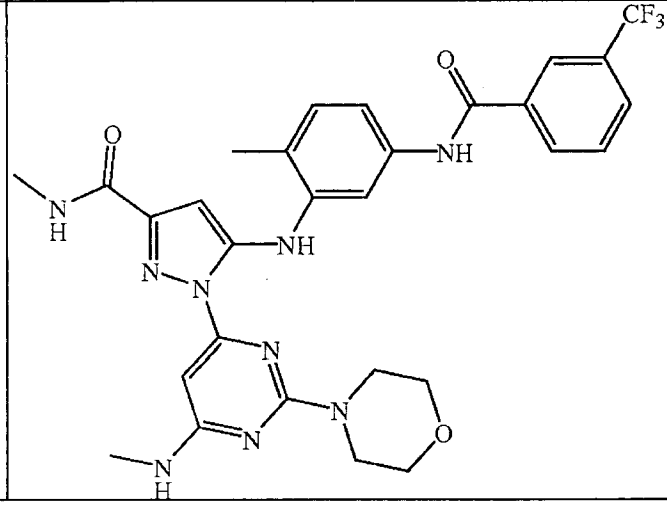
182		MS *m/z* 459.2 (M + 1)
183		MS *m/z* *A51.2* (M + 1)
184		MS *m/z* 565.3 (M + 1)
185		MS *m/z* 555.3 (M + 1)
186		MS *m/z* 559.3 (M + 1)
187		MS *m/z* 571.3 (M + 1)

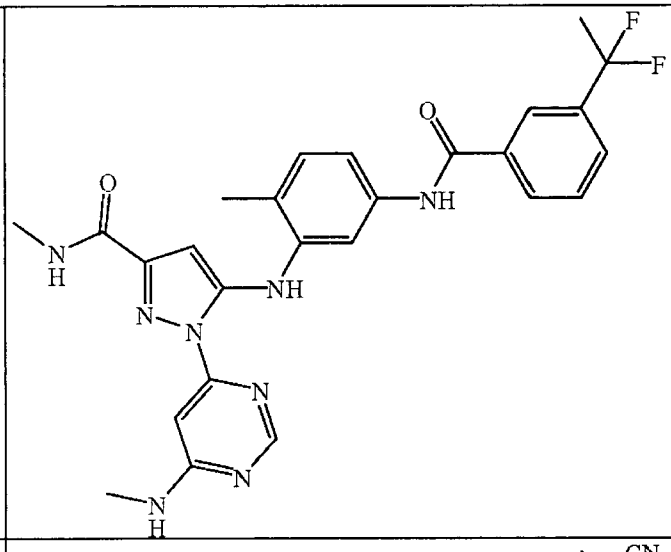
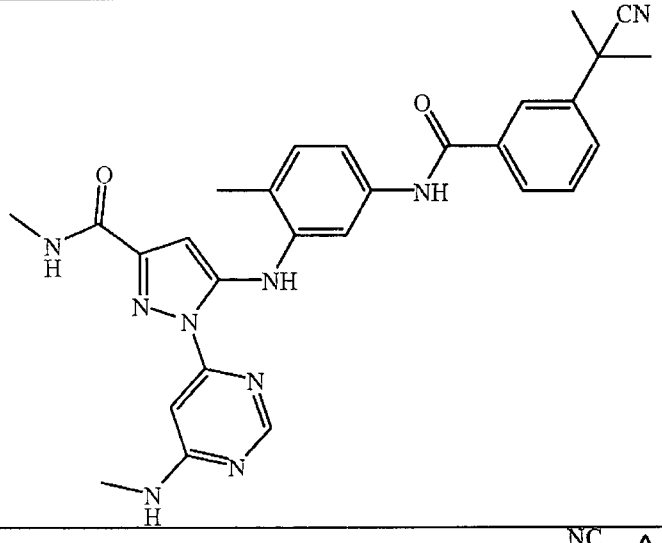
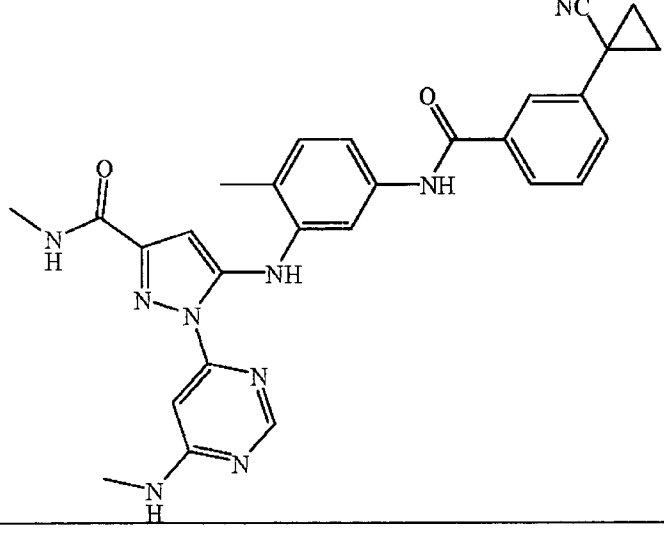
188		MS *m/z* 557.3 (M + 1)
189		MS *m/z* 563.3 (M + 1)
190		MS *m/z* 464.2 (M + 1)
191		MS *m/z* 640.3 (M + 1)
192		MS *m/z* 640.3 (M + 1)
193		MS *m/z* *A51.2* (M + 1)

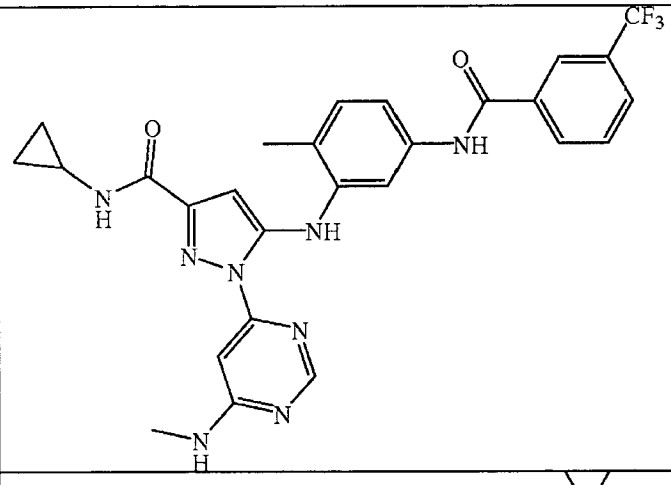
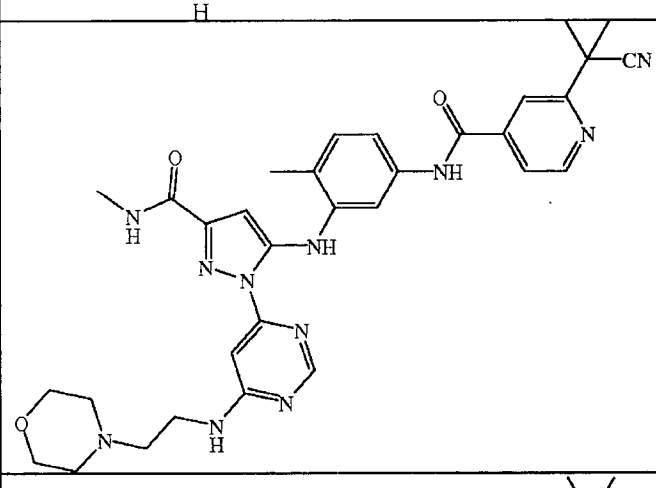
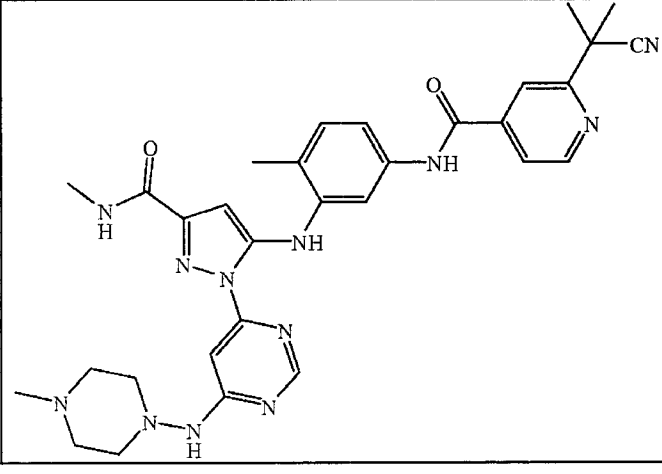
194		MS *m/z* *A51.2* (M + 1)
195		MS *m/z* 585.3 (M + 1)
196		MS *m/z* 585.3 (M + 1)
197		MS *m/z* 585.3 (M + 1)
198		MS *m/z* 555.3 (M + 1)

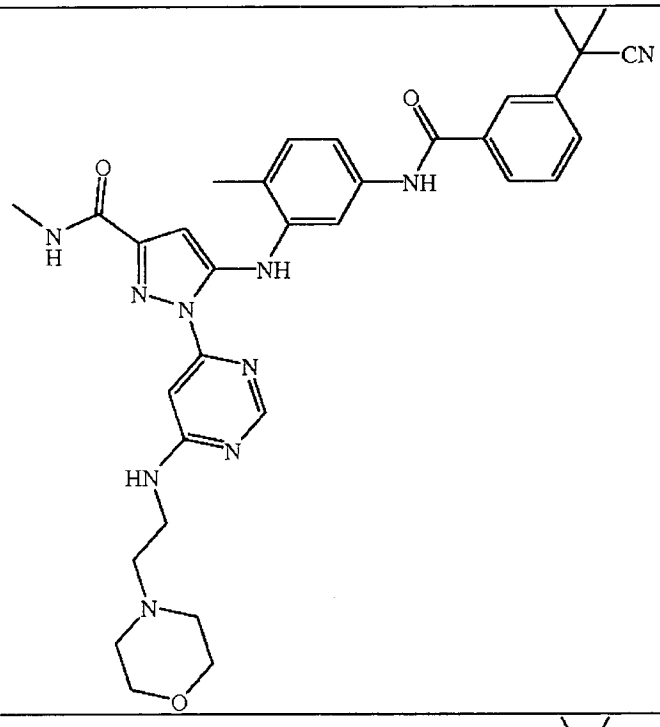
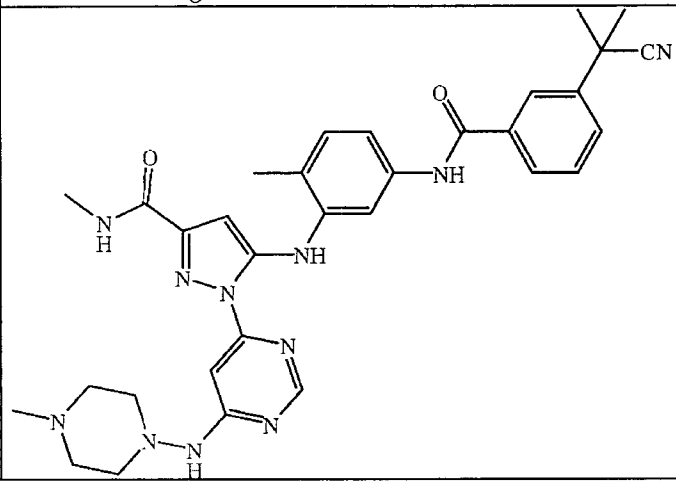
199		MS *m/z* 571.3 (M + 1)
200		MS *m/z* 478.2 (M + 1)
201		MS *m/z* 482.2 (M + 1)
202		MS *m/z* 461.2 (M + 1)
203		MS 443.2 *m/z* (M + 1)
204		MS 563.3 *m/z* (M + 1)

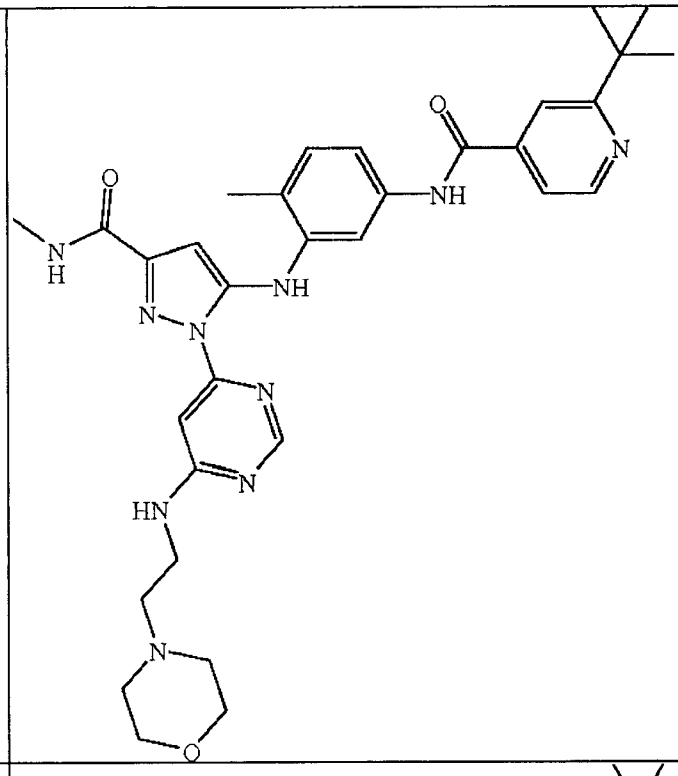
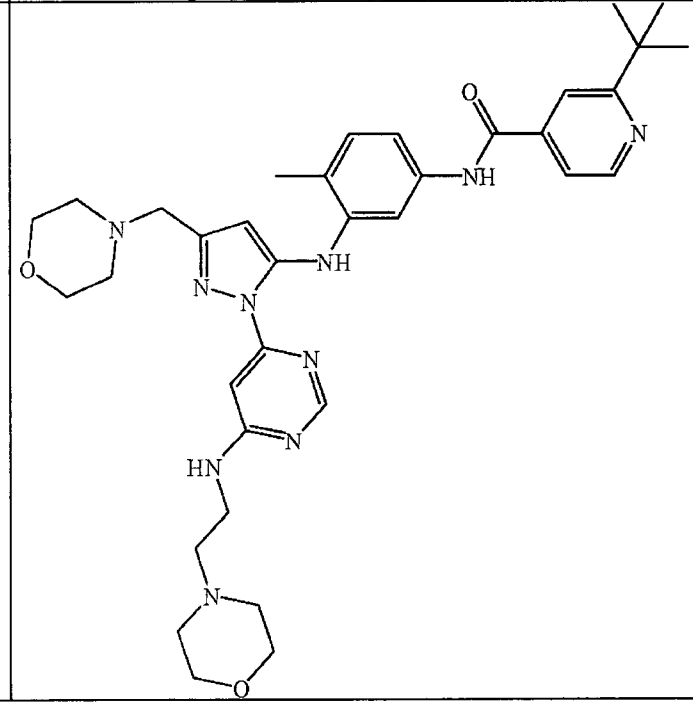
205		Ms 528.3 *m/z* (M + 1)
206		Ms 577.3 *m/z* (M + 1)
207		Ms 620.3 *m/z* (M + 1)
208		Ms 613.3 *m/z* (M + 1)

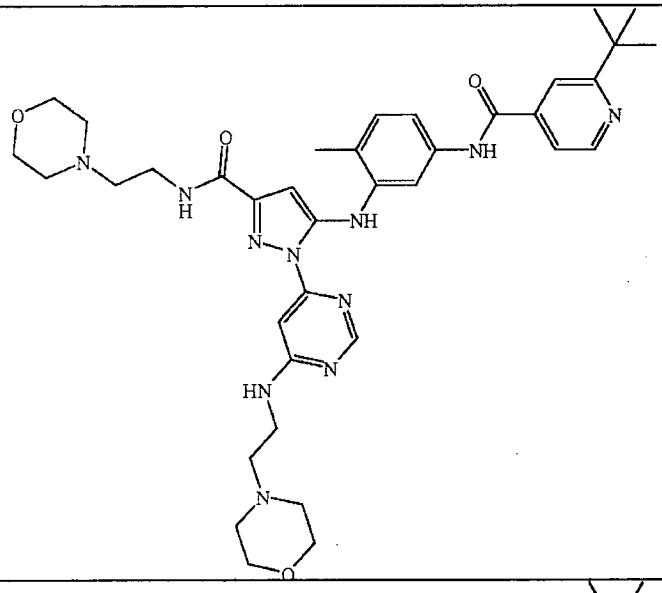
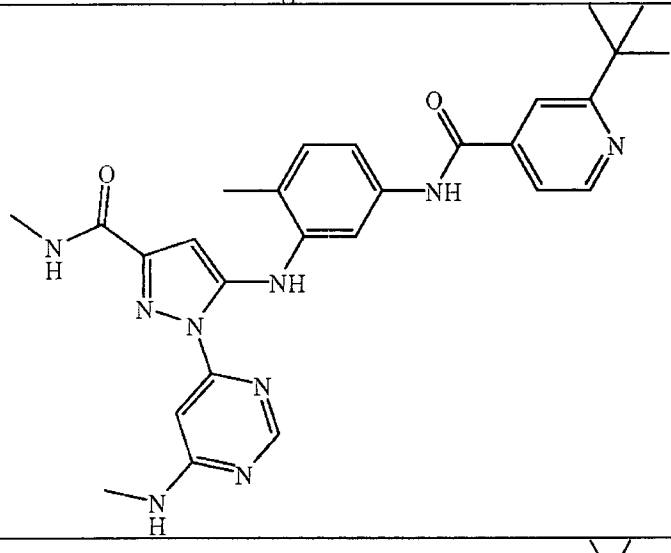
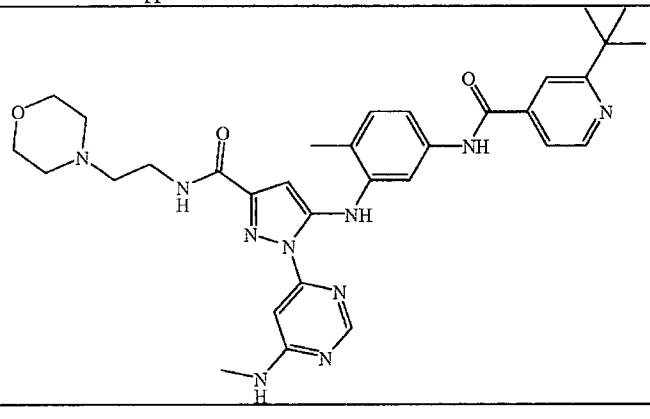
209		Ms 598.3 *m/z* (M + 1)
210		MS *m/z* 623.3 (M + 1)
211		MS *m/z* 610.3 (M + 1)

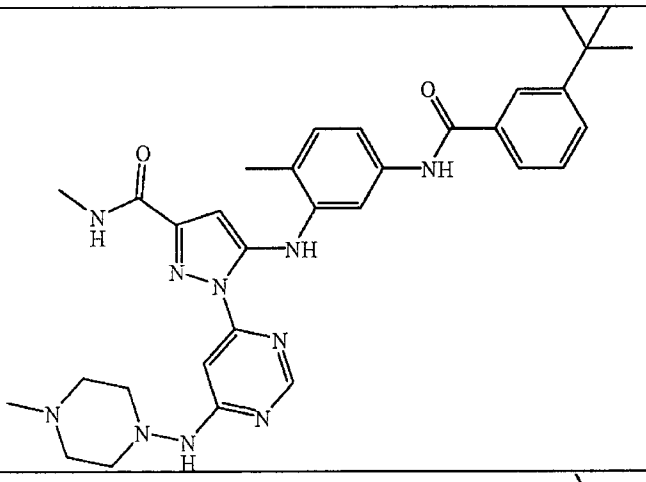
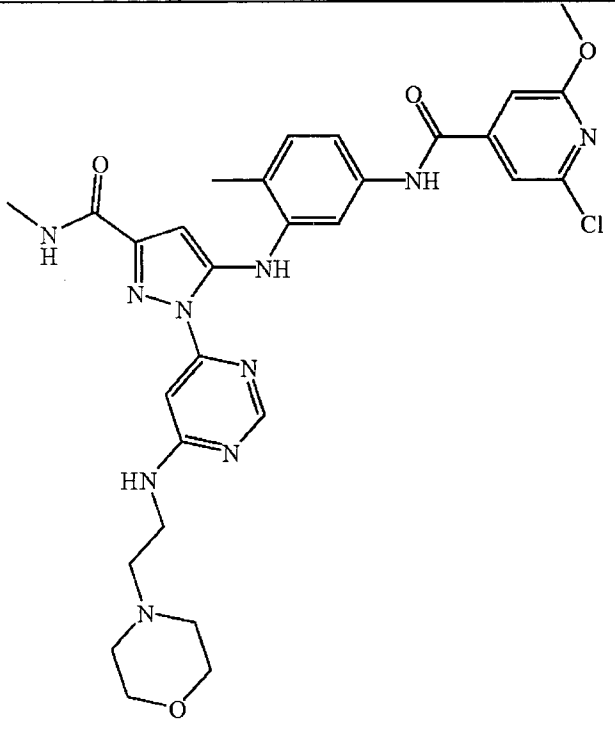
212		MS *m/z* 521.3 (M + 1)
213		MS *m/z* 524.3 (M + 1)
214		MS *m/z* 522.3 (M + 1)

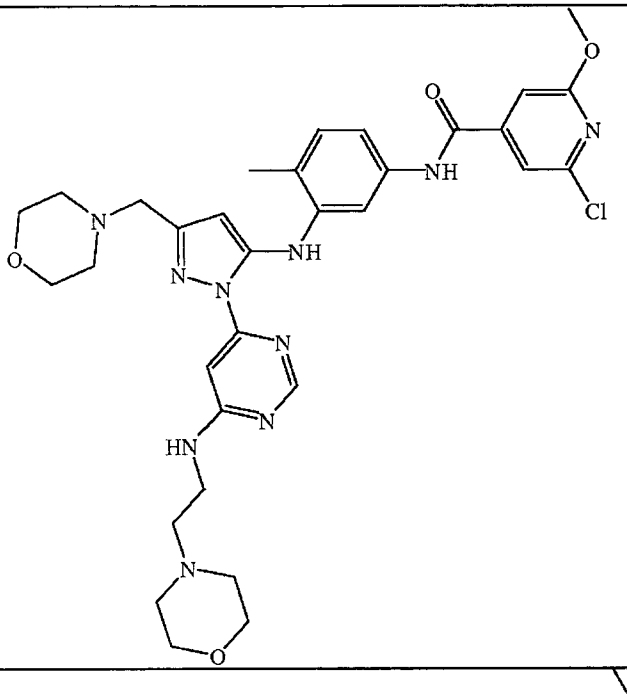
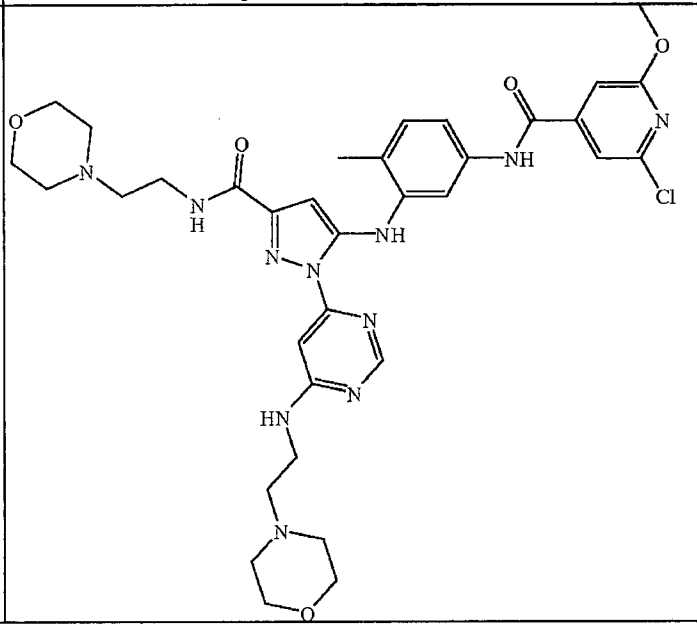
215		MS *m/z* 551.3 (M + 1)
216		MS *m/z* *62M* (M + 1)
217		MS *m/z* 609.3 (M + 1)

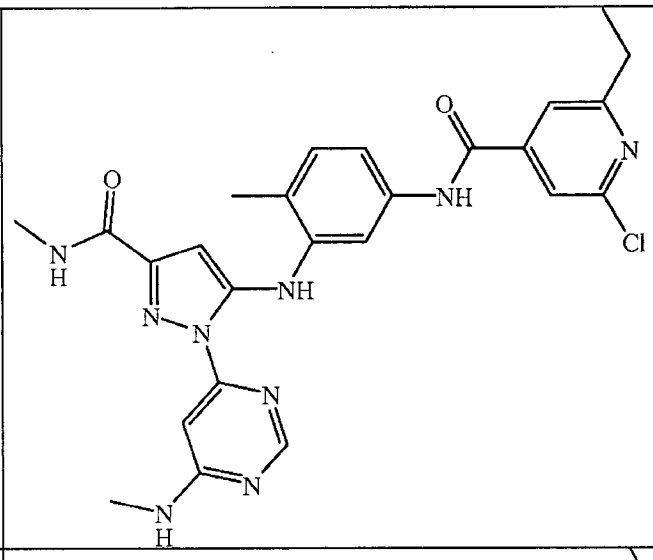
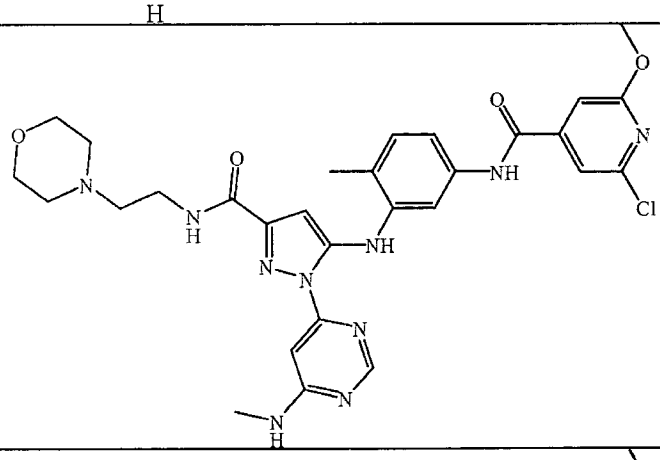
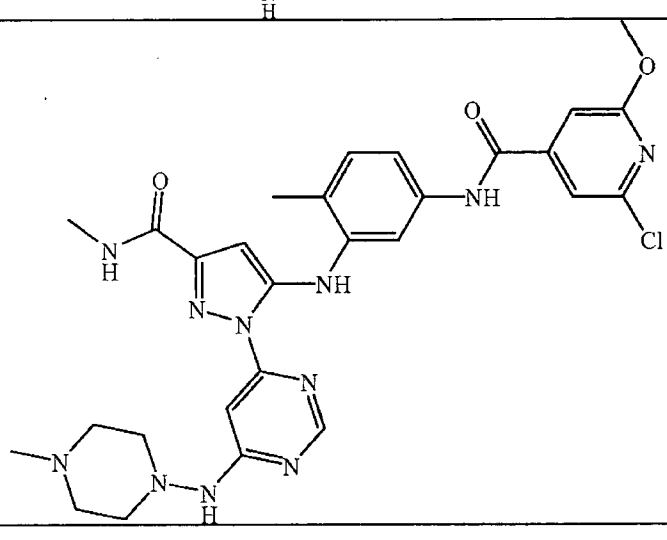
218		MS *m/z* 623.3 (M + 1)
219		MS *m/z* 608.3 (M + 1)

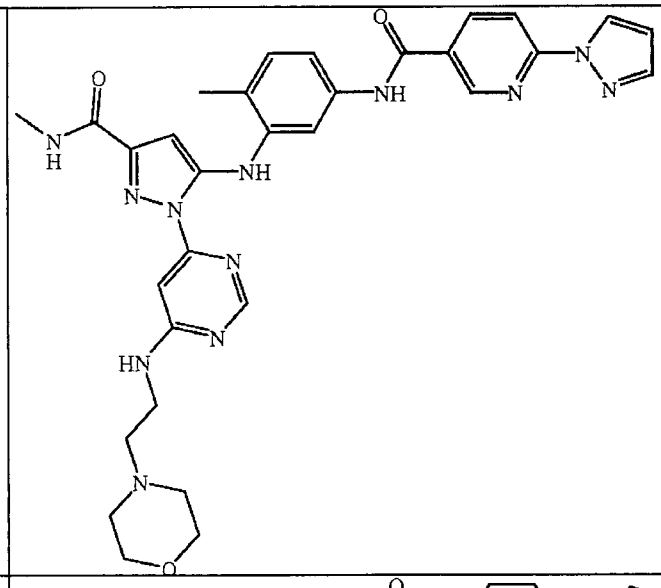
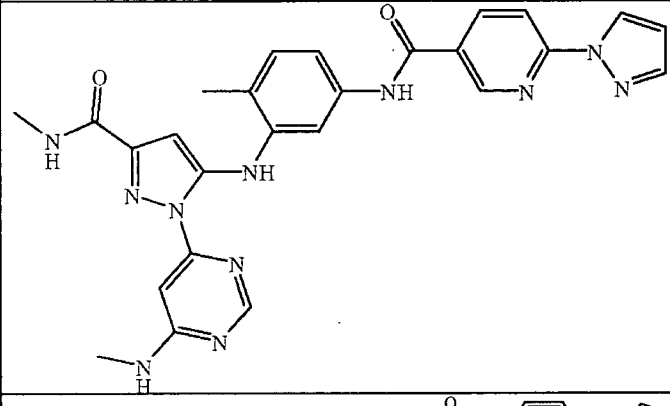
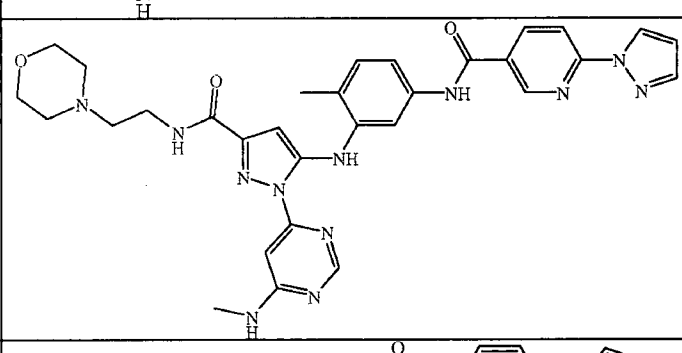
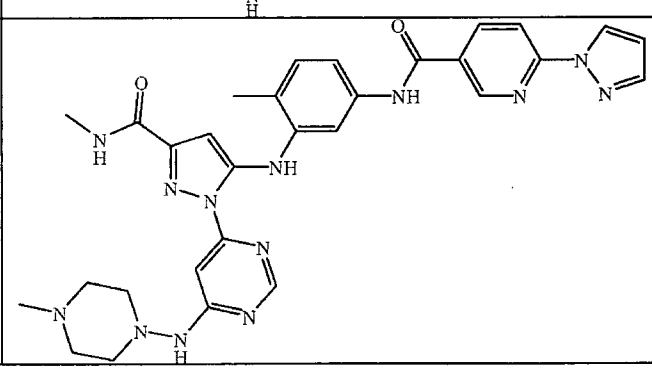
220		MS *m/z* 613.3 (M + 1)
221		MS *m/z* 655.4 (M + 1)

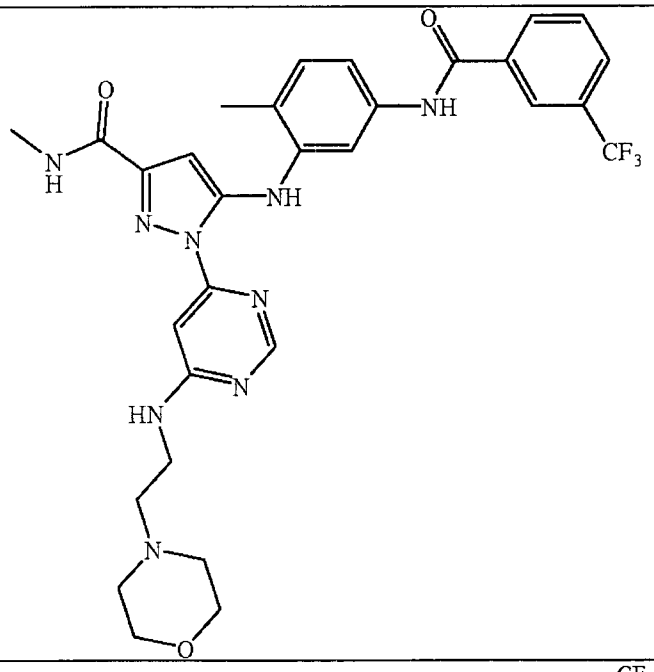
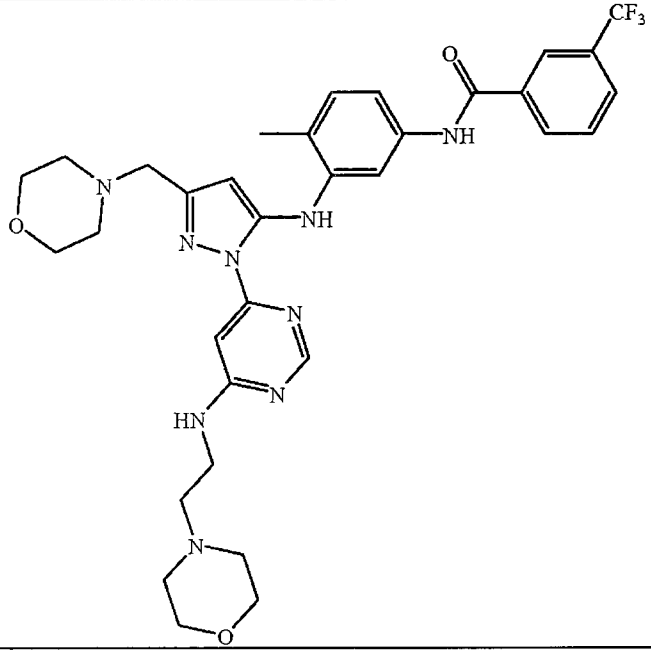
222		MS *m/z* 712.4 (M + 1)
223		MS *m/z* 514.3 (M + 1)
224		MS *m/z* 613.3 (M + 1)

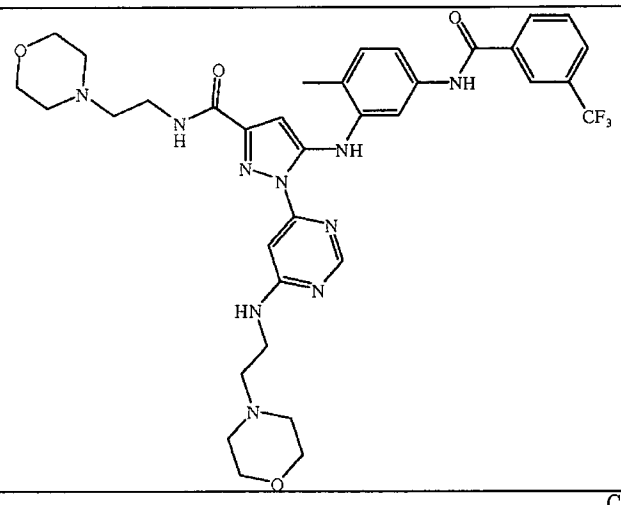
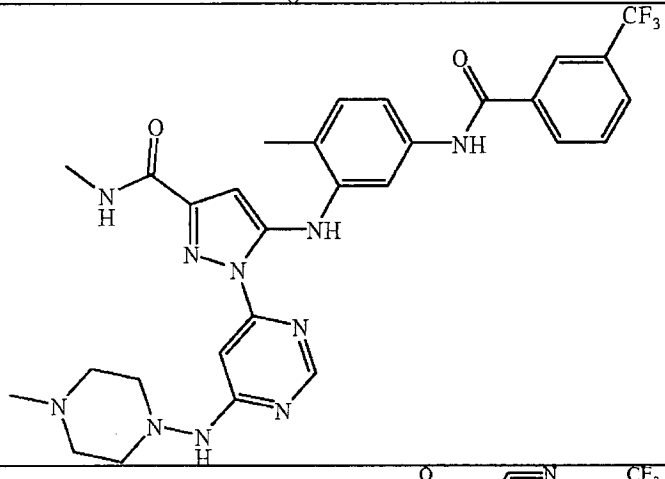
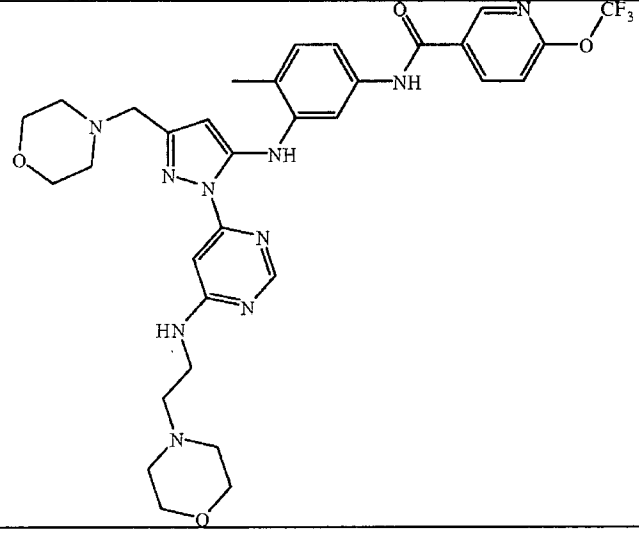
225		MS *m/z* 597.3 (M + 1)
226		MS *m/z* 620.3 (M + 1)

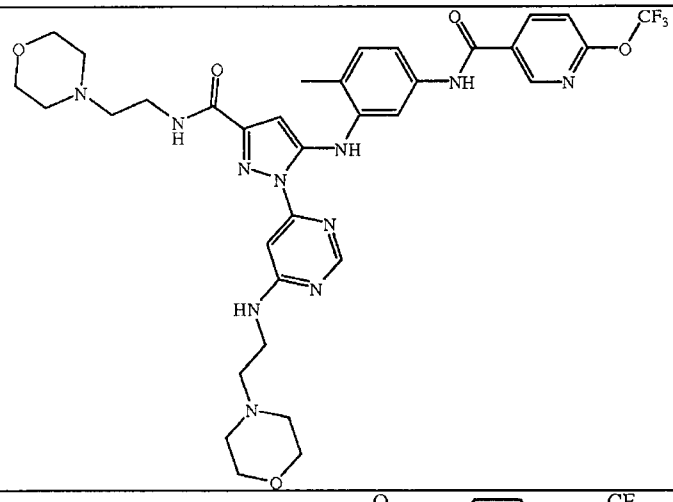
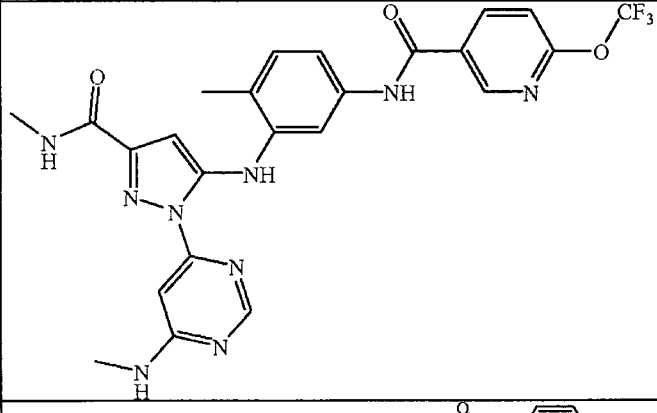
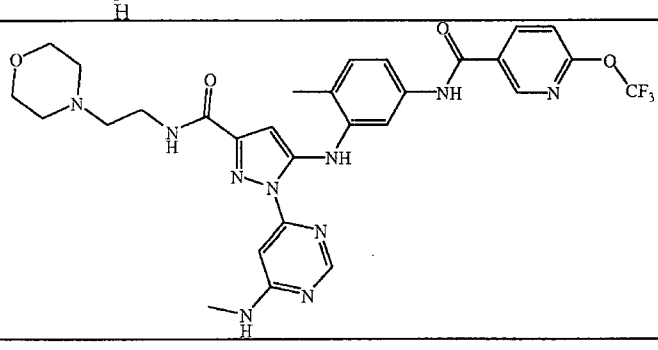
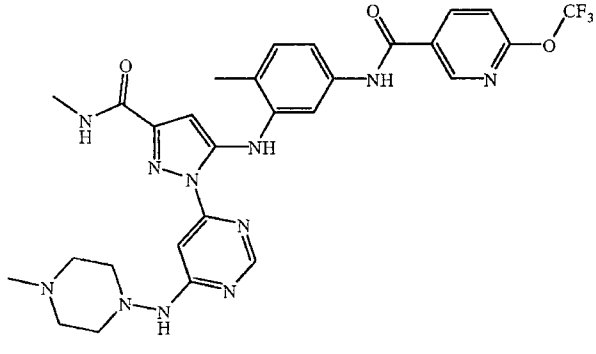
227		MS *m/z* 663.3 (M + 1)
228		MS *m/z* 720.3 (M + 1)

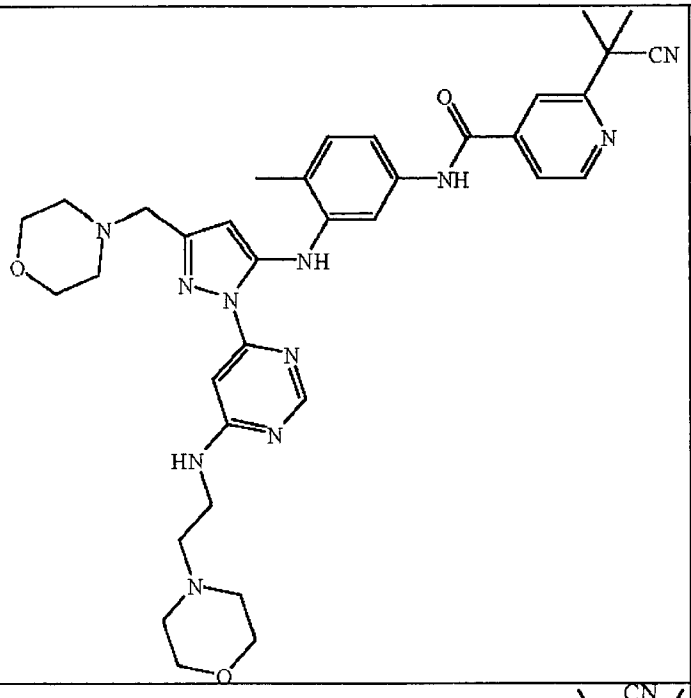
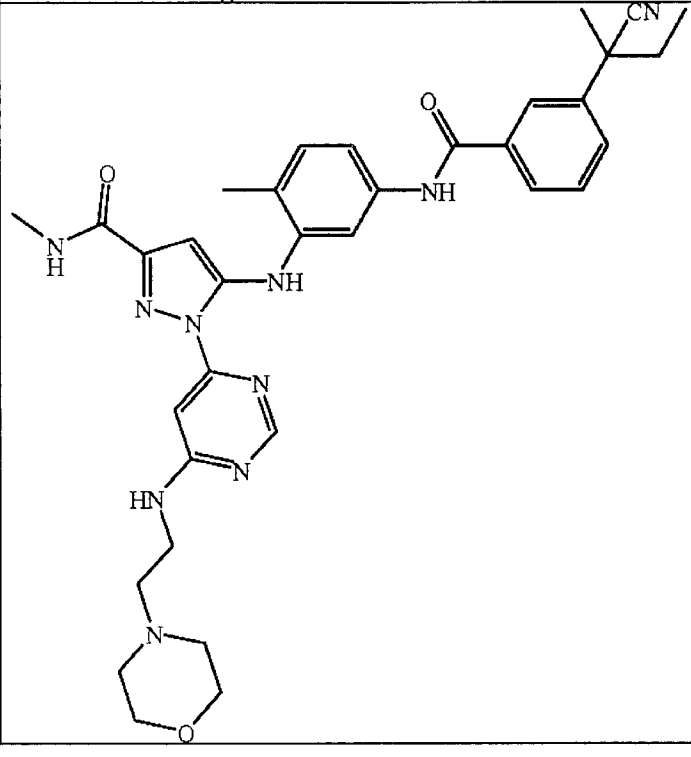
229		MS *m/z* 520.2 (M + 1)
230		MS *m/z* 620.2 (M + 1)
231		MS *m/z* 606.2 (M + 1)

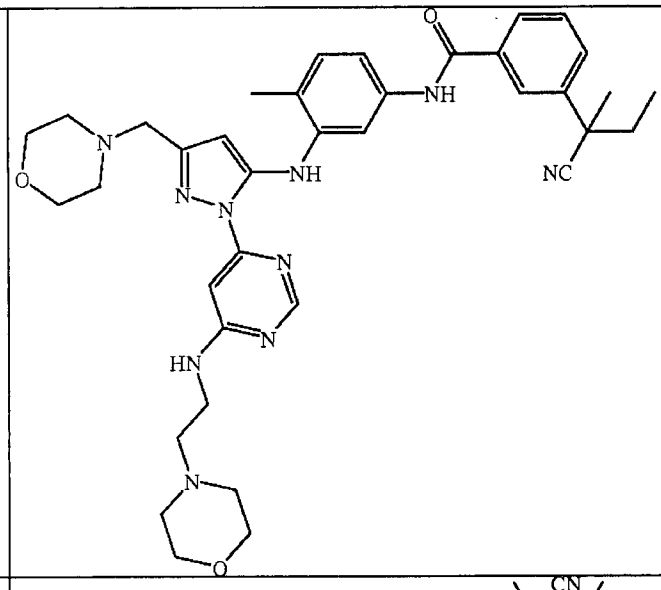
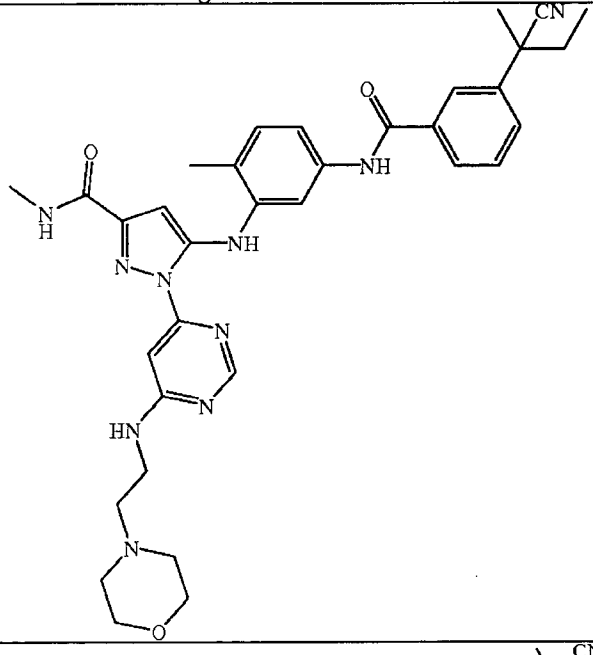
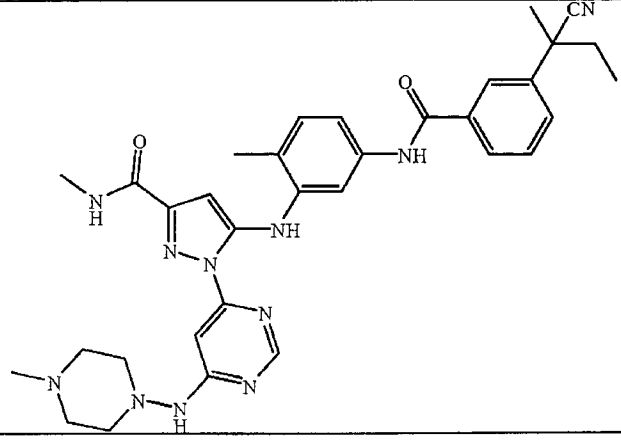
232		MS *m/z* 623.3 (M + 1)
233		MS *m/z* 524.2 (M + 1)
234		MS *m/z* 623.3 (M + 1)
235		MS *m/z* 608.3 (M + 1)

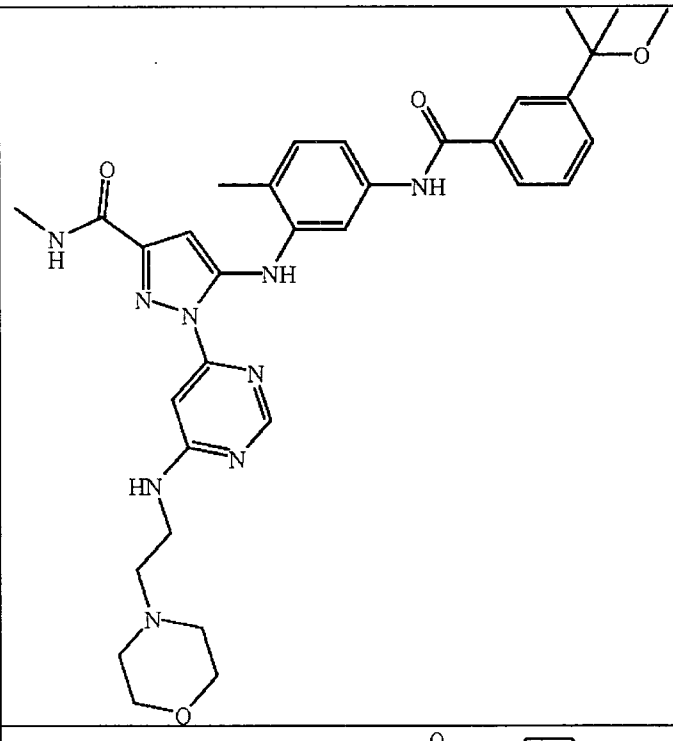
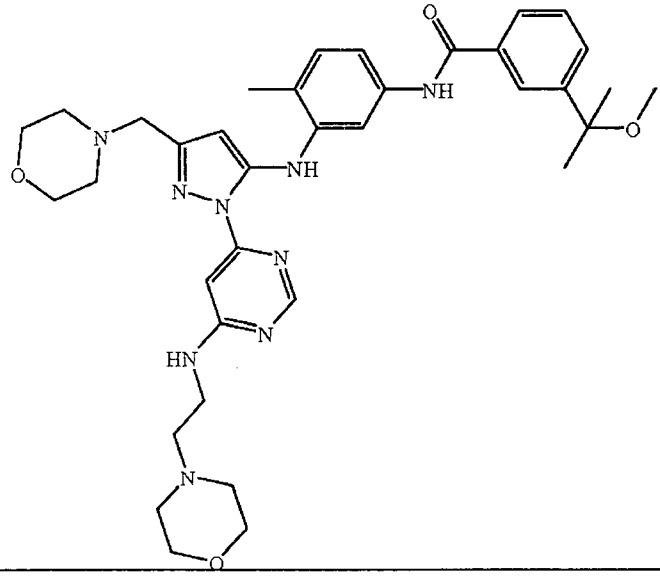
236		MS *m/z* 624.3 (M + 1)
237		MS *m/z* 666.3 (M + 1)

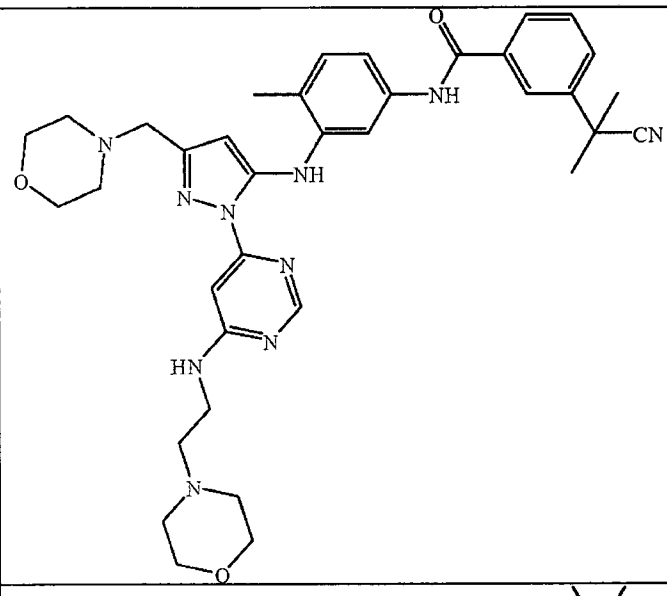
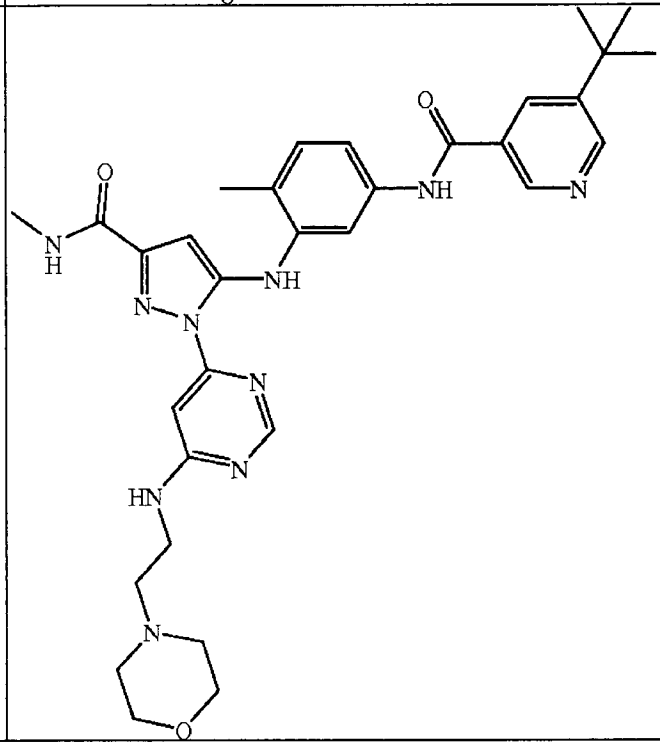
238		MS *m/z* 723.3 (M + 1)
239		MS *m/z* 609.3 (M + 1)
240		MS *m/z* 683.3 (M + 1)

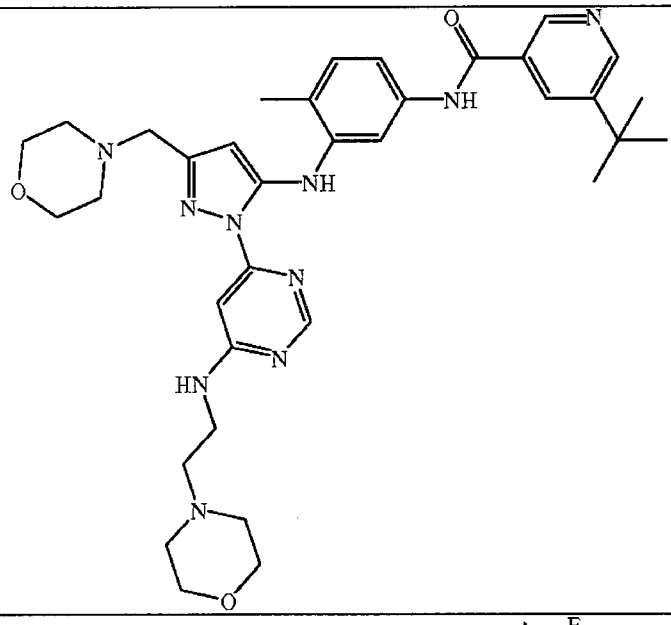
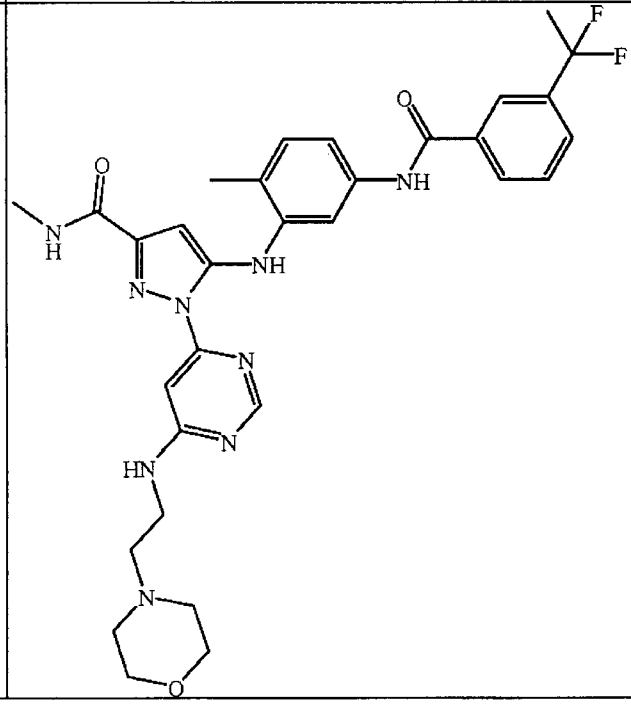
241		MS *m/z* 740.3 (M + 1)
242		MS *m/z* 542.2 (M + 1)
243		MS *m/z* 640.3 (M + 1)
244		MS *m/z* 626.3 (M + 1)

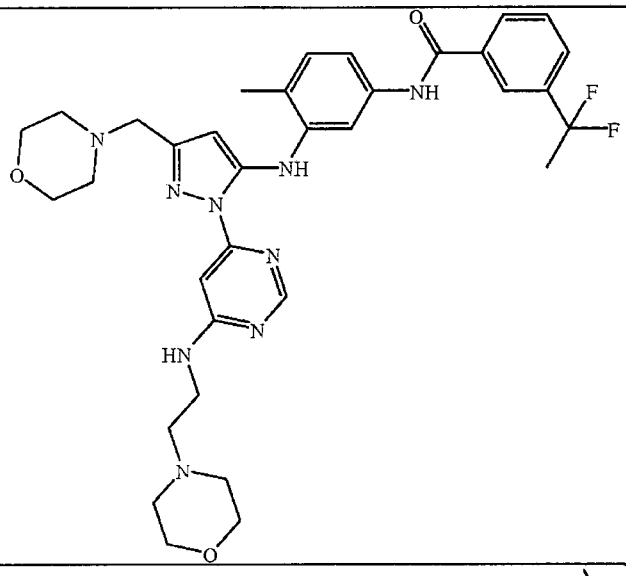
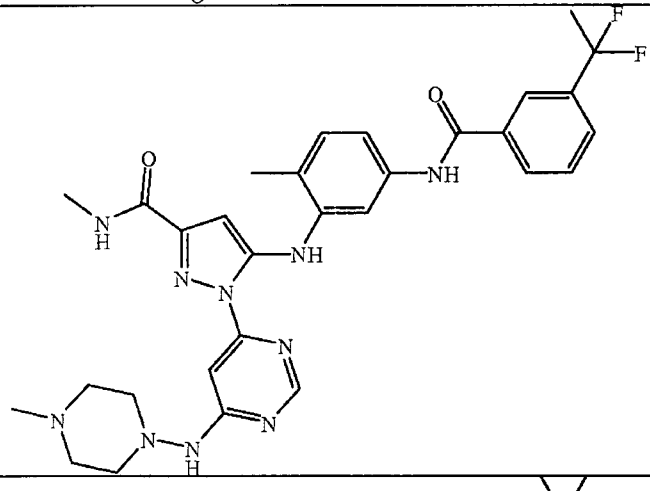
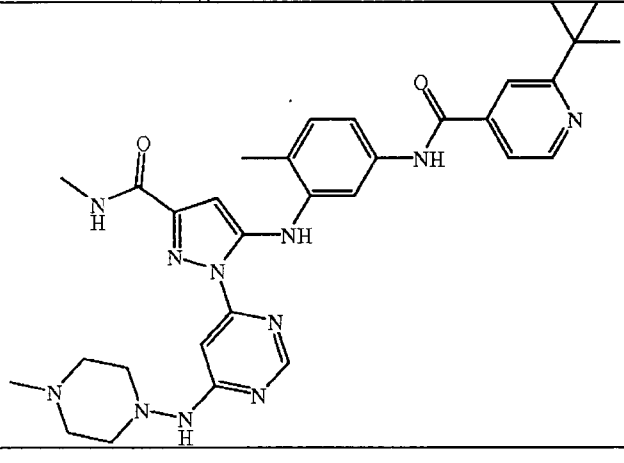
245		MS *m/z* 666.4 (M + 1)
246		MS *m/z* 637.3 (M + 1)

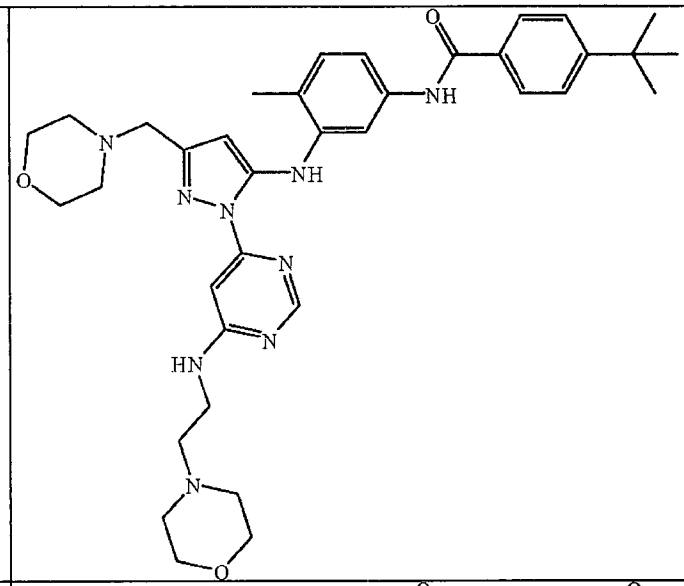
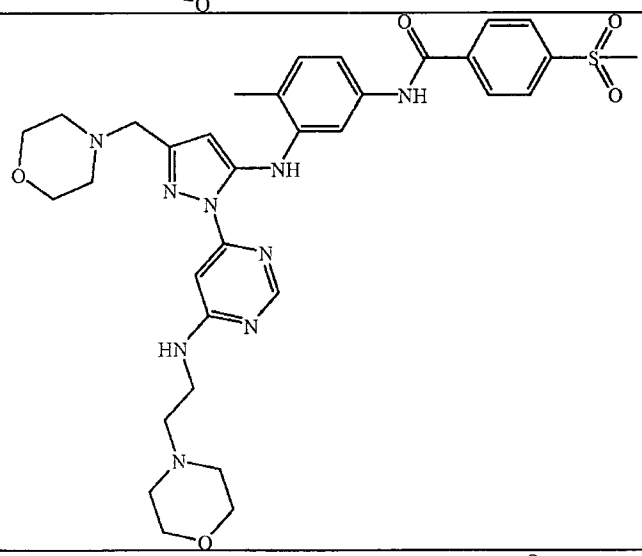
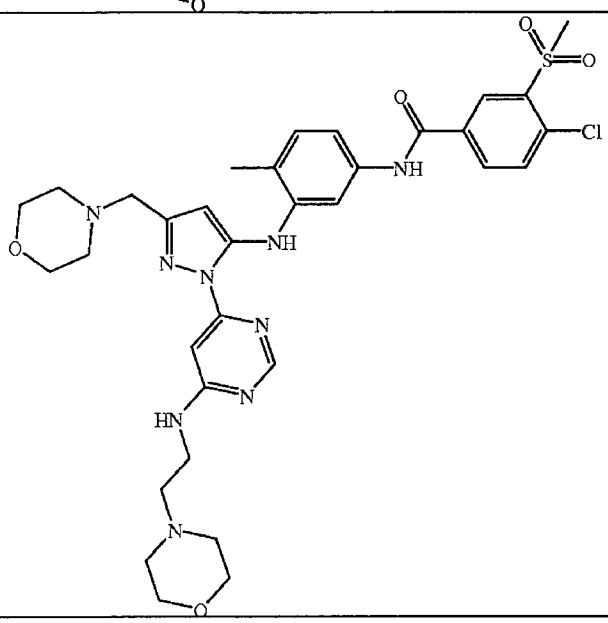
247		MS *m/z 619 A* (M + 1)
248		MS *m/z* 637.3 (M + 1)
249		MS *m/z* 622.3 (M + 1)

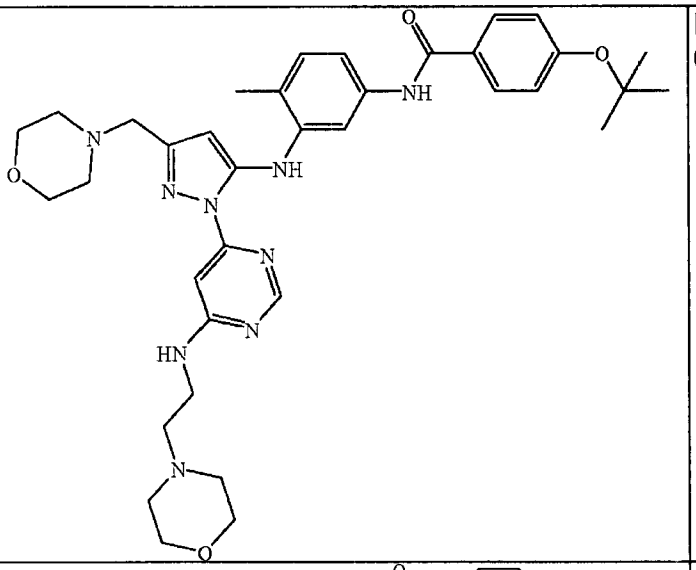
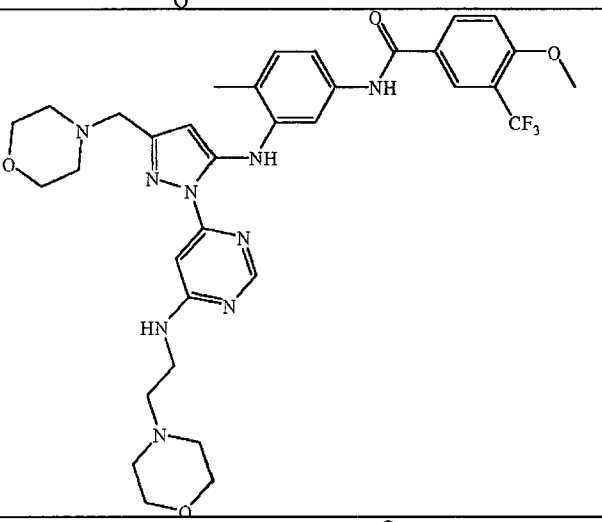
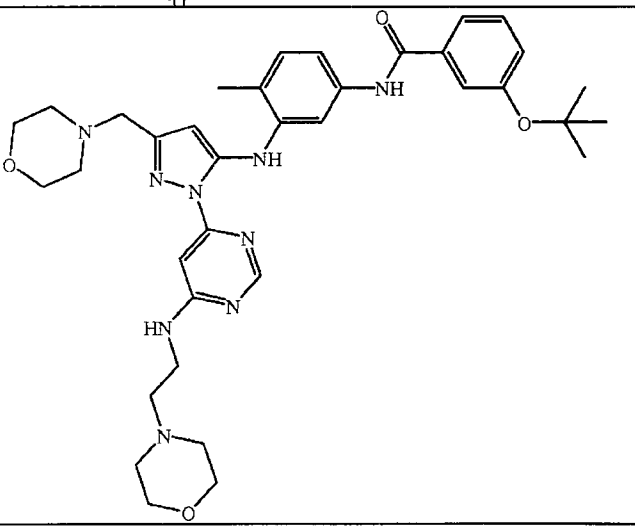
250		MS *m/z* 628.3 (M + 1)
251		MS *m/z* 670.4 (M + 1)

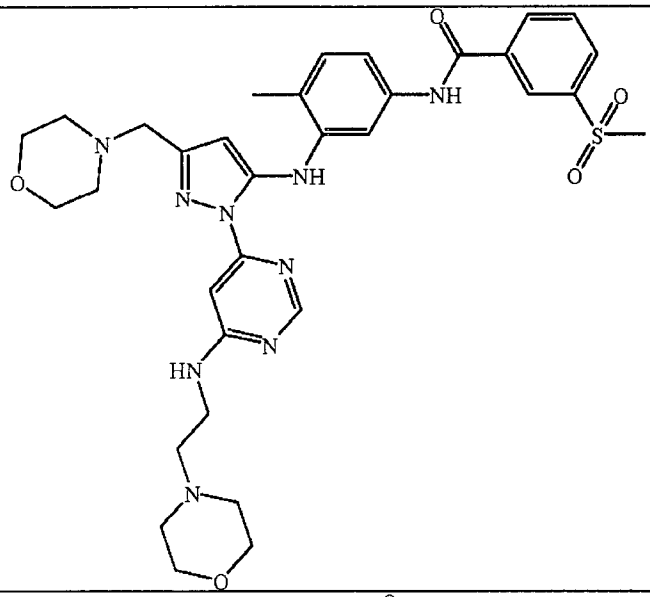
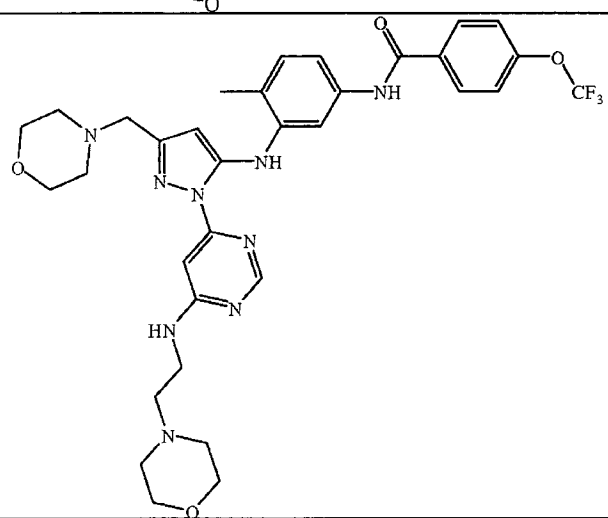
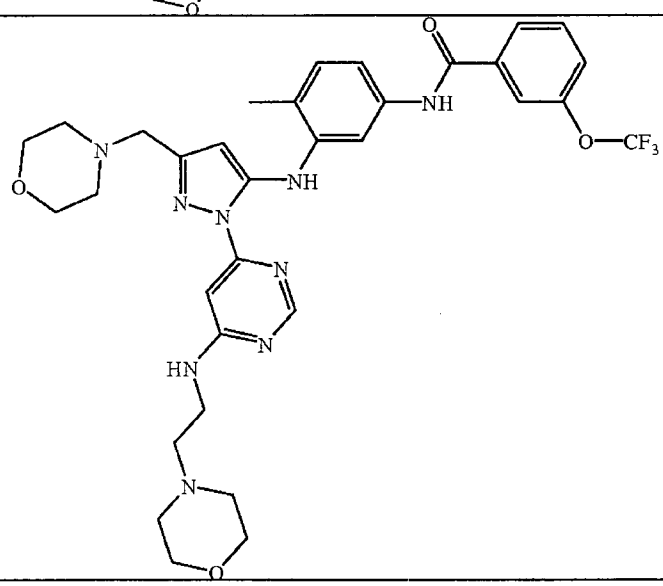
252		MS *m/z* 665.4 (M + 1)
253		MS *m/z* 613.3 (M + 1)

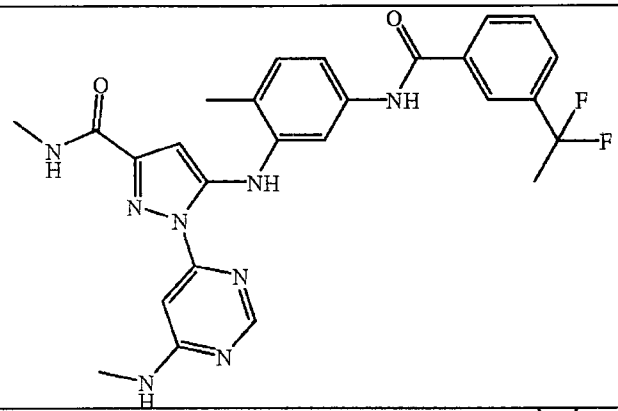
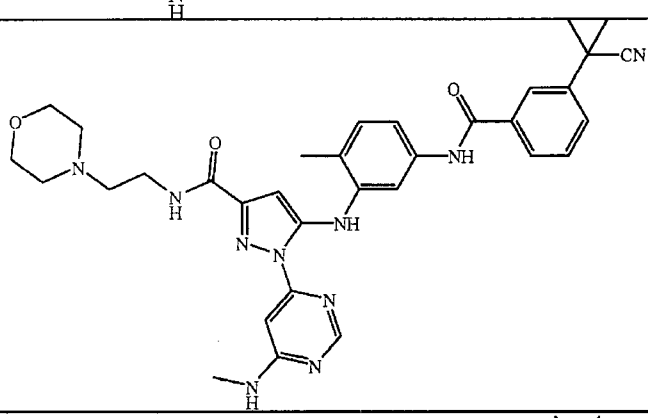
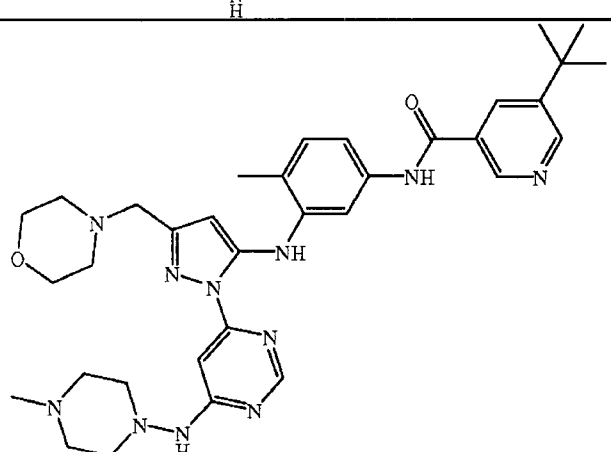
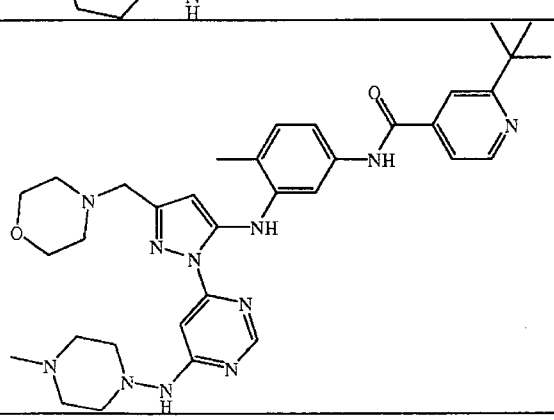
254		MS *m/z* 655.4(M + 1)
255		MS *m/z* 620.3 (M + 1)

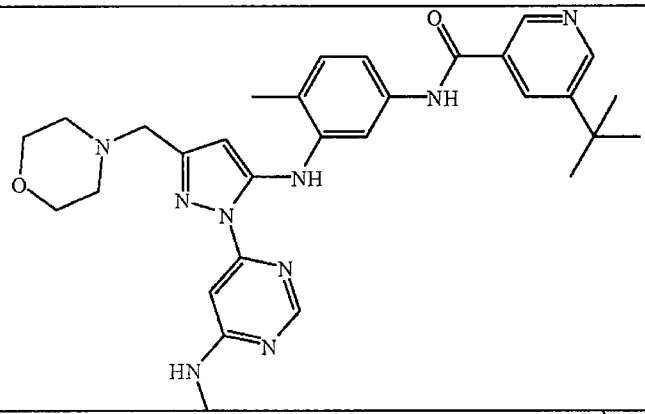
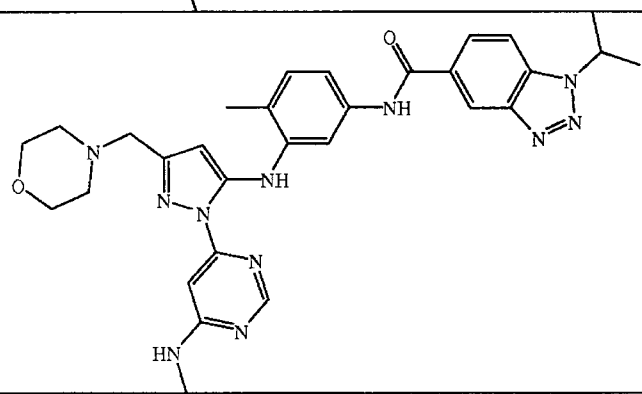
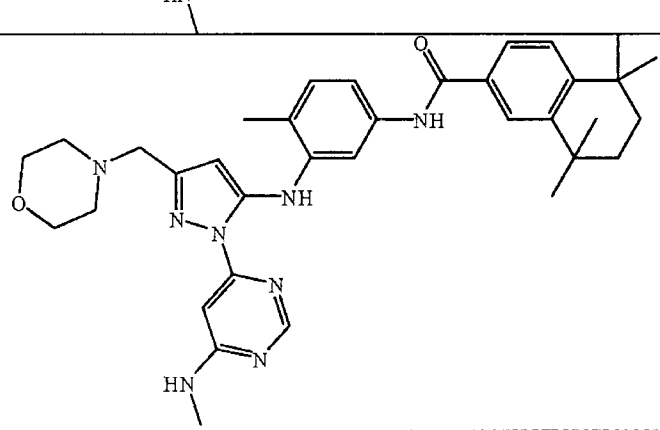
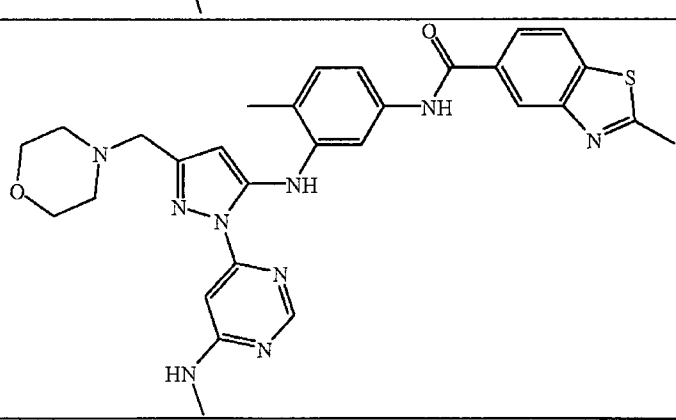
256		MS *m/z* 662.3 (M + 1)
257		MS *m/z* 605.3 (M + 1)
258		MS *m/z* 598.3 (M + 1)

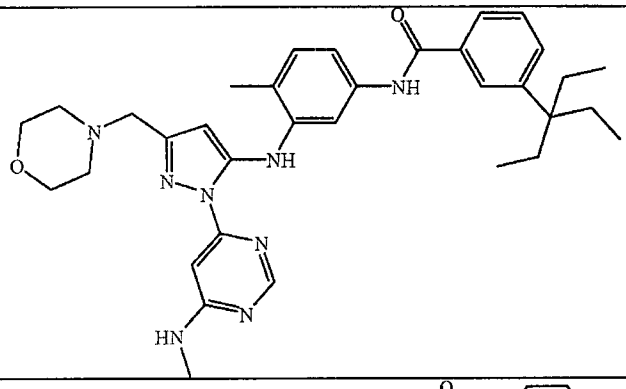
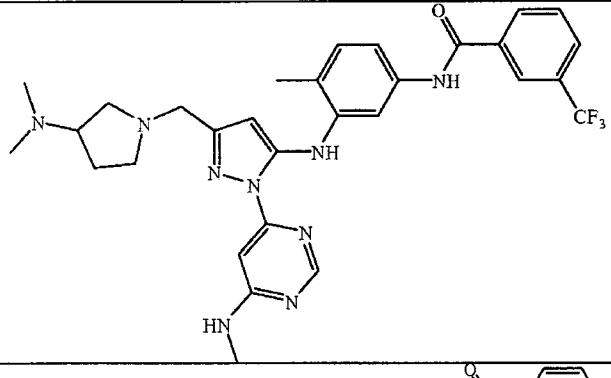
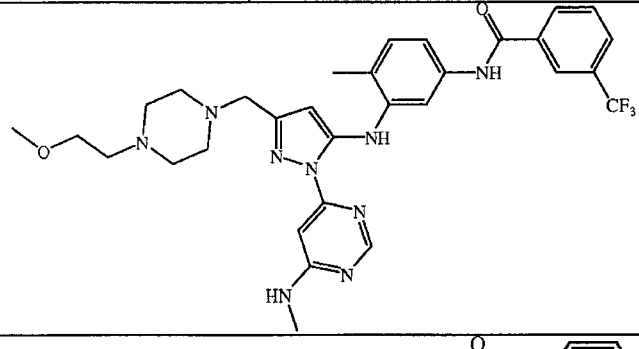
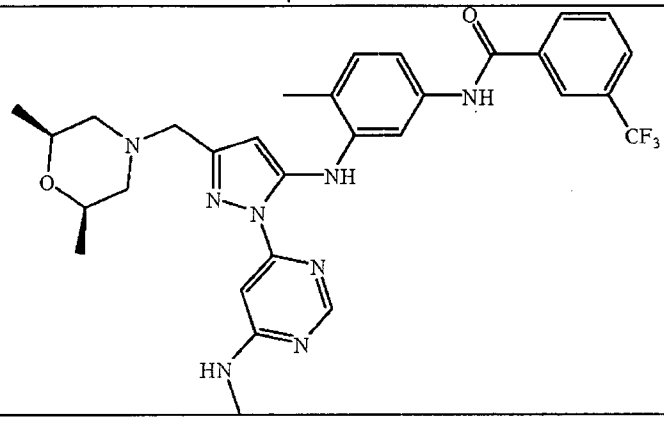
259		MS *m/z* 654.4 (M + 1)
260		MS *m/z* 676.3 (M + 1)
261		MS *m/z* 710.3 (M + 1)

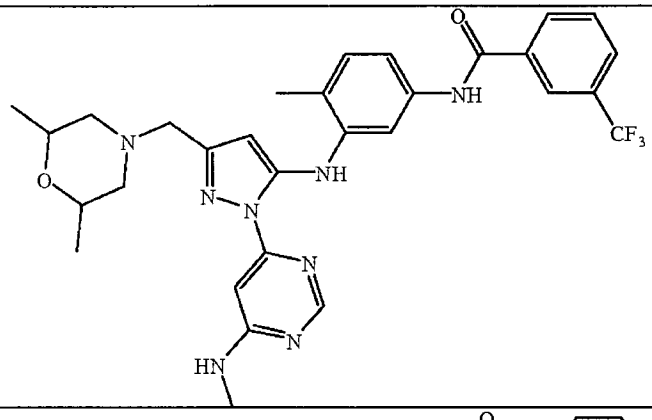
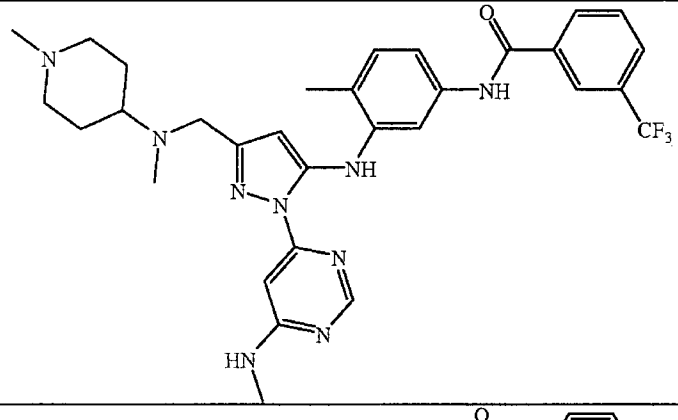
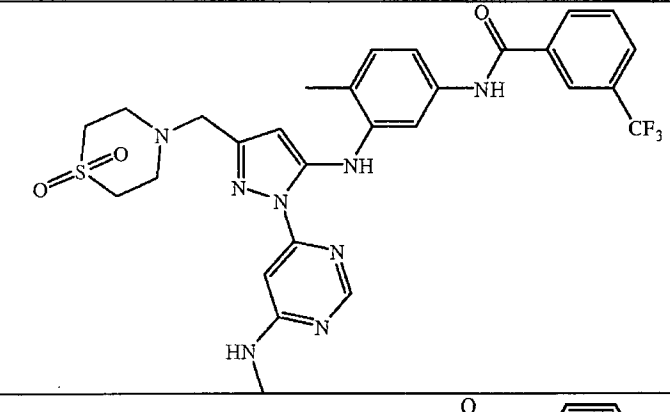
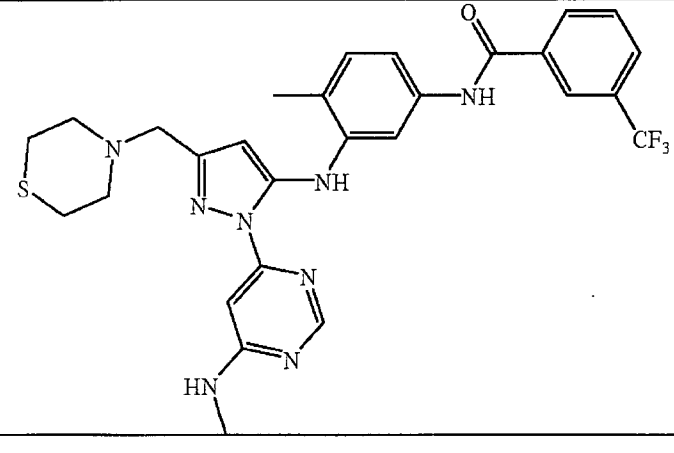
262		MS *m/z* 670.4 (M + 1)
263		MS *m/z* 696.3 (M + 1)
264		MS *m/z* 670.4 (M + 1)

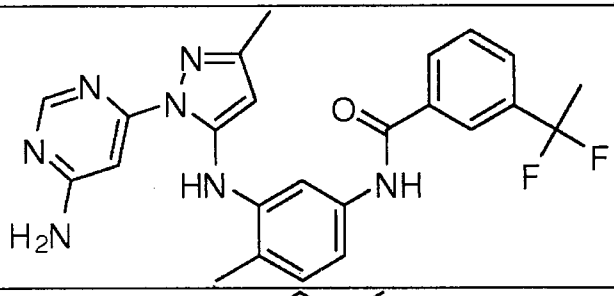
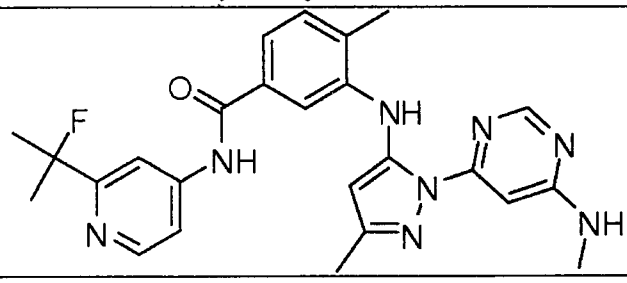
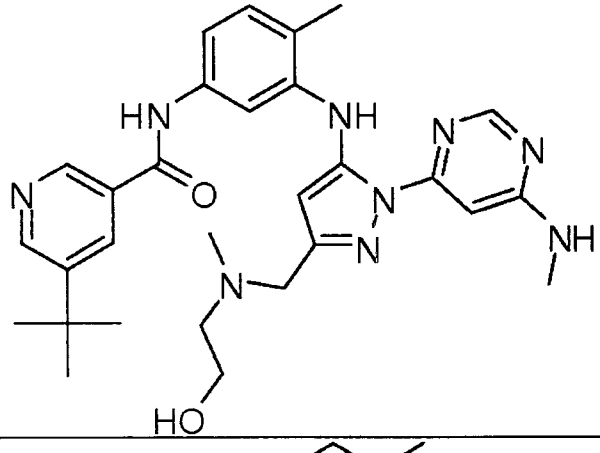
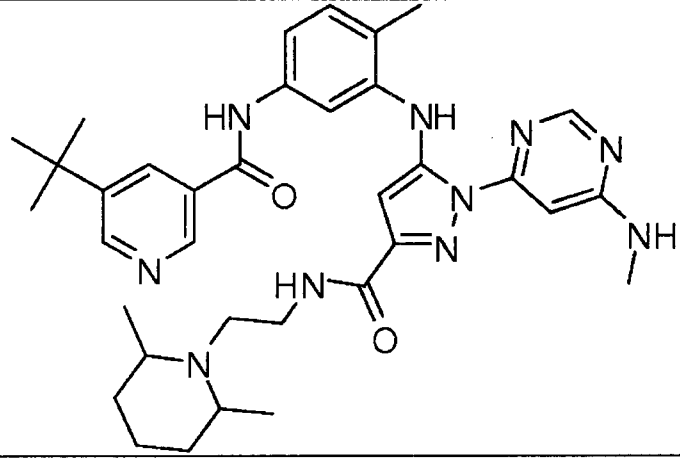
265		MS *m/z* 676.3 (M + 1)
266		MS *m/z* 682.3 (M + 1)
267		MS *m/z* 682.3 (M + 1)

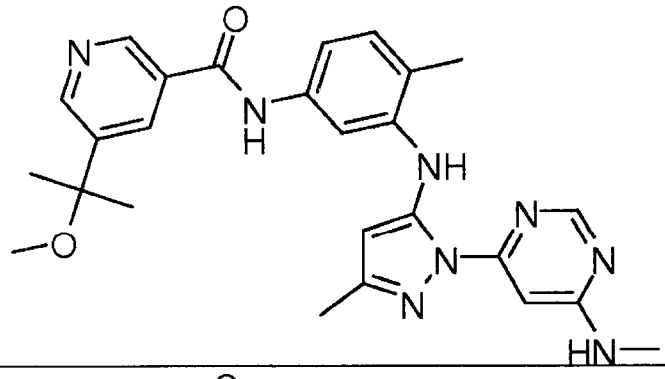
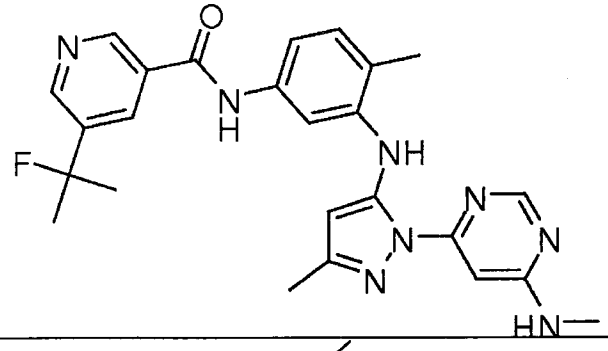
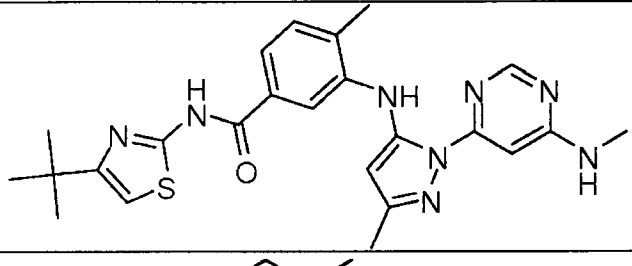
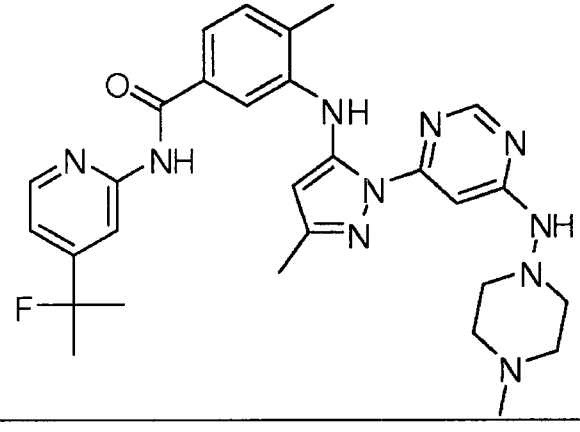
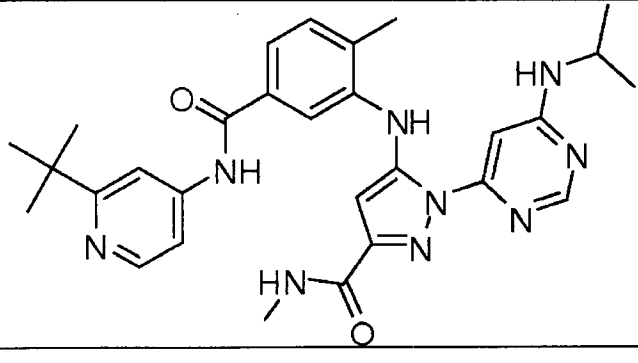
268		MS *m/z* 521.2 (M + 1)
269		MS *m/z* 623.3 (M + 1)
270		MS *m/z* 640.4 (M + 1)
271		MS *m/z* 682.3 (M + 1)

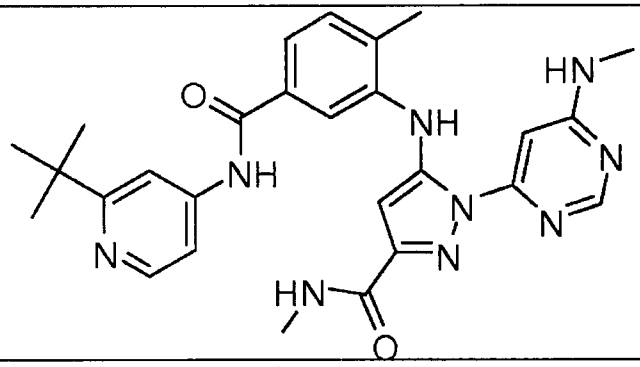
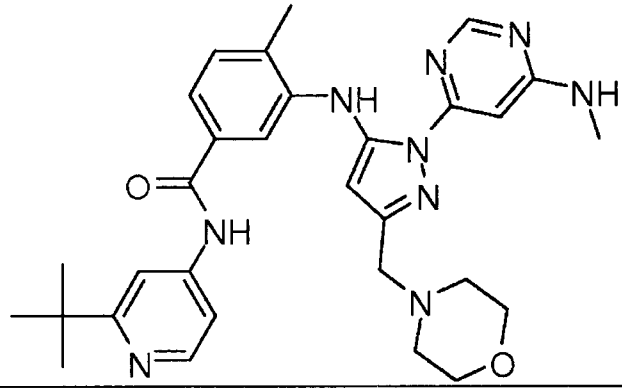
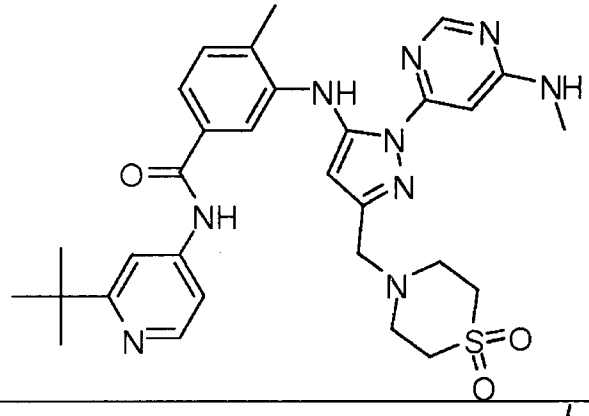
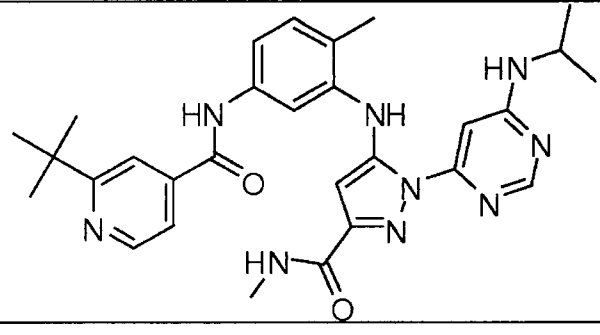
272		MS *m/z* 556.3 (M + 1)
273		MS *m/z* 582.3 (M + 1)
274		MS *m/z* 609.4 (M + 1)
275		MS *m/z* 570.2 (M + 1)

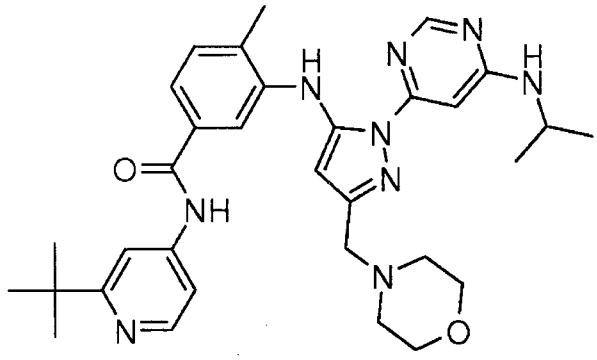
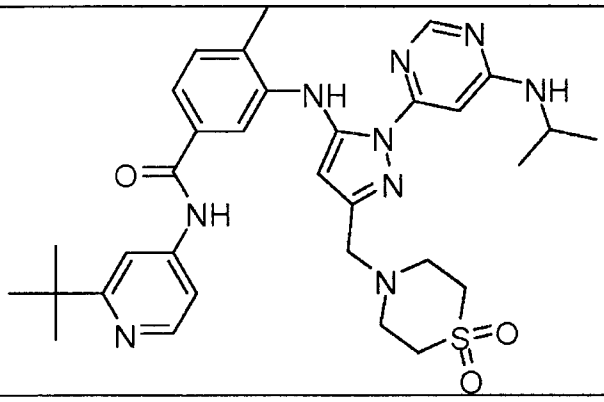
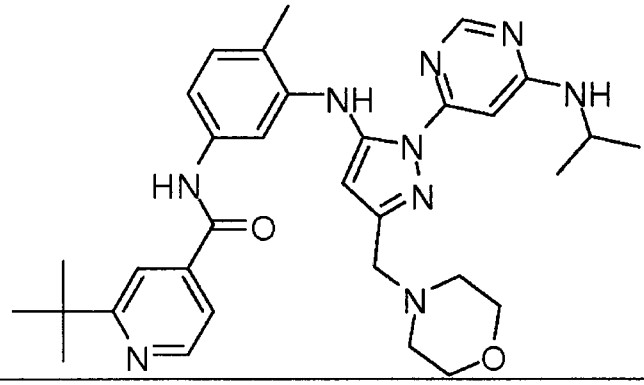
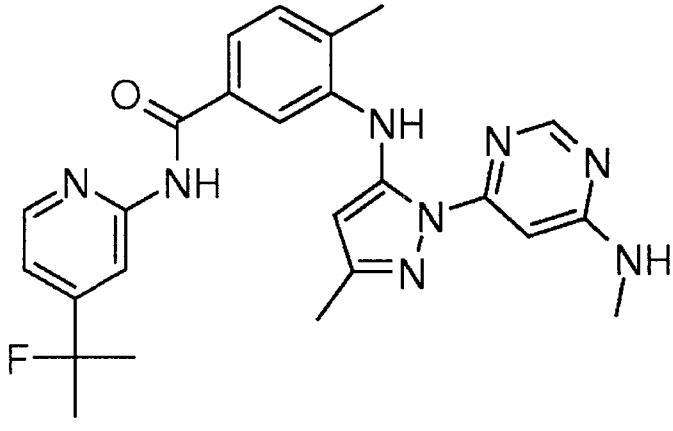
276		MS *m/z* 597.4 (M + 1)
277		MS *m/z* 594.3 (M + 1)
278		MS *m/z* *62M* (M + 1)
279		MS *m/z* 595.3 (M + 1)

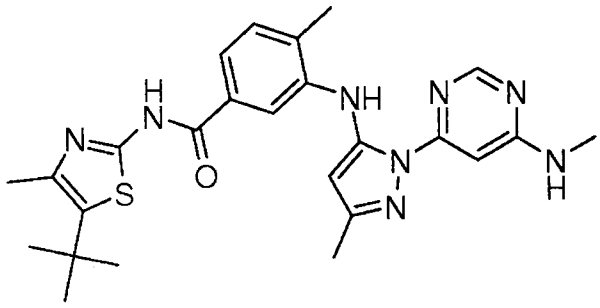
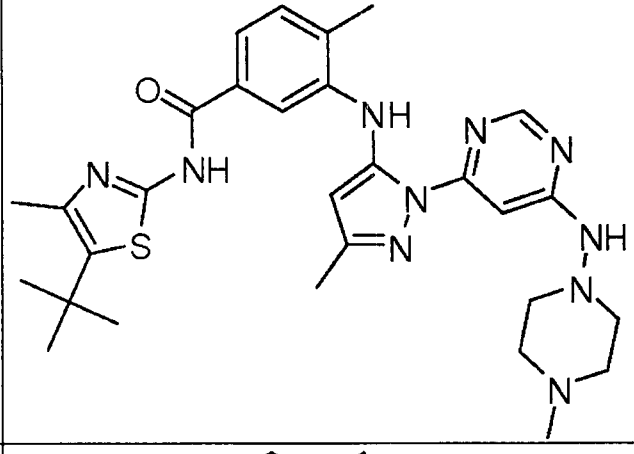
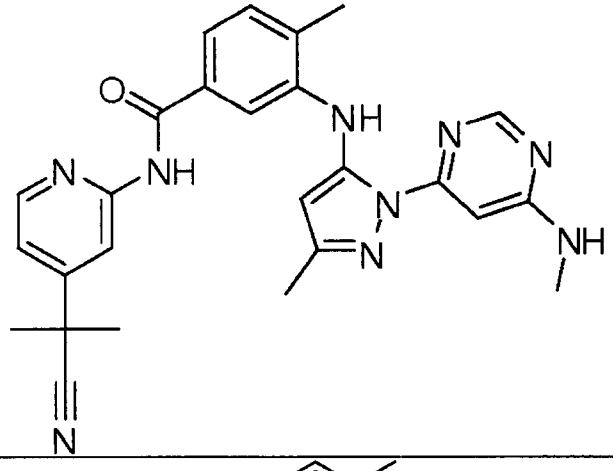
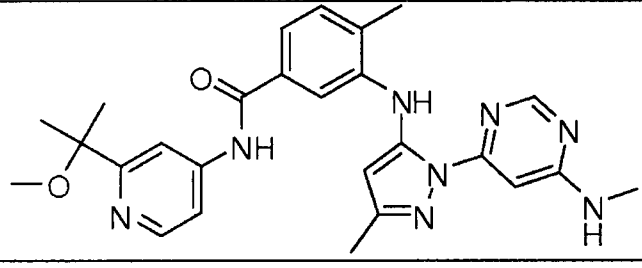
280		MS *m/z* 595.3 (M + 1)
281		MS *m/z* 608.3 (M + 1)
282		MS *m/z* 615.2 (M + 1)
283		MS *m/z* 583.2 (M + 1)

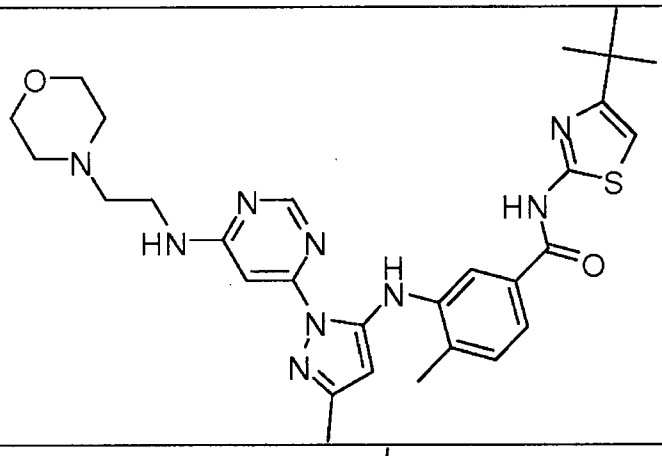
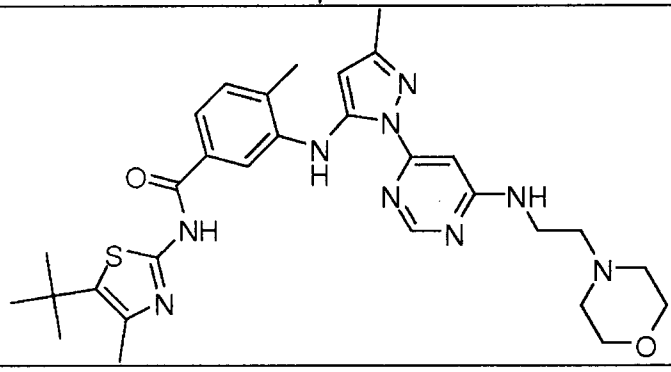
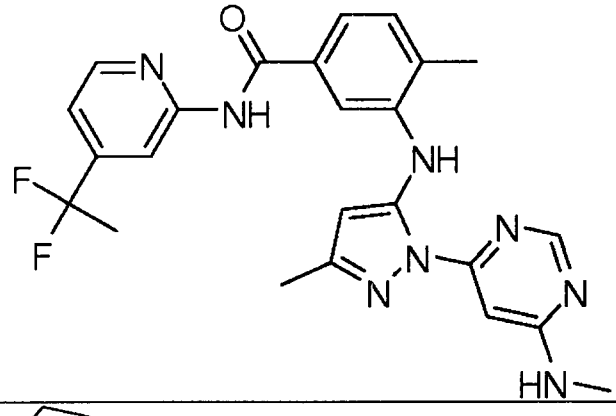
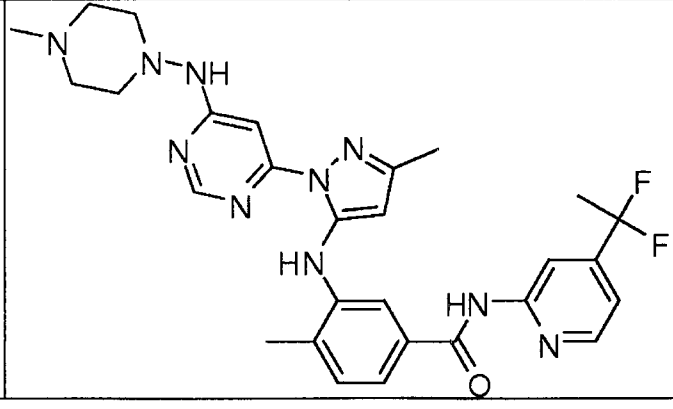
284		MS m/z 464.2 (M + 1)
285		MS 474.2 m/z (M + 1)
286		MS m/z 544.3 (M + 1)
287		MS m/z 639.4 (M + 1)

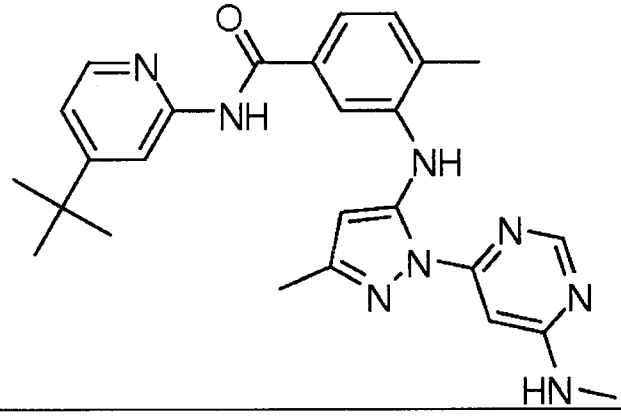
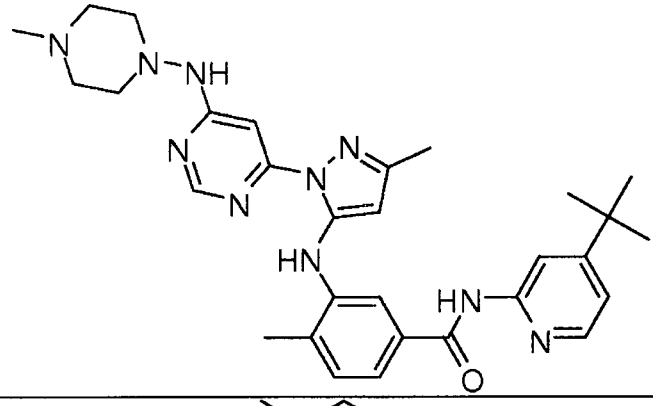
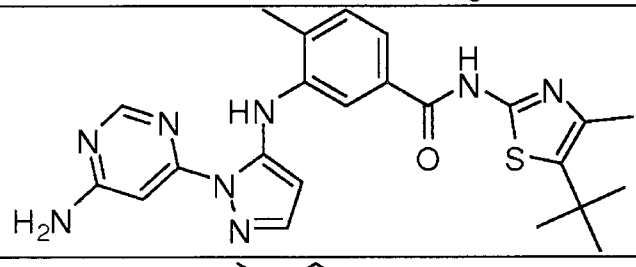
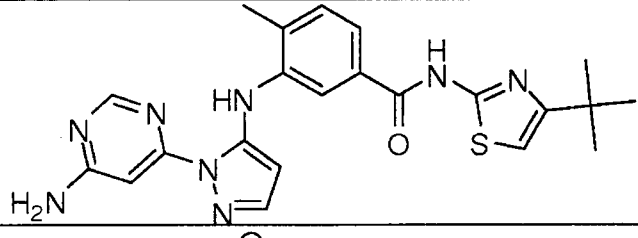
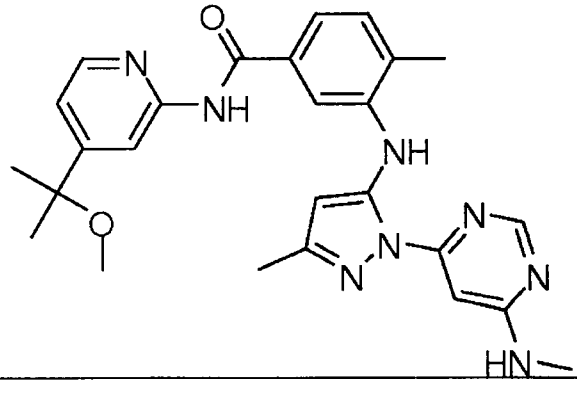
288		MS m/z 487.3 (M + 1)
289		MS m/z 475.2 (M + 1)
290		MSm/z 477.2 (M + 1)
291		MS m/z 559.3 (M + 1)
292		MS m/z 542.3 (M + 1)

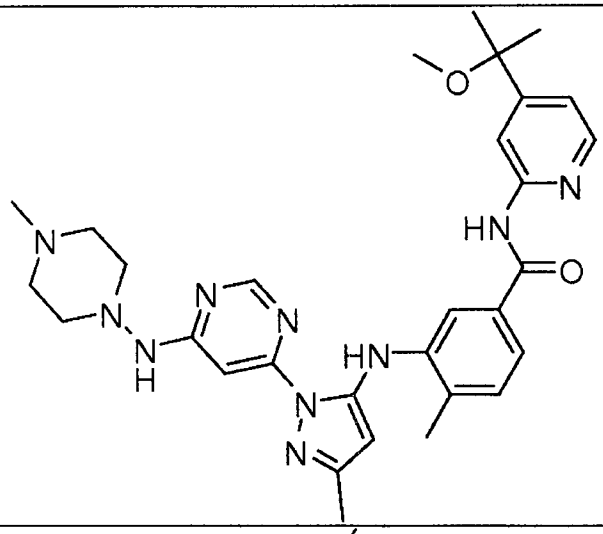
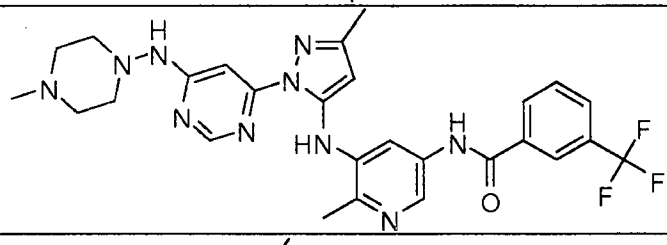
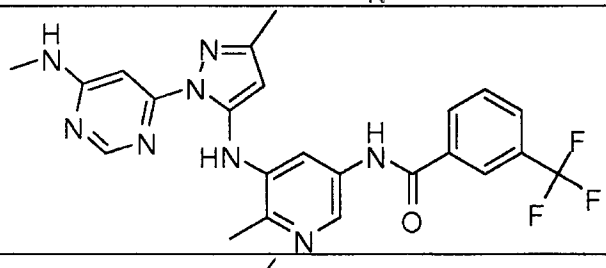
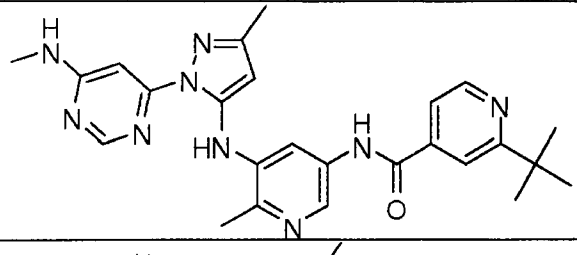
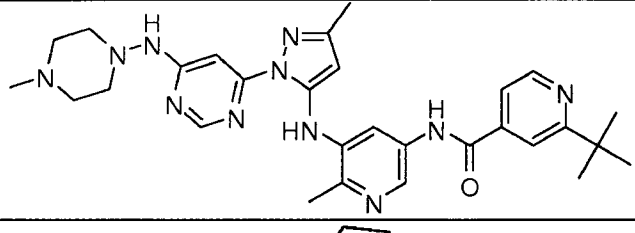
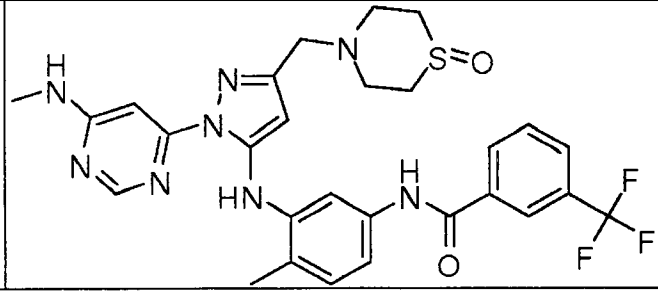
293		MS m/z 514.3 (M + 1)
294		MS m/z 556.3 (M + 1)
295		MSm/z 604.3(M + 1)
296		MS m/z 542.3 (M + 1)

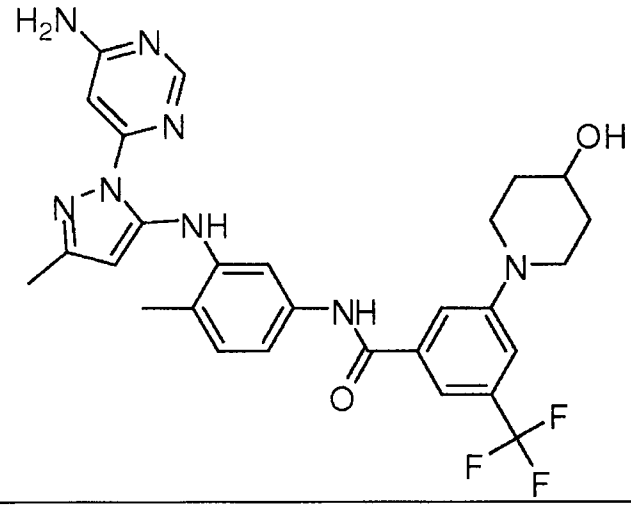
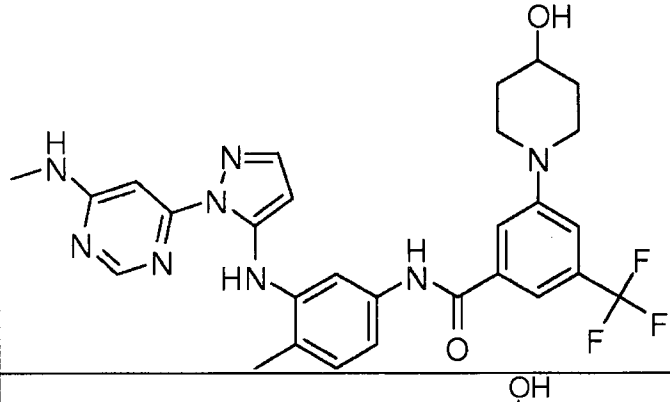
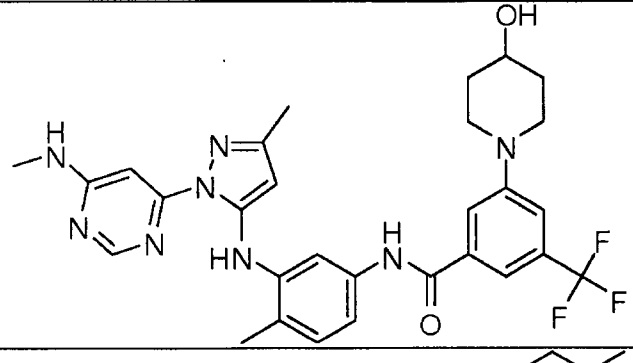
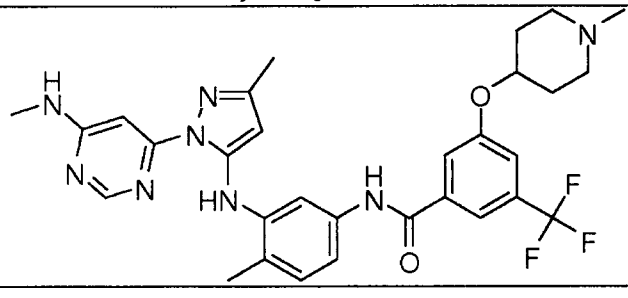
297		MS m/z 584.3 (M + 1)
298		MS m/z 632.3 (M + 1)
299		MS m/z 584.3 (M + 1)
300		MSm/z 475.3 (M + 1)

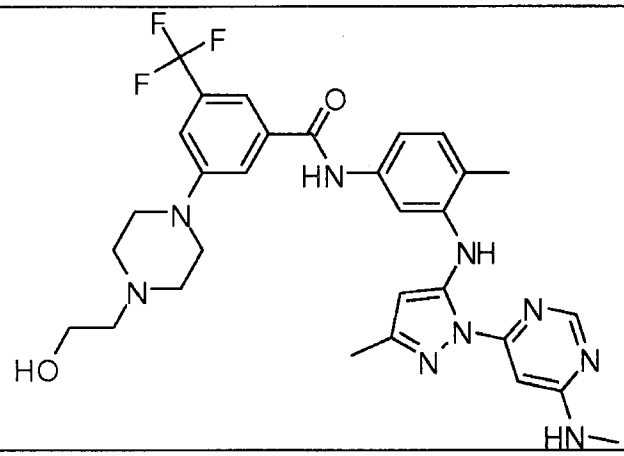
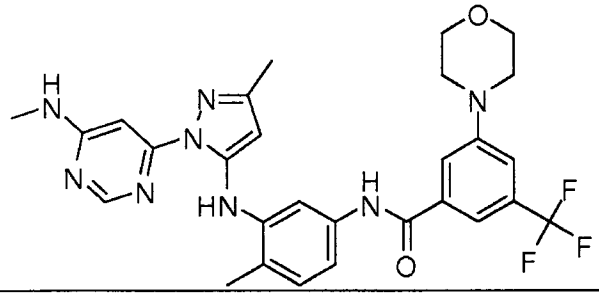
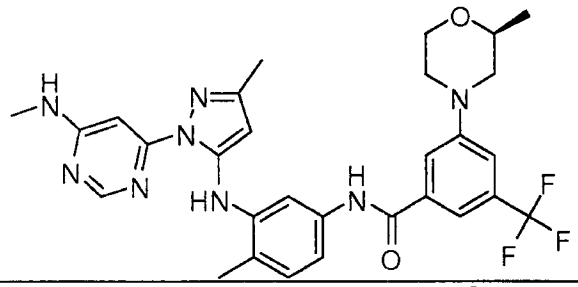
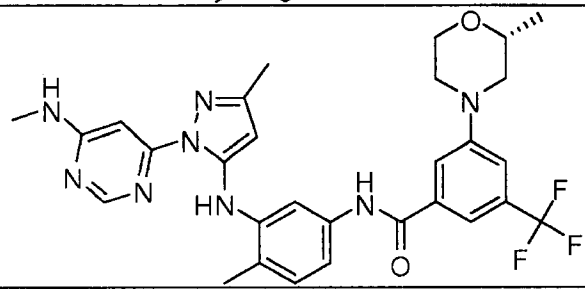
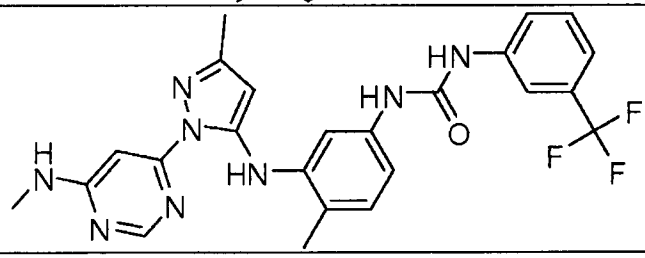
301		MS m/z 491.2 (M + 1)
302		MS m/z 575.3 (M + 1)
303		MS m/z 482.2 (M + 1)
304		MS m/z 487.3 (M + 1)

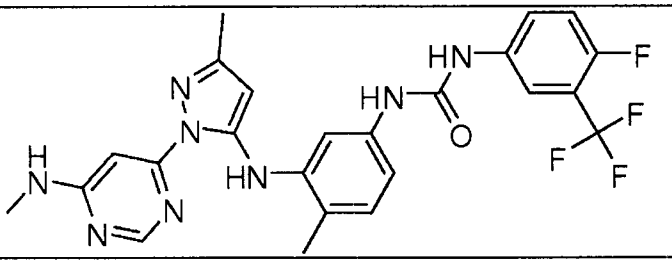
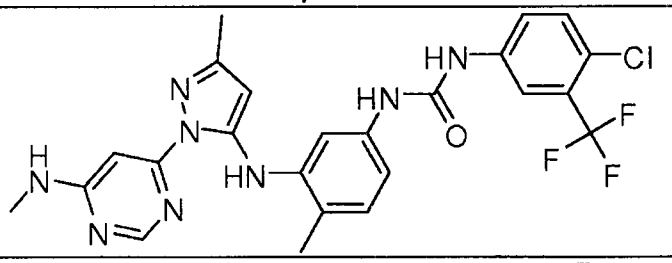
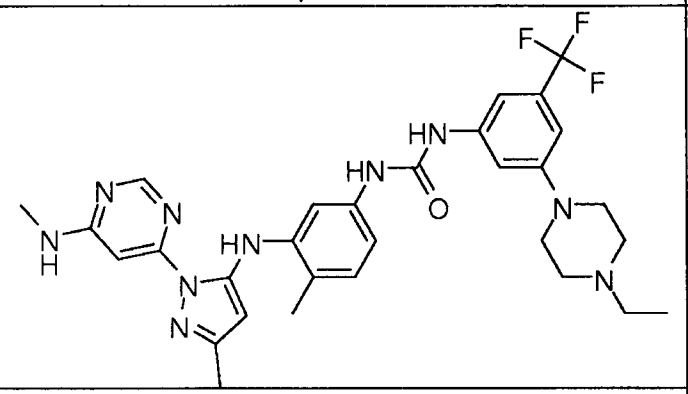
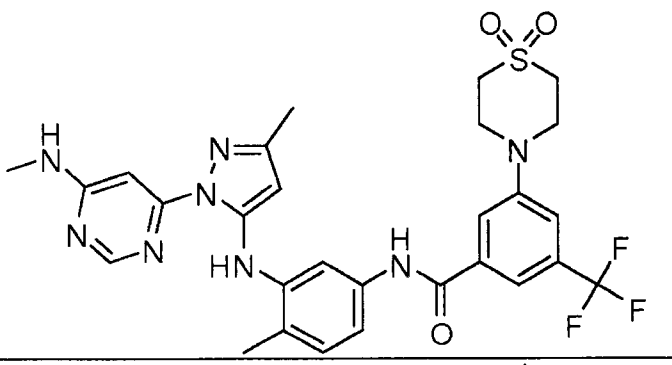
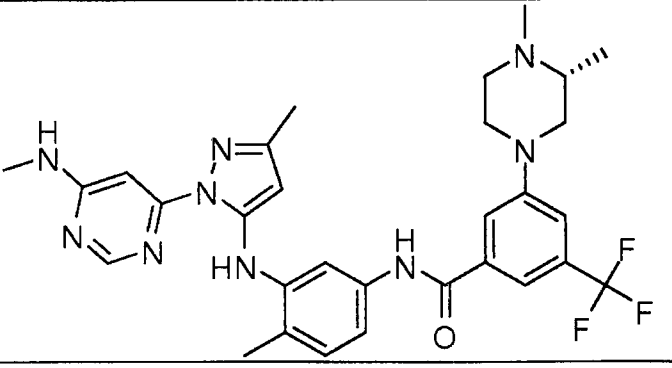
305		MSm/z 576.3 (M + 1)
306		MS m/z 590.3 (M + 1)
307		MS m/z 479.2 (M + 1)
308		MS m/z 563.3 (M + 1)

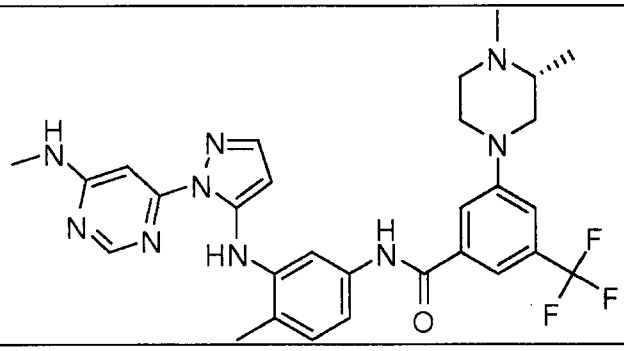
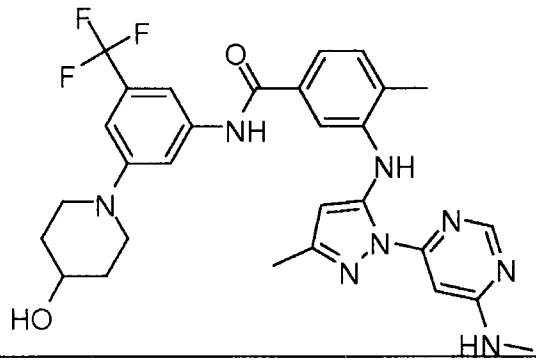
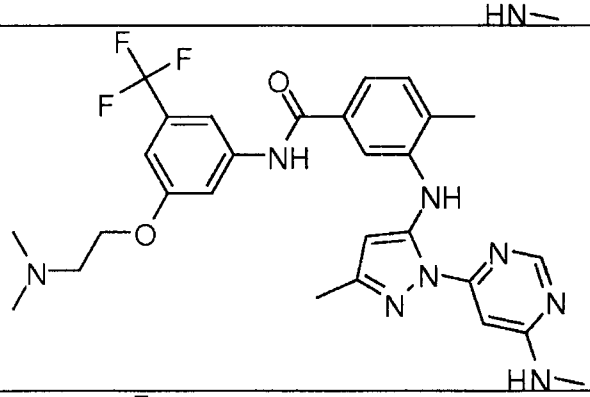
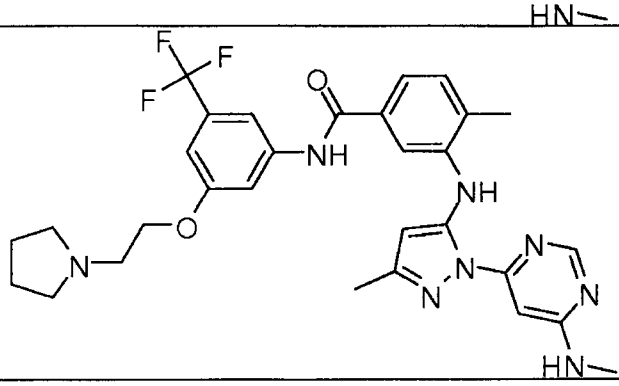
309		MSm/z 471.3 (M + 1)
310		MS m/z 555.3 (M + 1)
311		MS m/z 463.2 (M + 1)
312		MS m/z 449.2 (M + 1)
313		MS m/z 487.3 (M + 1)

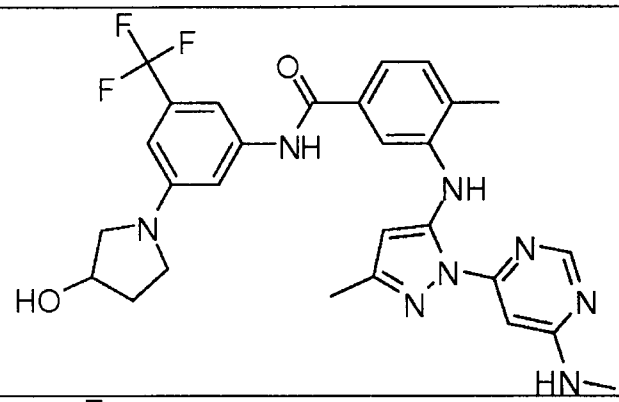
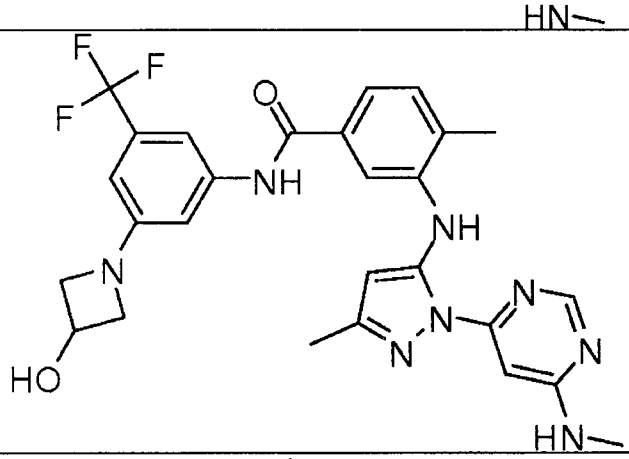
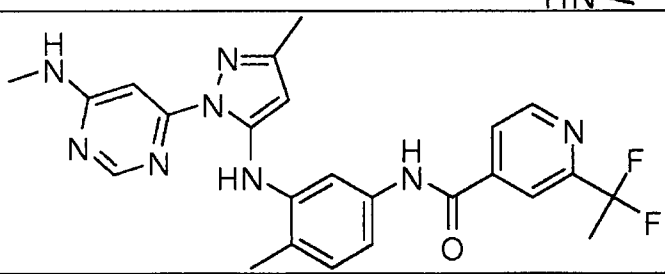
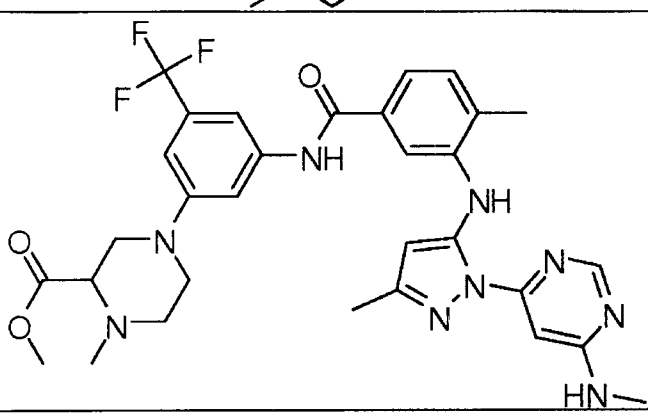
314		MSm/z 571.3 (M + 1)
315		MS m/z 567.3 (M + 1)
316		MS m/z 483.2 (M + 1)
317		MS m/z 472.3 (M + 1)
318		MS m/z 556.3 (M + 1)
319		MSm/z 599.6 (M + 1)

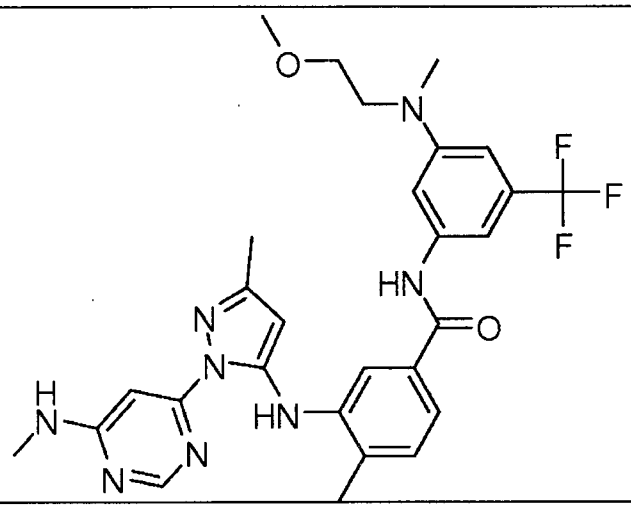
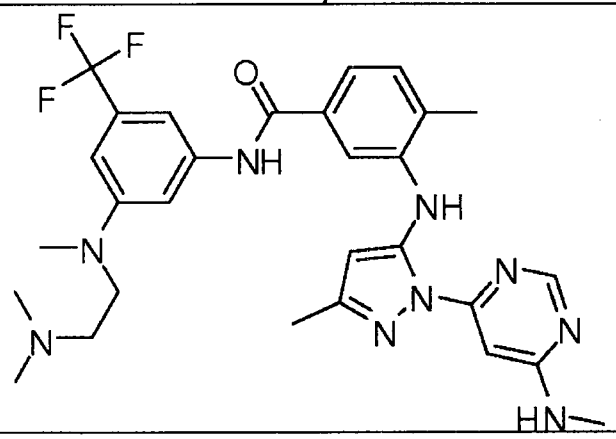
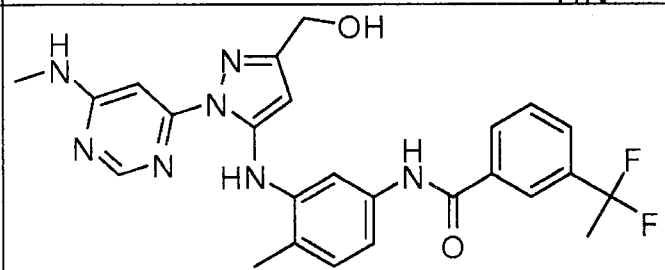
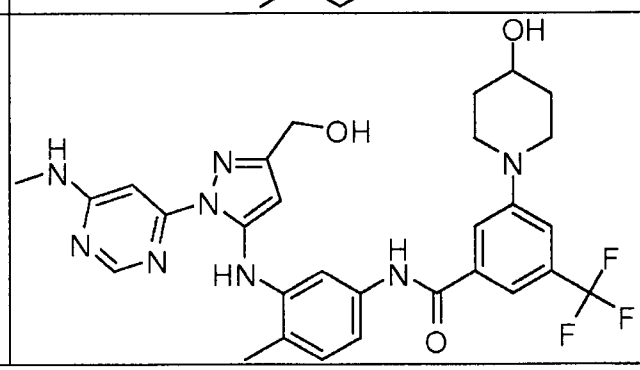
320		MS m/z 567.2 (M + 1)
321		MS m/z 567.2 (M + 1)
322		MS m/z 581.3 (M + 1)
323		MS m/z 595.3 (M + 1)

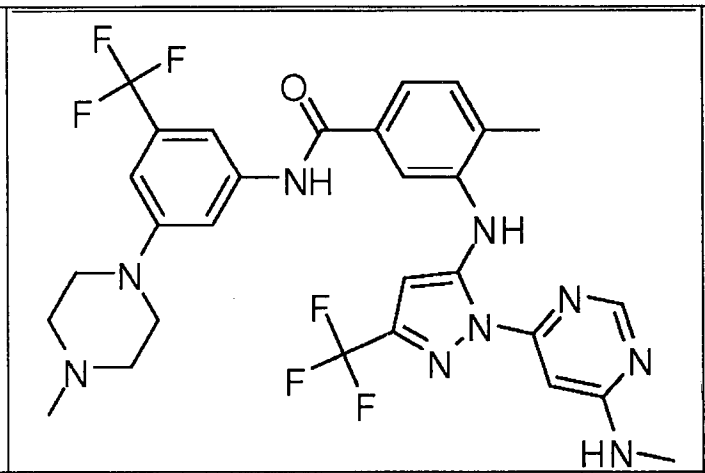
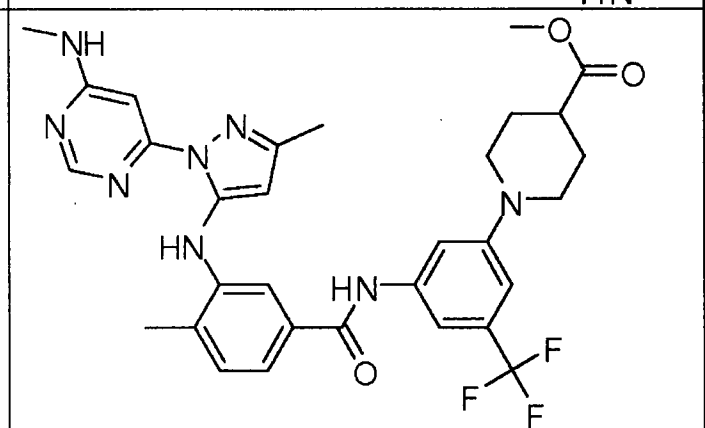
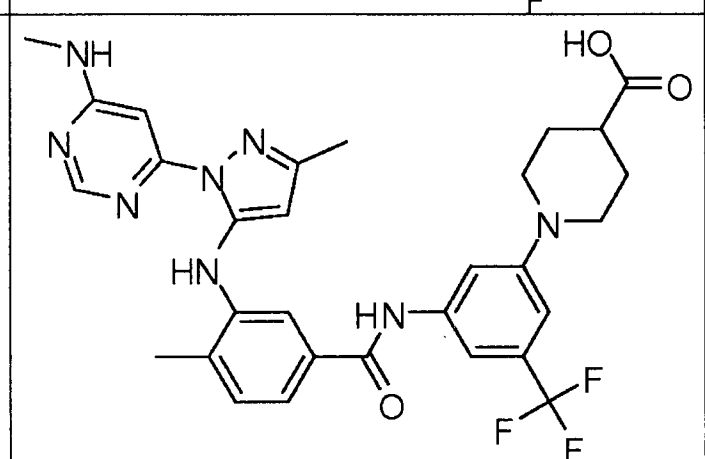
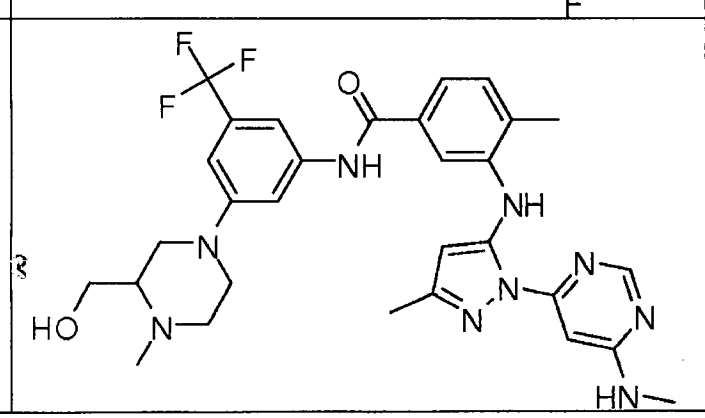
324		MSm/z 610.3 (M + 1)
325		MS m/z 567.2 (M + 1)
326		MS m/z 581.3 (M + 1)
327		MS m/z 581.3 (M + 1)
328		MS m/z 497.2 (M + 1)

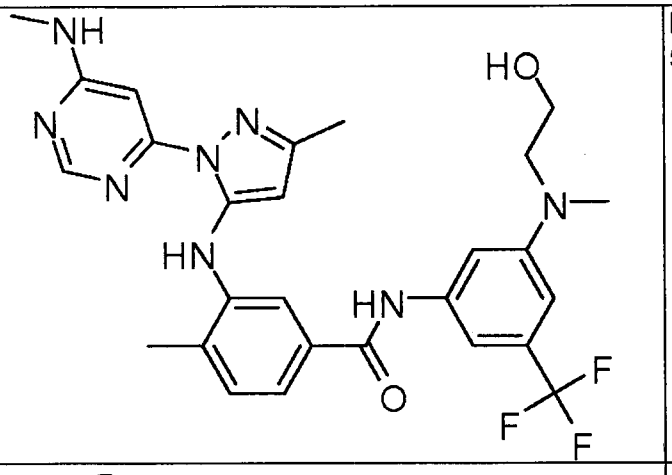
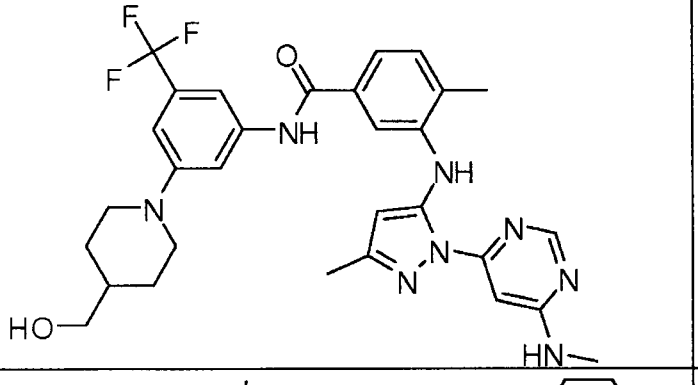
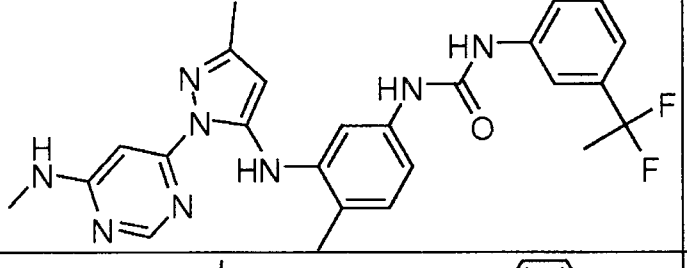
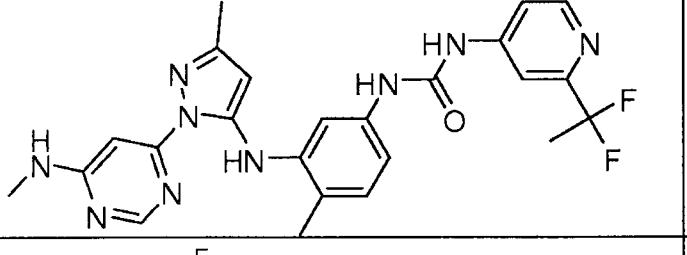
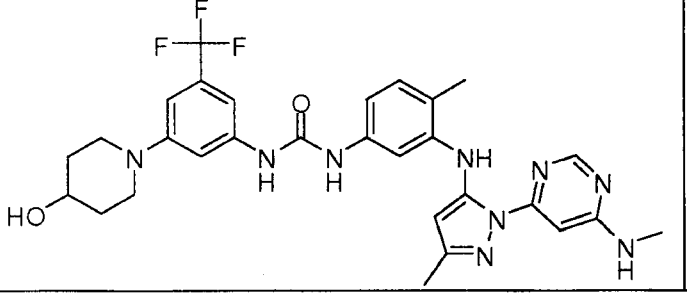
329		MSm/z 515.2 (M + 1)
330		MS m/z 531.2 (M + 1)
331		MS m/z 609.3 (M + 1)
332		MS m/z 615.2 (M + 1)
333		MS m/z 594.3 (M + 1)

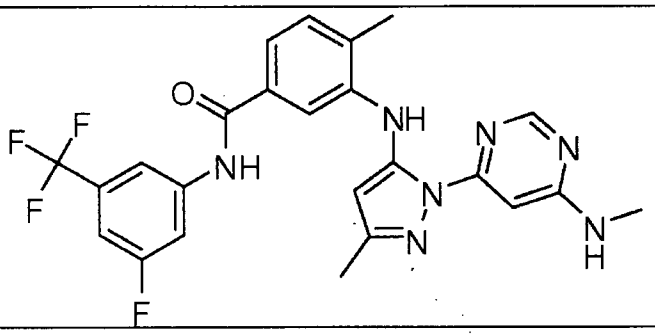
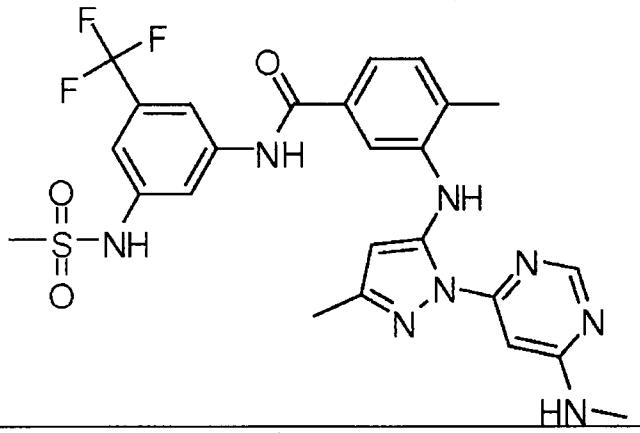
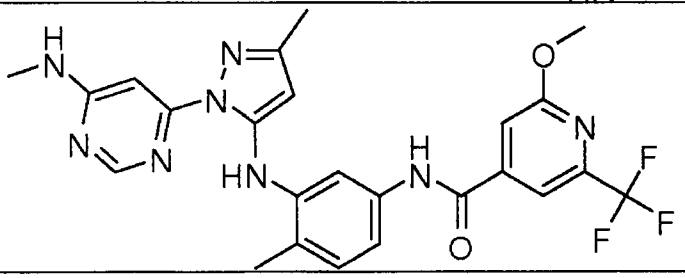
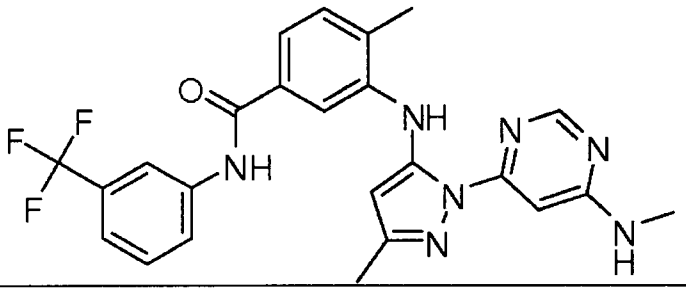
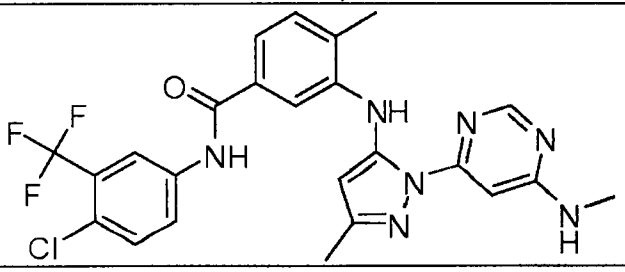
334		MSm/z 580.3 (M + 1)
335		MS m/z 581.3 (M + 1)
336		MS m/z 569.3 (M + 1)
337		MS m/z 595.3 (M + 1)

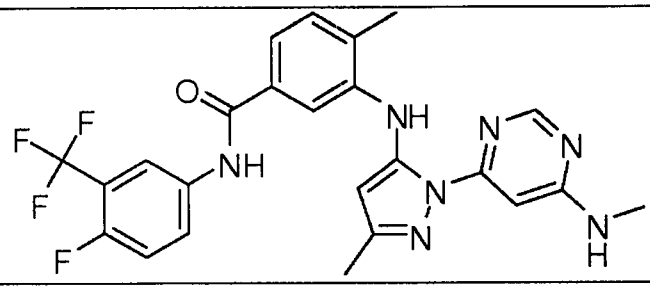
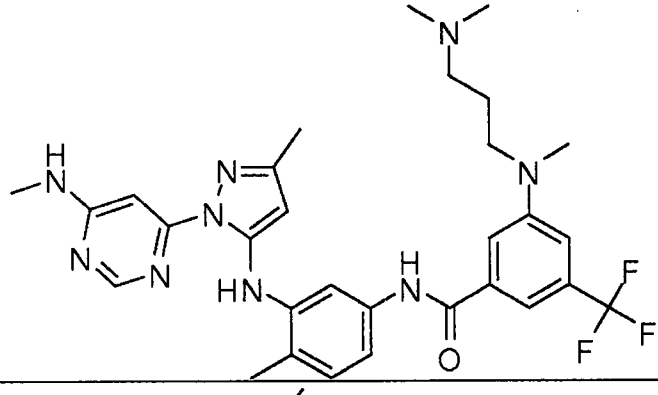
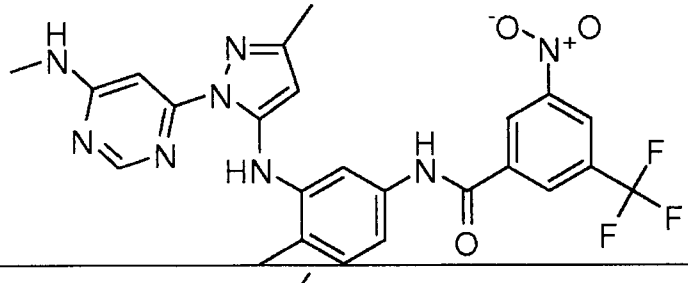
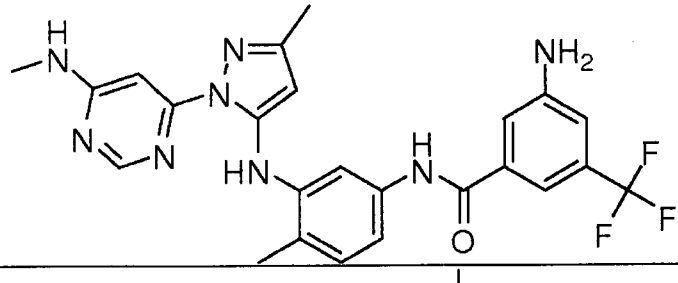
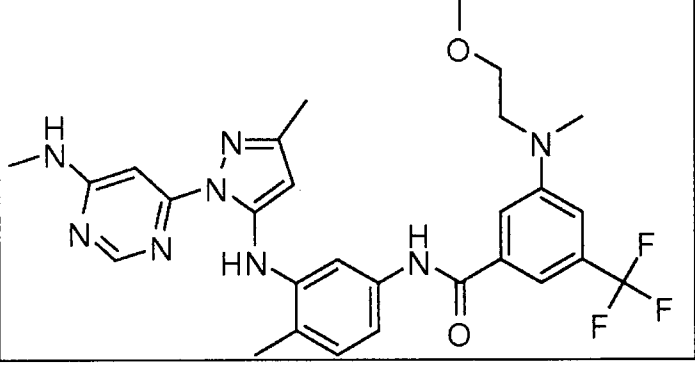
338		MSm/z 567.2 (M + 1)
339		MS m/z 553.2 (M + 1)
340		MS m/z 479.2 (M + 1)
341		MS m/z 638.3 (M + 1)

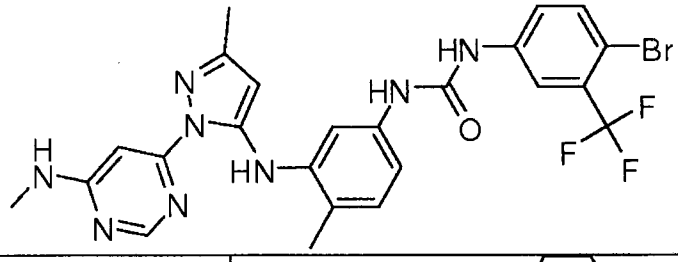
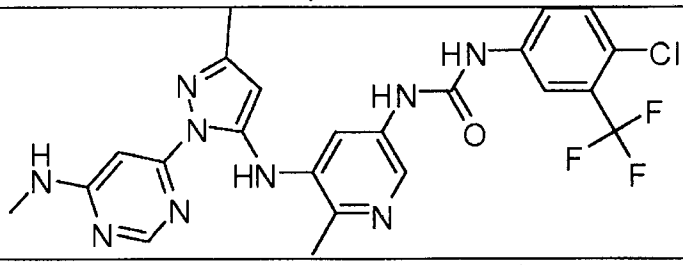
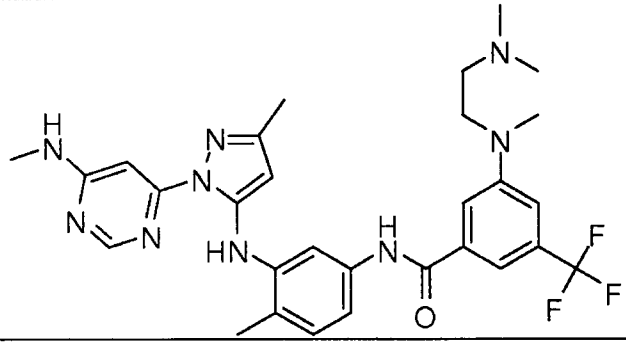
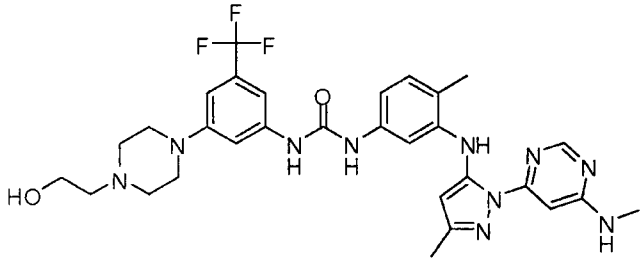
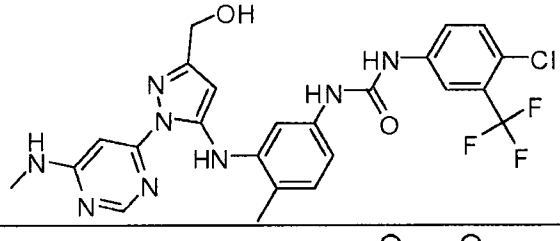
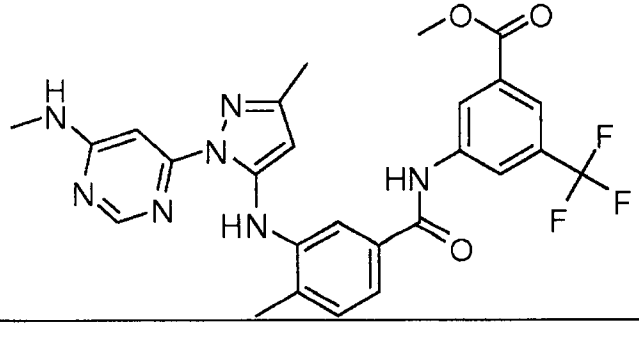
342		MSm/z 569.3 (M + 1)
343		MS m/z 582.3 (M + 1)
344		MS m/z 494.2 (M + 1)
345		MS m/z 597.3 (M + 1)

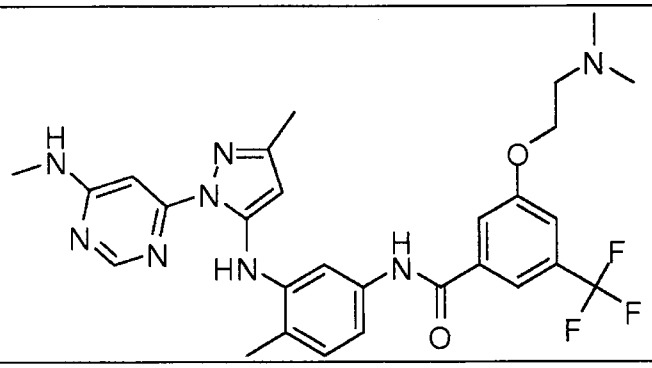
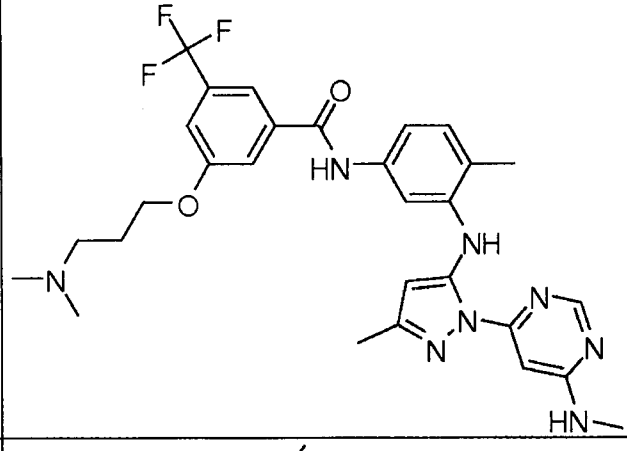
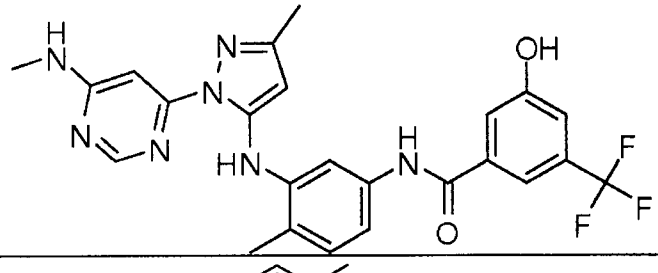
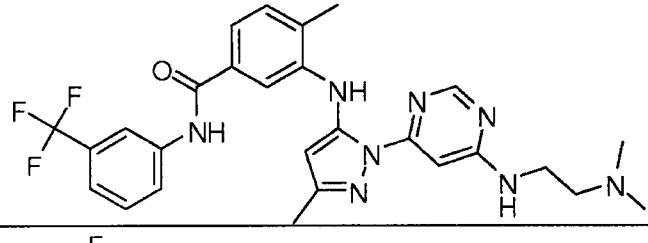
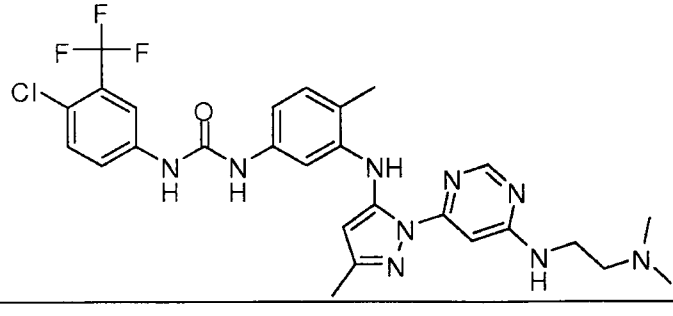
346		MSm/z 634.2 (M + 1)
347		MS m/z 623.3 (M + 1)
348		MS m/z 609.3 (M + 1)
349		MS m/z 610.3 (M + 1)

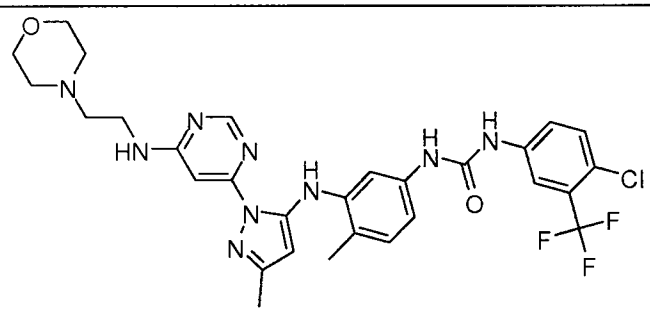
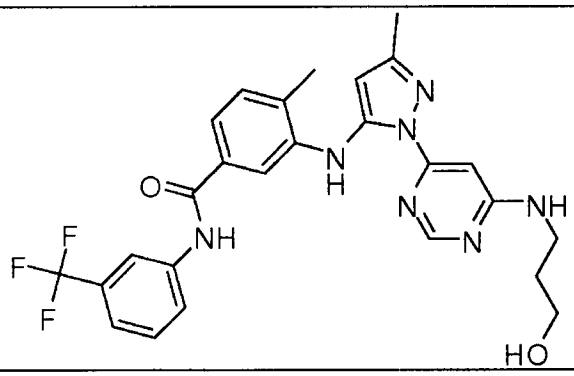
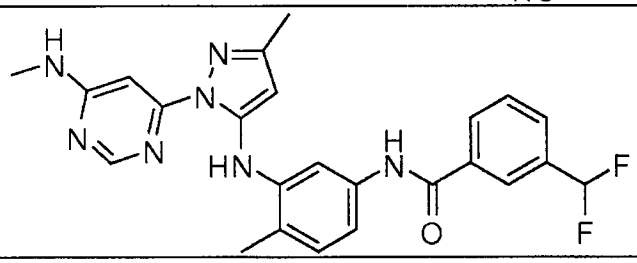
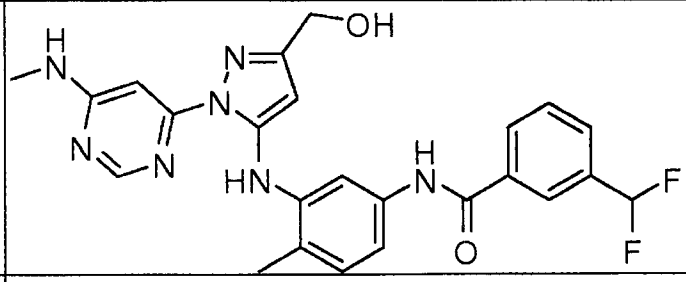
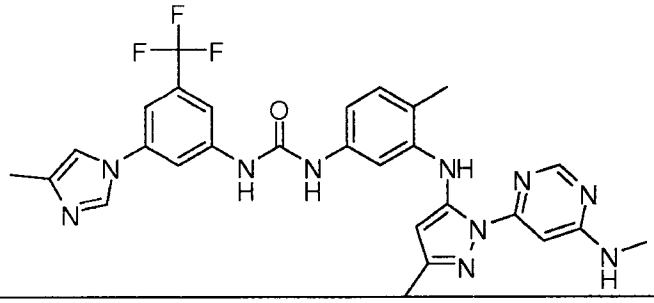
350		MSm/z 555.2 (M + 1)
351		MS m/z 595.3 (M + 1)
352		MS m/z 493.2 (M + 1)
353		MS m/z 494.2 (M + 1)
354		MS m/z 596.3 (M + 1)

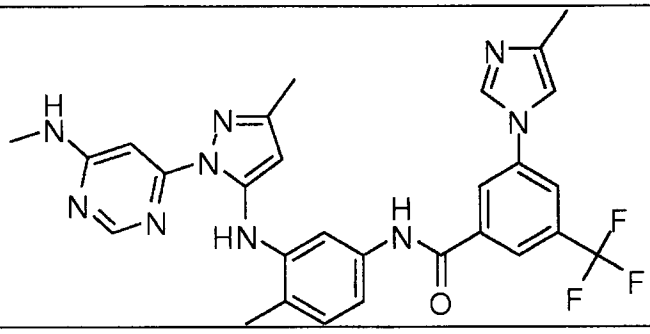
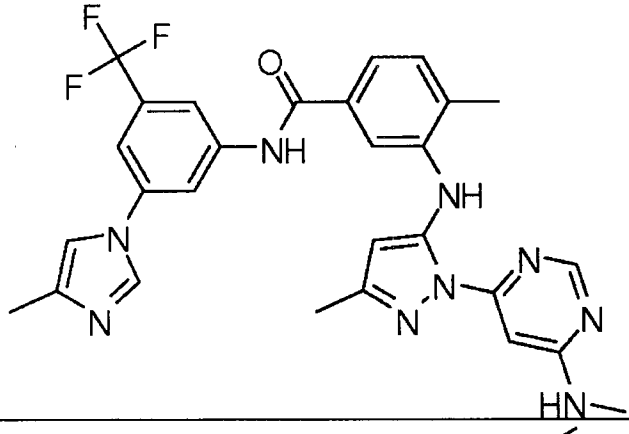
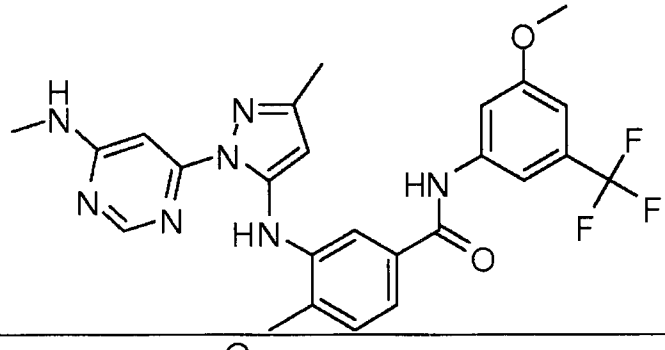
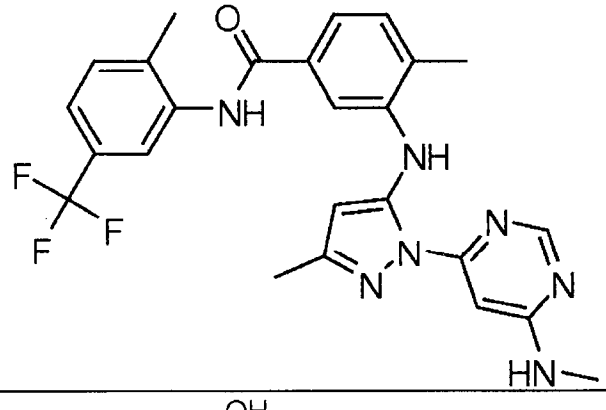
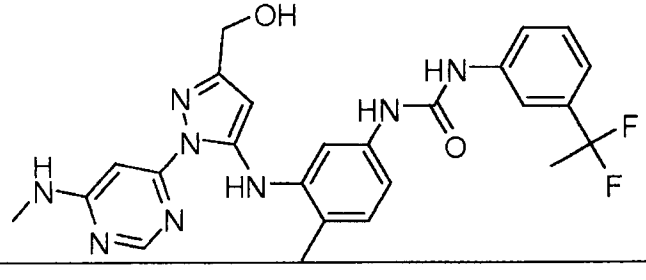
355		MSm/z 500.2 (M + 1)
356		MS m/z 575.2 (M + 1)
357		MS m/z 513.2 (M + 1)
358		MS m/z 482.2 (M + 1)
359		MS m/z 516.1 (M + 1)

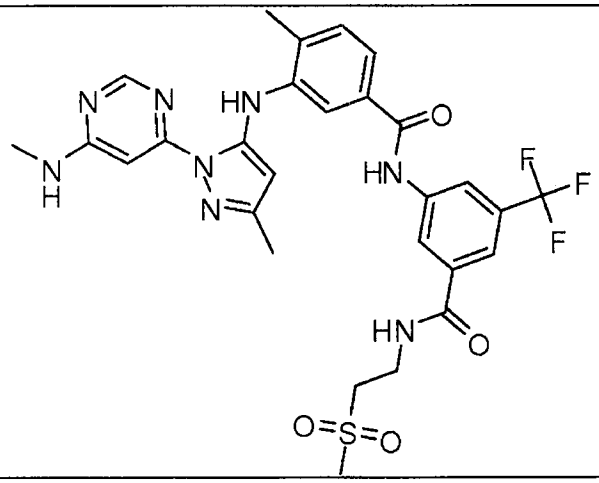
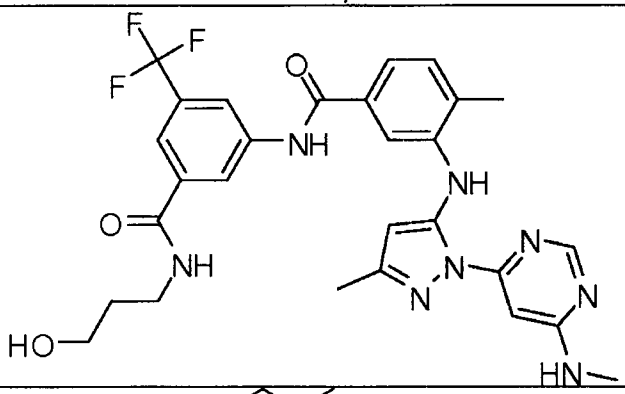
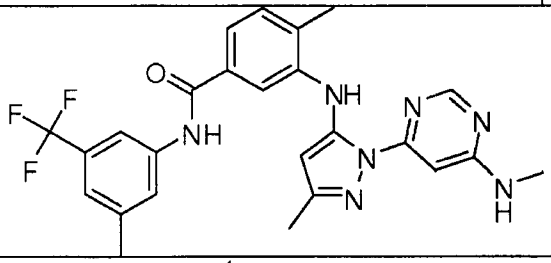
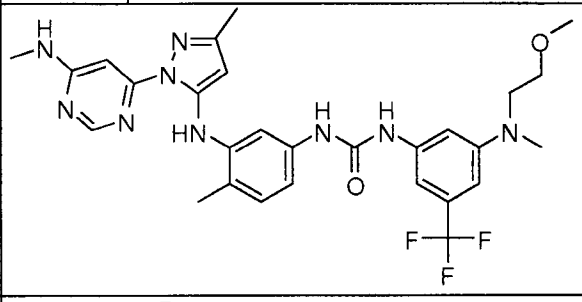
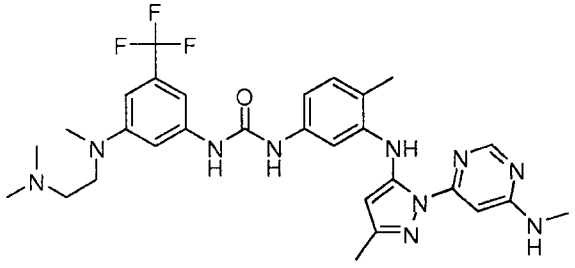
360		MS m/z 500.2 (M + 1)
361		MSm/z 596.3 (M + 1)
362		MS m/z 527.2 (M + 1)
363		MS m/z 497.2 (M + 1)
364		MS m/z 569.3 (M + 1)

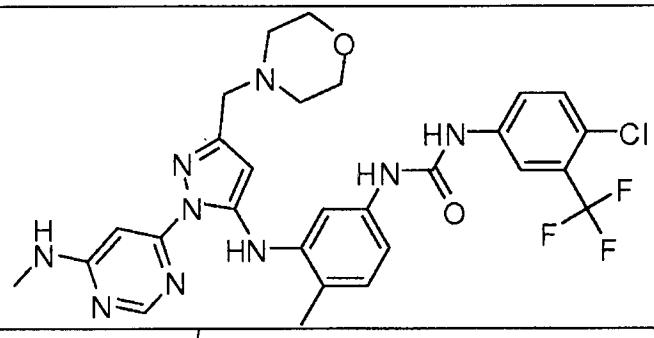
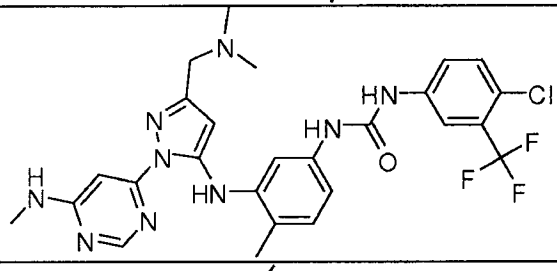
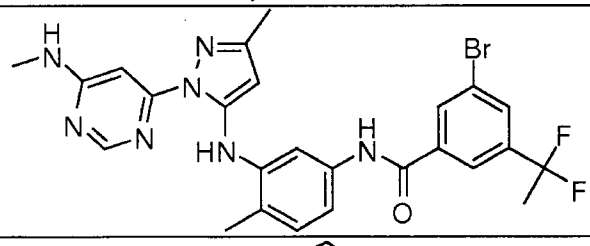
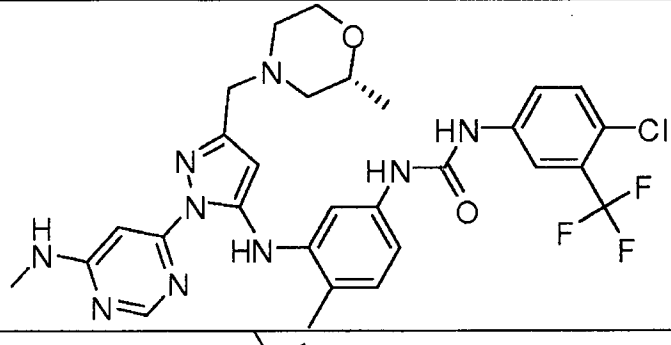
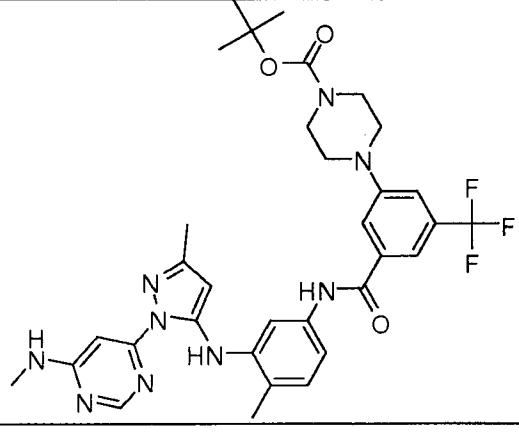
365		MS m/z 575.1 (M + 1)
366		MS m/z 532.2 (M + 1)
367		MSm/z 582.3 (M + 1)
368		MS m/z 625.3 (M + 1)
369		MS m/z 547.2 (M + 1)
370		MS m/z 540.2 (M + 1)

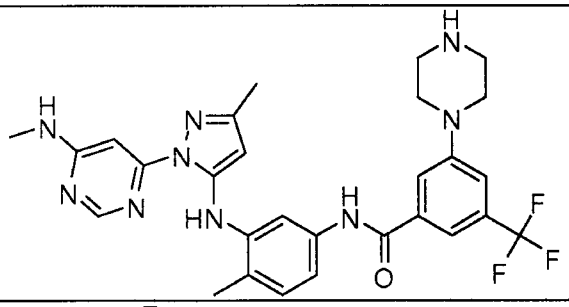
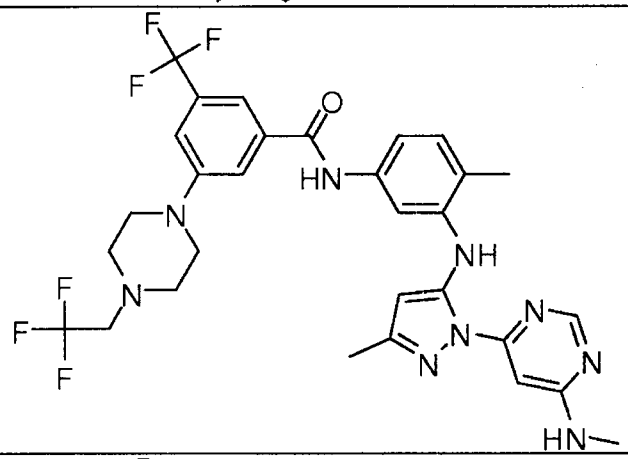
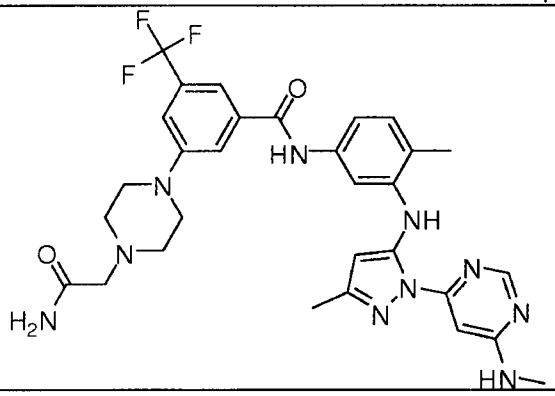
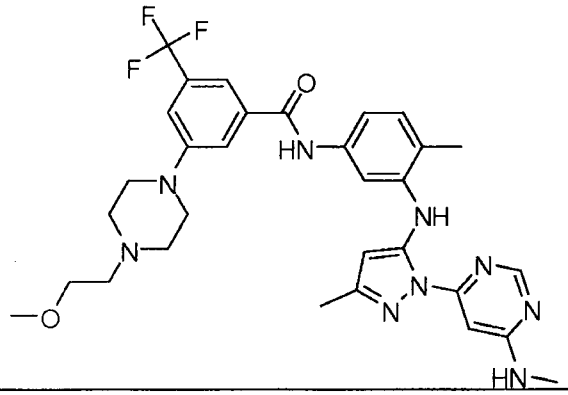
371		MS m/z 569.3 (M + 1)
372		MSm/z 583.3 (M + 1)
373		MS m/z 498.2 (M + 1)
374		MS m/z 539.2 (M + 1)
375		MS m/z 588.2 (M + 1)

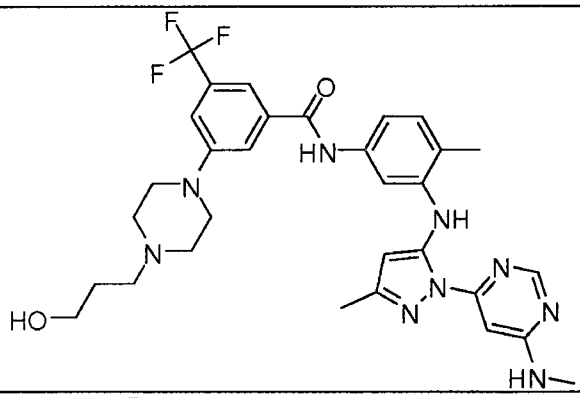
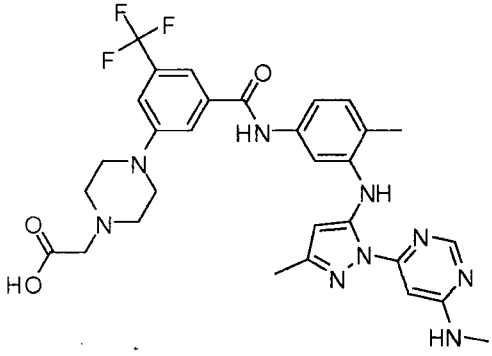
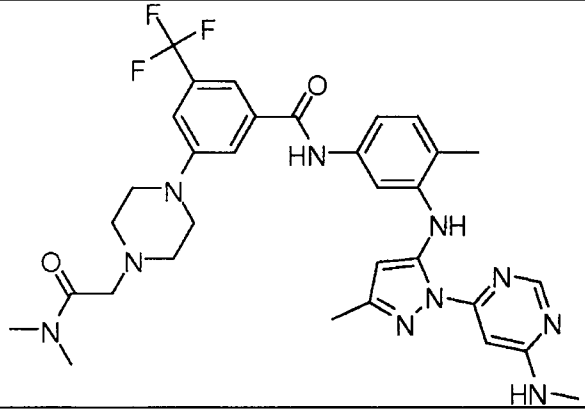
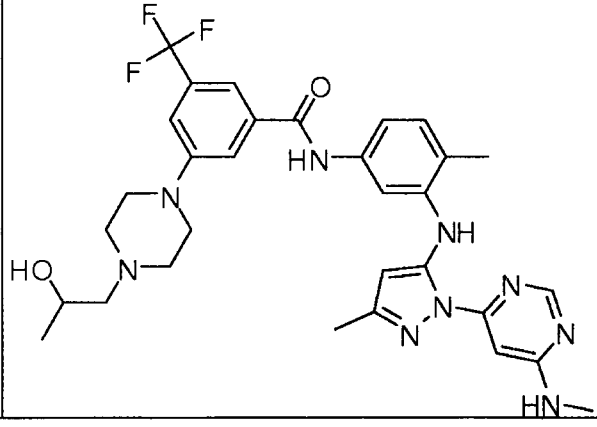
376		MS m/z 630.22 (M + 1)
377		MSm/z 526.2 (M + 1)
378		MS m/z 464.2 (M + 1)
379		MS m/z 480.2 (M + 1)
380		MS m/z 577.2 (M + 1)

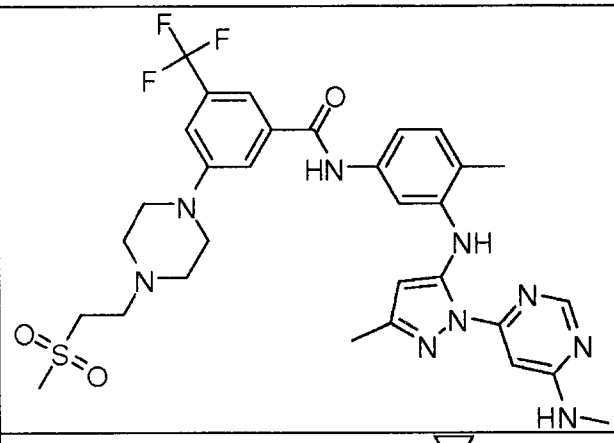
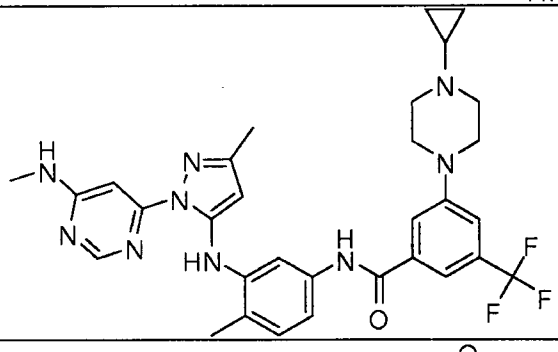
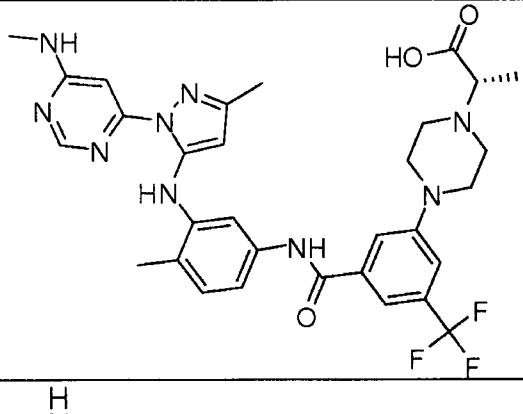
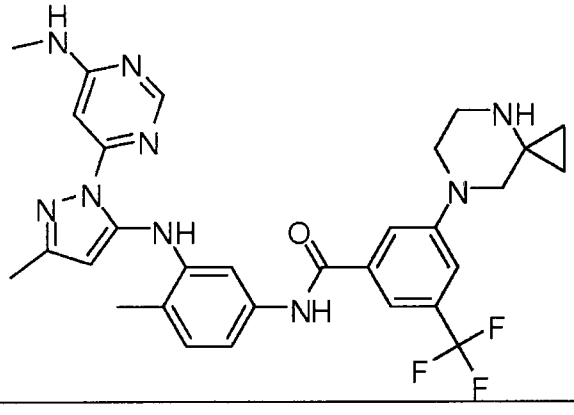
381		MS m/z 562.2 (M + 1)
382		MSm/z 562.2 (M + 1)
383		MS m/z 512.2 (M + 1)
384		MS m/z 496.2 (M + 1)
385		MS m/z 509.2 (M + 1)

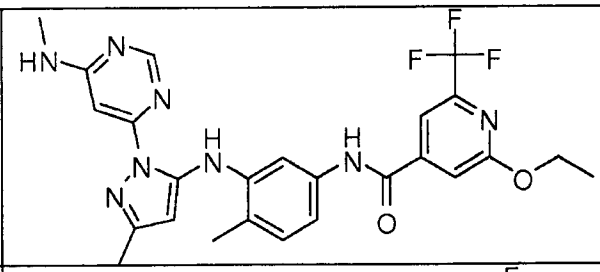
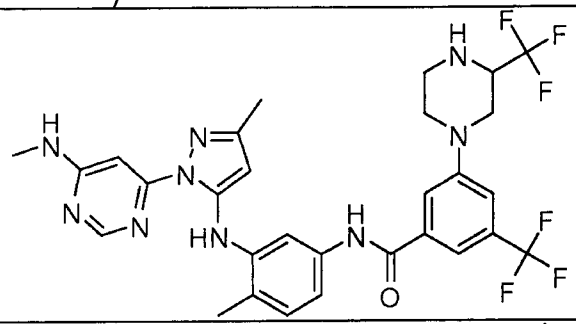
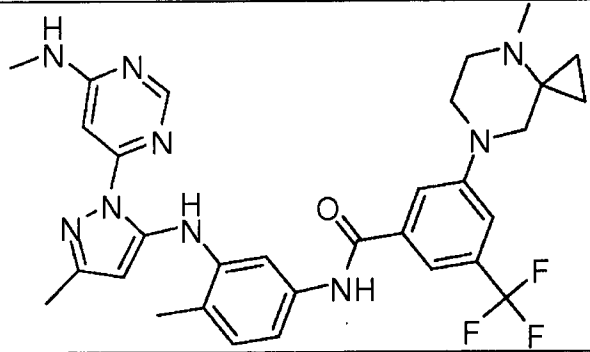
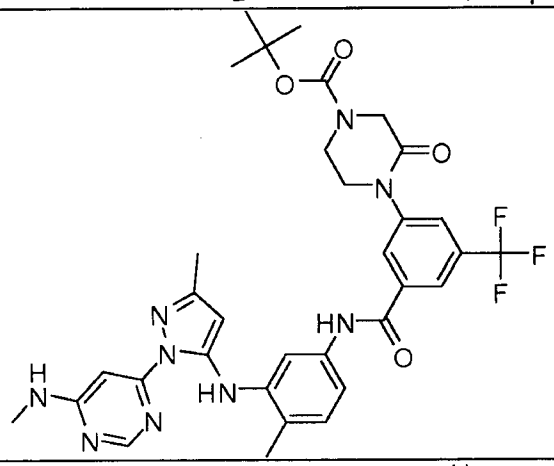
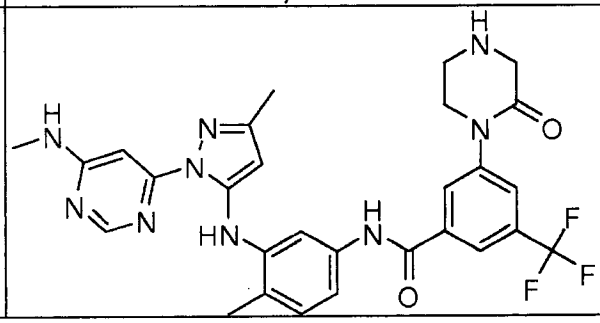
386		MS m/z 631.2 (M + 1)
387		MSm/z 583.2 (M + 1)
388		MS m/z 496.2 (M + 1)
389		MS m/z 584.3 (M + 1)
390		MS m/z 597.3 (M + 1)

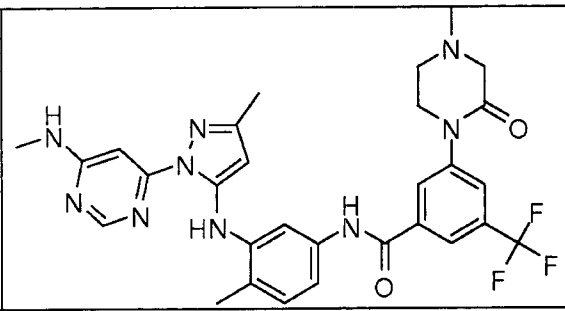
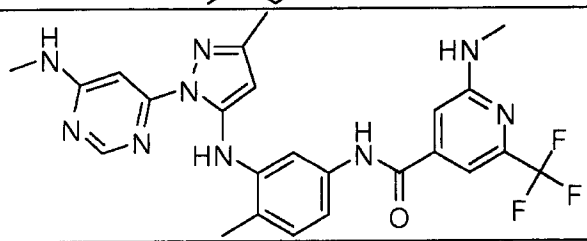
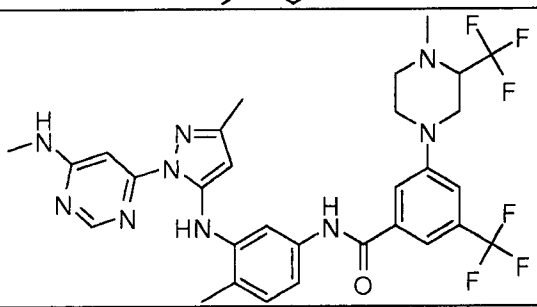
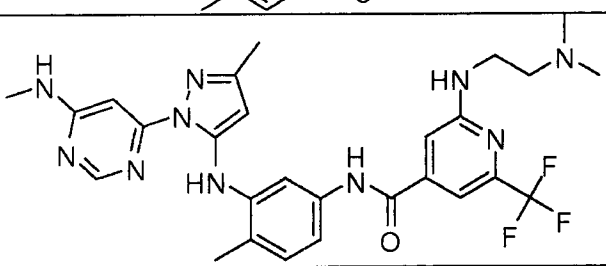
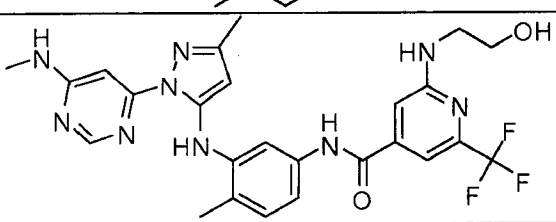
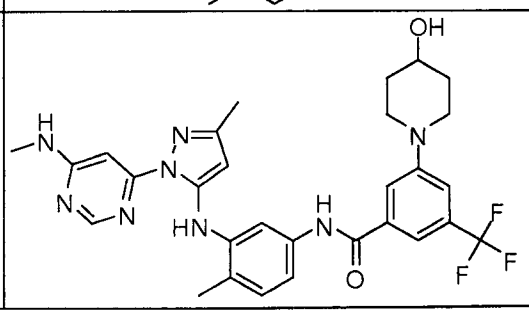
391		MS m/z 616.2 (M + 1)
392		MSm/z 574.2 (M + 1)
393		MS m/z 556.1 (M + 1)
394		MS m/z 630.2 (M + 1)
395		MS m/z 666.3 (M + 1)

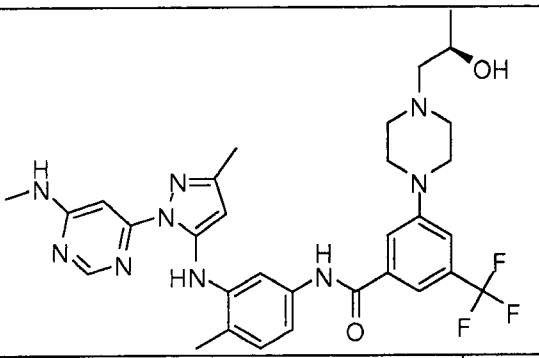
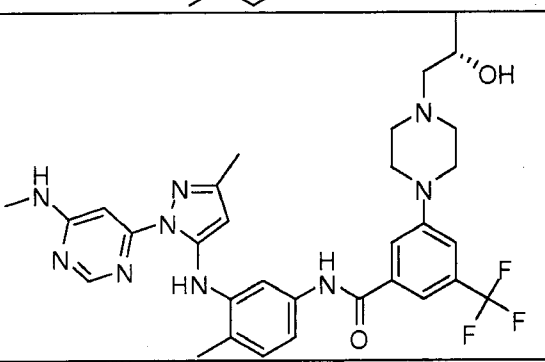
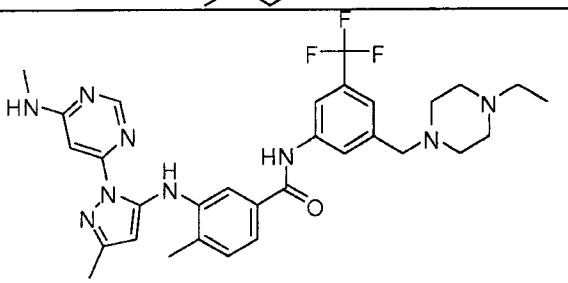
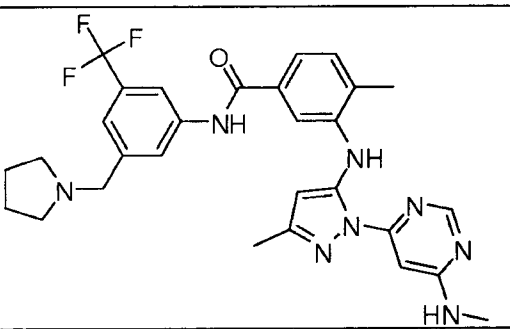
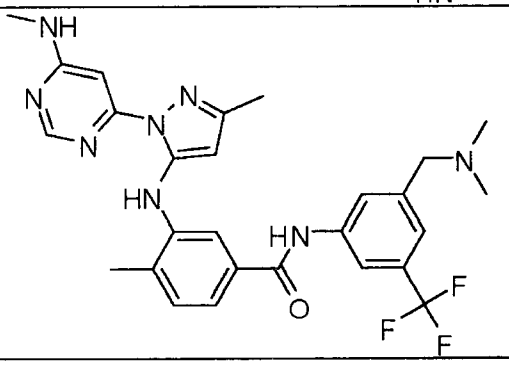
396		MS m/z 566.3 (M + 1)
397		MSm/z 648.3 (M + 1)
398		MS m/z 623.3 (M + 1)
399		MS m/z 624.3 (M + 1)

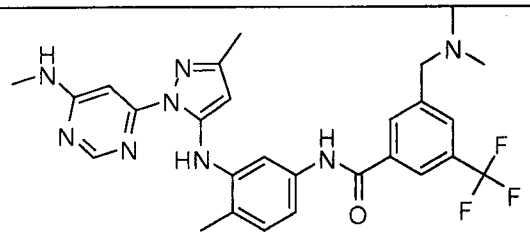
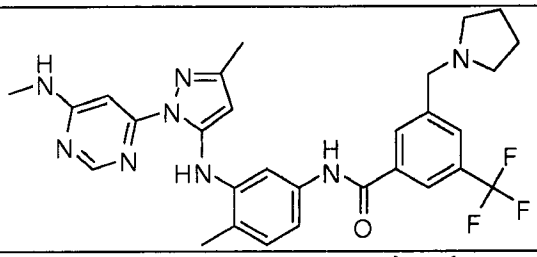
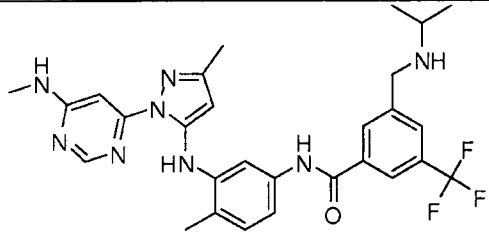
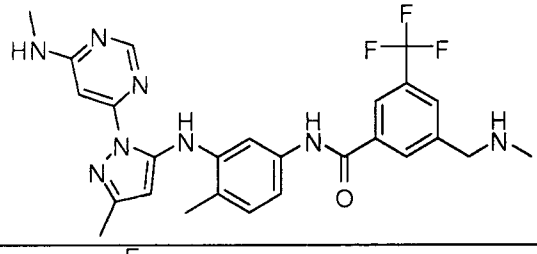
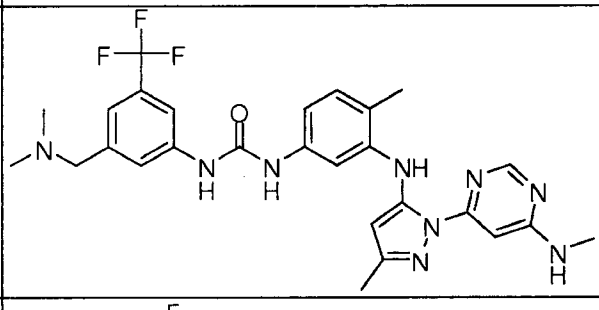
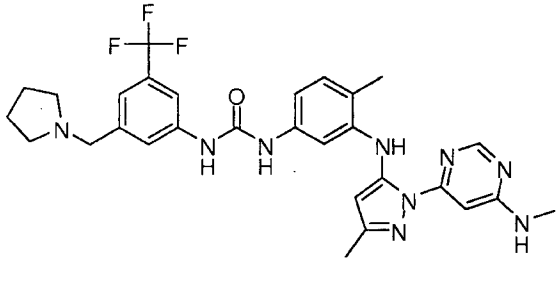
400		MSm/z 624.3 (M + 1)
401		MS m/z 624.3 (M + 1)
402		MS m/z 651.3 (M + 1)
403		MSm/z 624.3 (M + 1)

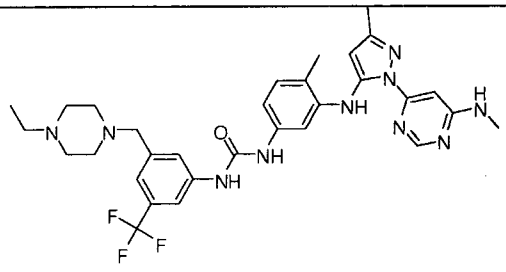
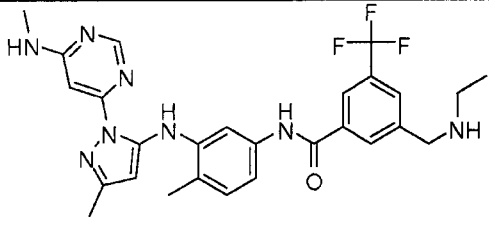
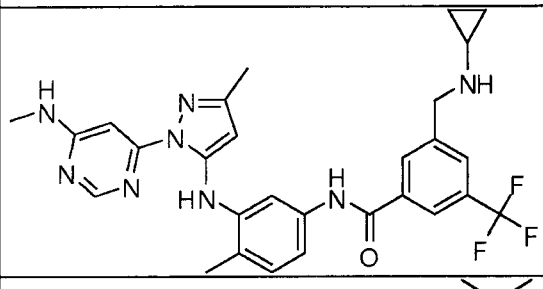
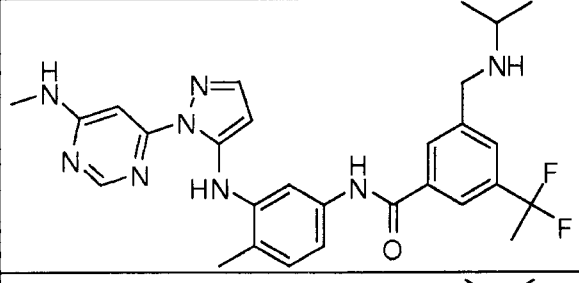
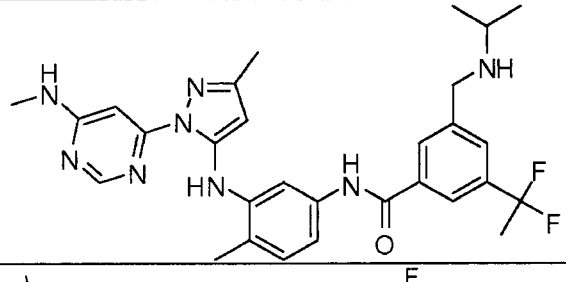
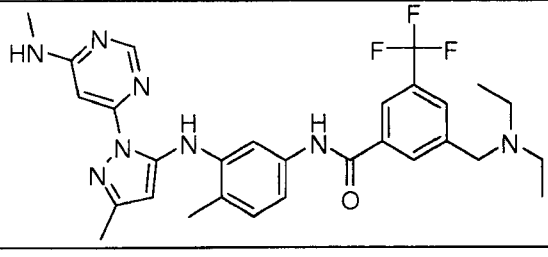
404		MS m/z 672.3 (M + 1)
405		MS m/z 606.3 (M + 1)
406		MS m/z 638.3 (M + 1)
407		MSm/z 592.3 (M + 1)

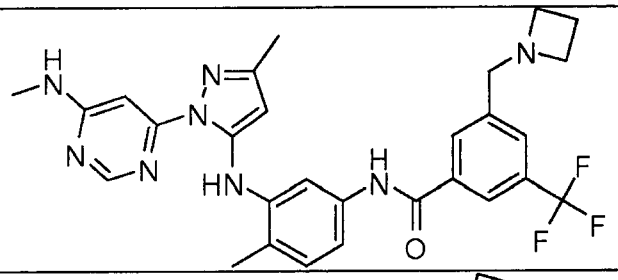
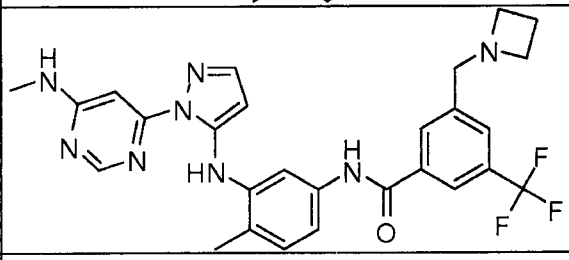
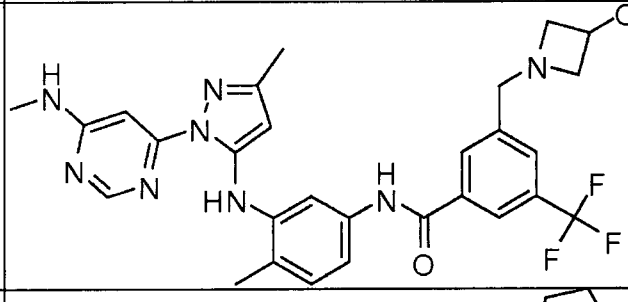
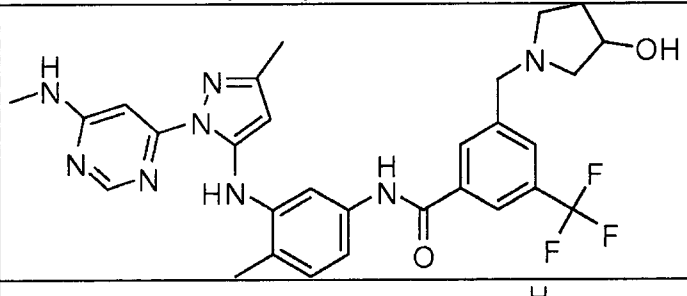
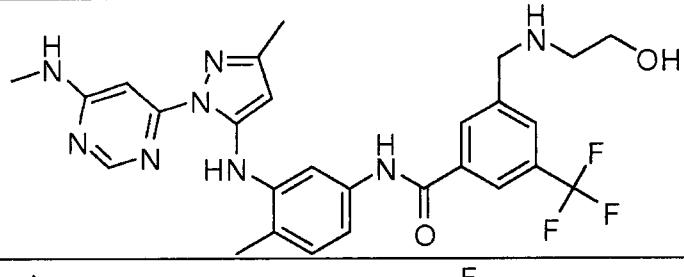
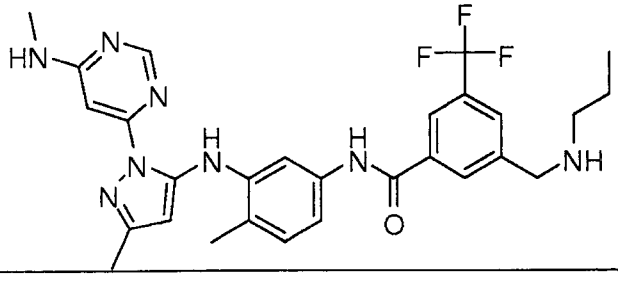
408		MS m/z 527.2 (M + 1)
409		MS m/z 634.2 (M + 1)
410		MS m/z 606.3 (M + 1)
411		MSm/z 680.3 (M + 1)
412		MS m/z 580.2 (M + 1)

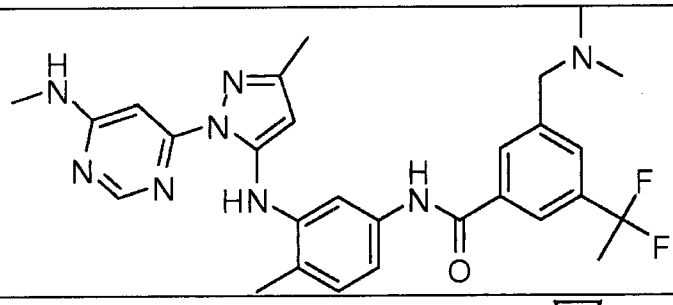
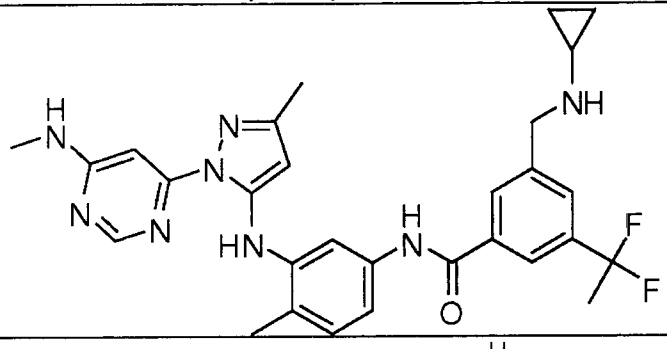
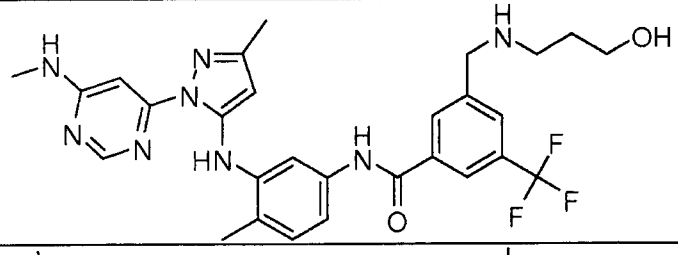
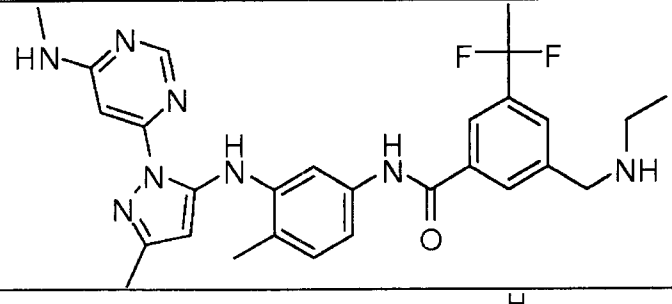
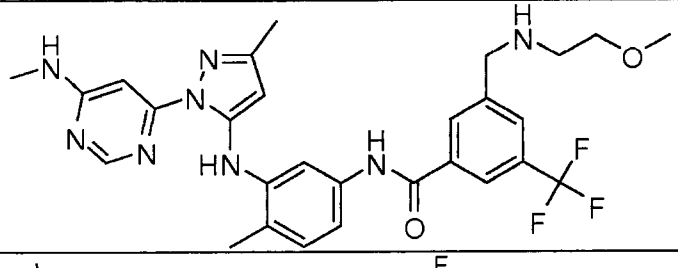
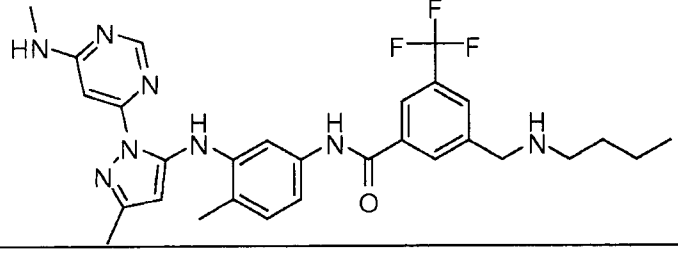
413		MS m/z 594.3 (M + 1)
414		MS m/z 512.2 (M + 1)
415		MSm/z 648.3 (M + 1)
416		MS m/z 569.3 (M + 1)
417		MS m/z 542.2 (M + 1)
418		MS m/z 581.3 (M + 1)

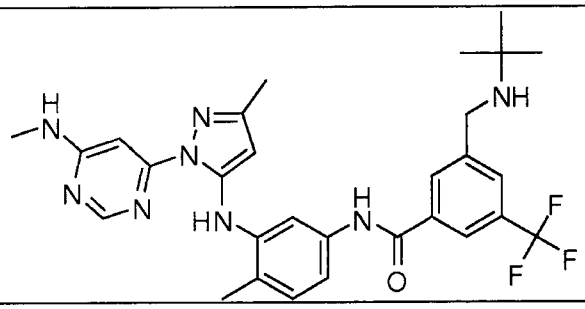
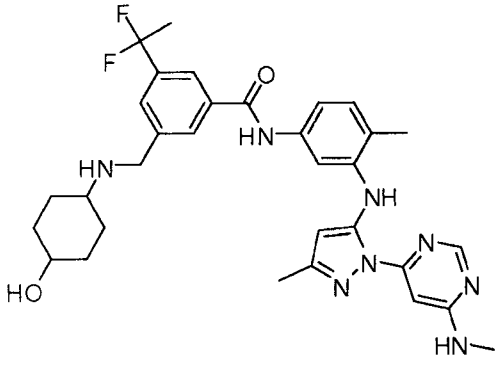
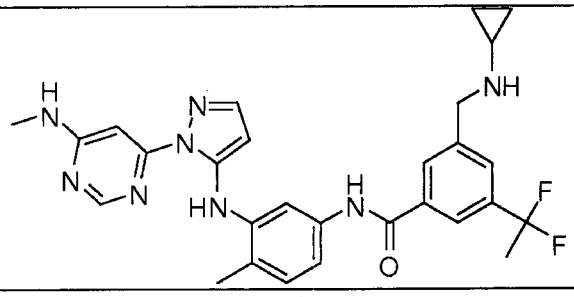
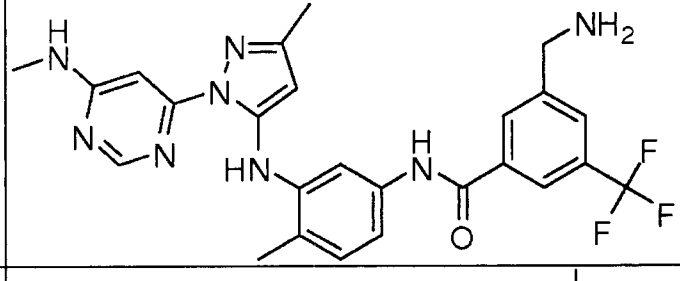
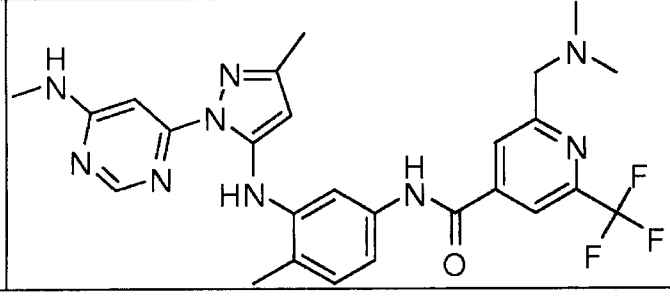
419		MS m/z 624.3 (M + 1)
420		MSm/z 624.3 (M + 1)
421		MS m/z 608.3 (M + 1)
422		MS m/z 565.3 (M + 1)
423		MS m/z 539.2 (M + 1)

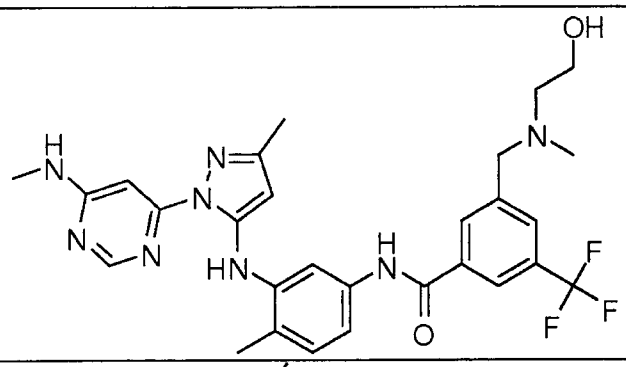
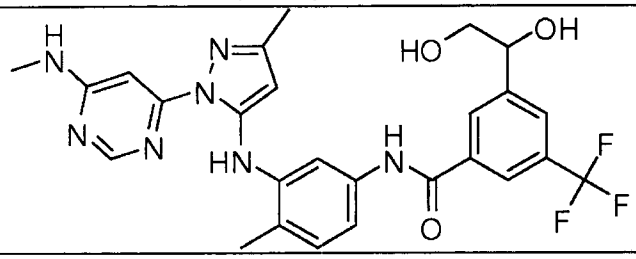
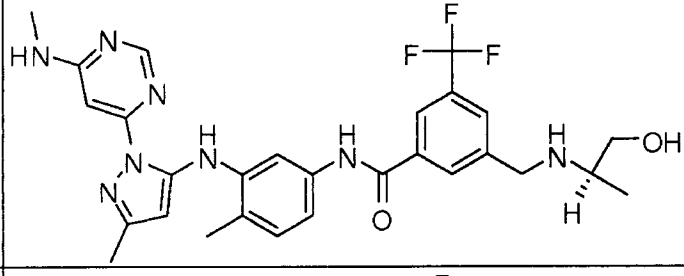
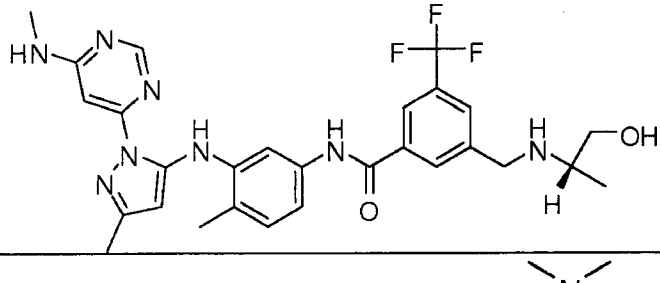
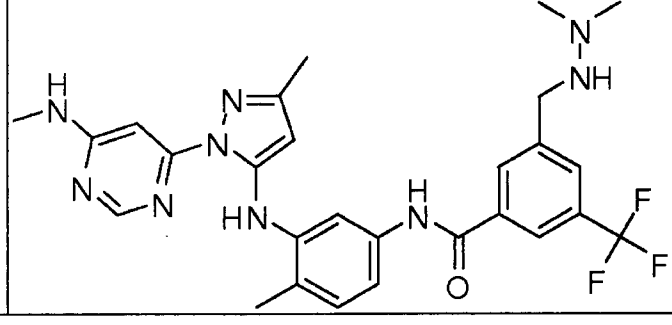
424		MSm/z 539.2 (M + 1)
425		MS m/z 565.3 (M + 1)
426		MS m/z 553.3 (M + 1)
427		MS m/z 525.2 (M + 1)
428		MS m/z 554.3 (M + 1)
429		MSm/z 580.3 (M + 1)

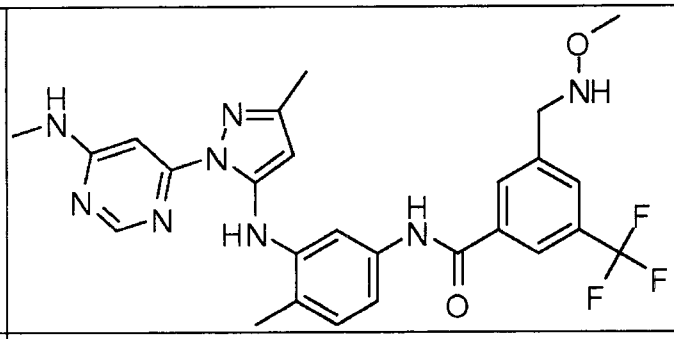
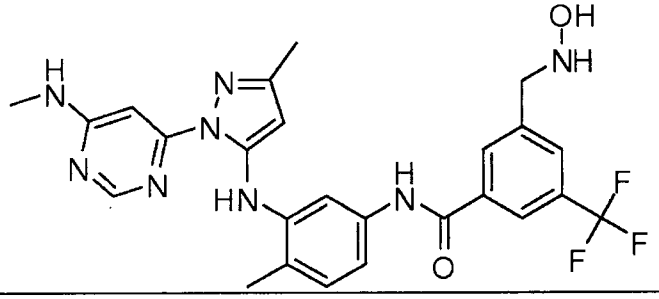
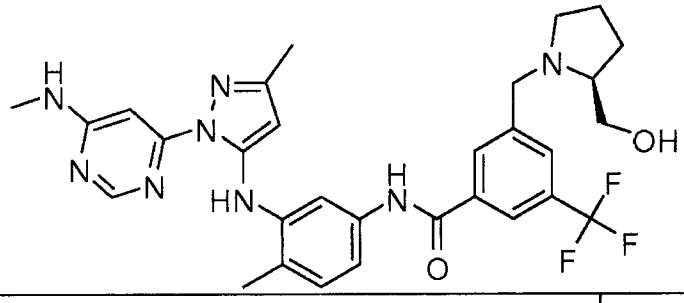
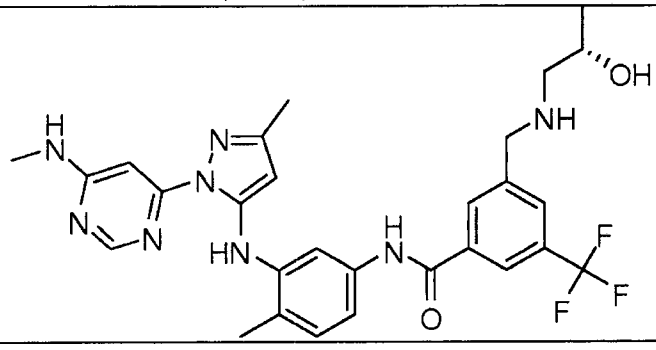
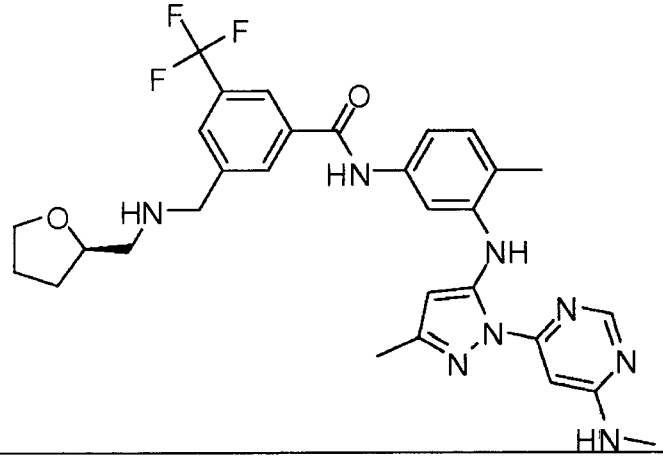
430		MS m/z 623.3 (M + 1)
431		MS m/z 539.2 (M + 1)
432		MS m/z 551.2 (M + 1)
433		MS m/z 535.3 (M + 1)
434		MSm/z 549.3 (M + 1)
435		MS m/z 567.3 (M + 1)

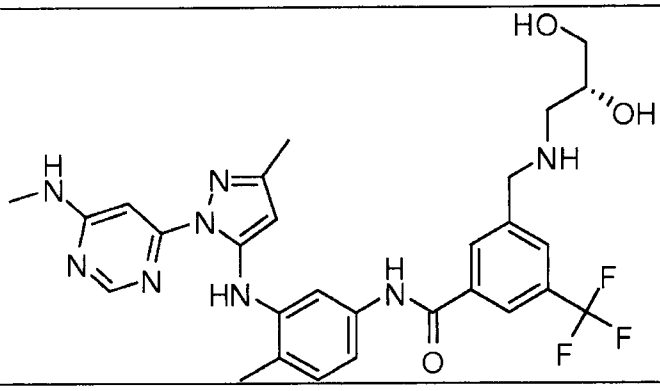
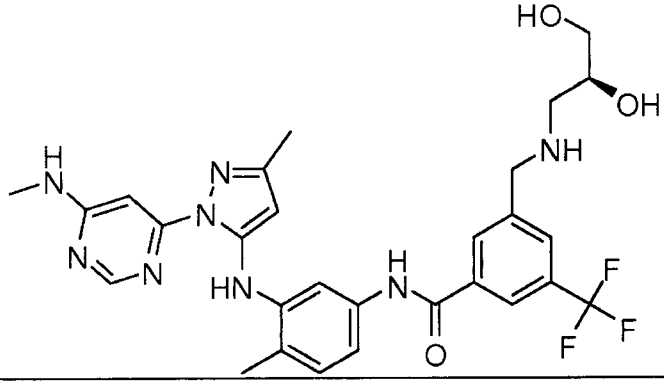
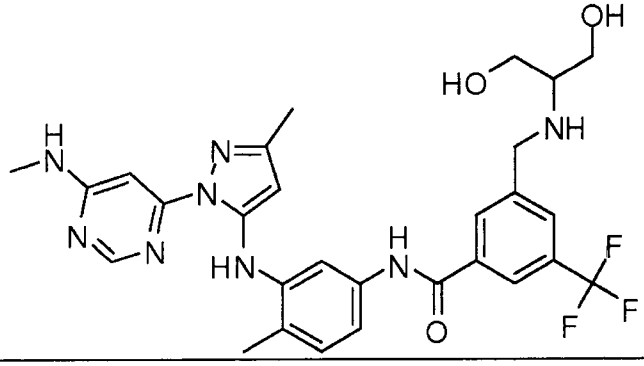
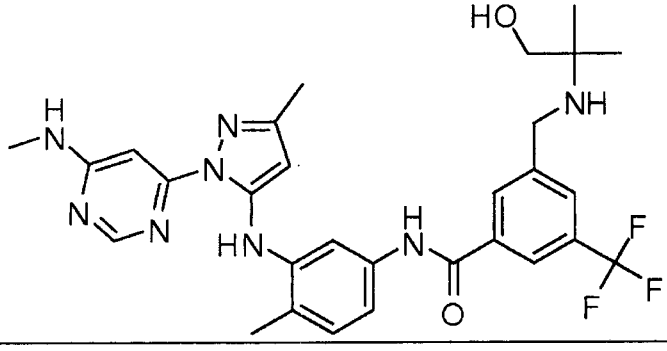
436		MS m/z 551.2 (M + 1)
437		MS m/z 537.2 (M + 1)
438		MS m/z 567.2 (M + 1)
439		MS m/z 581.3 (M + 1)
440		MSm/z 555.2 (M + 1)
441		MS m/z 553.3 (M + 1)

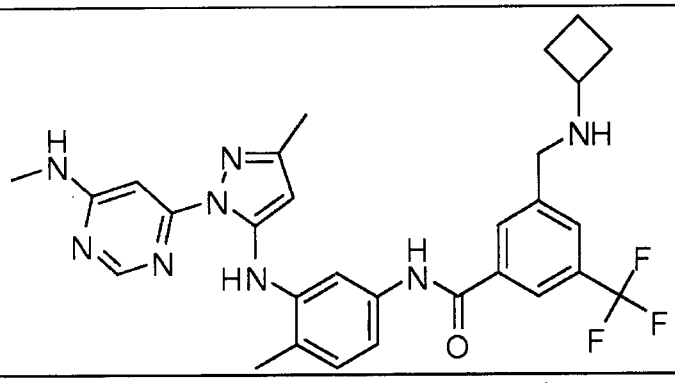
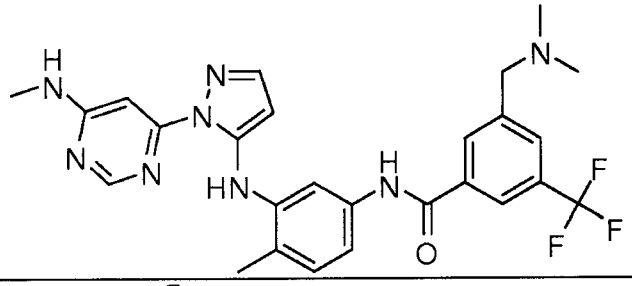
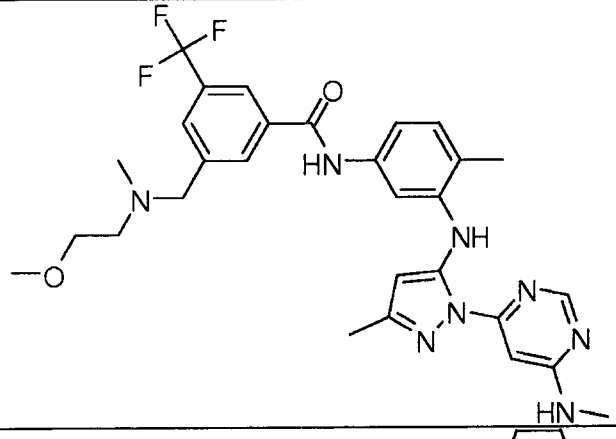
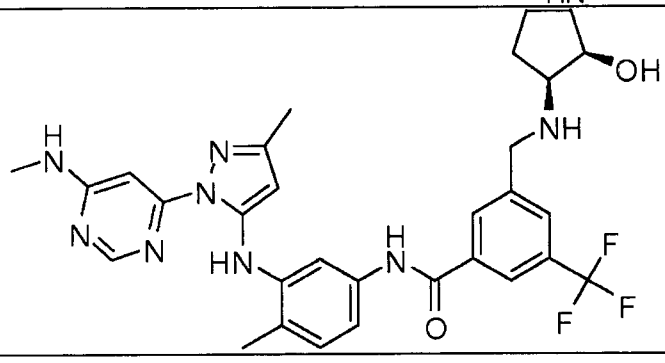
442		MS m/z 535.3 (M + 1)
443		MS m/z 547.3 (M + 1)
444		MS m/z 569.3 (M + 1)
445		MS m/z 535.3 (M + 1)
446		MSm/z 569.3 (M + 1)
447		MS m/z 567.3 (M + 1)

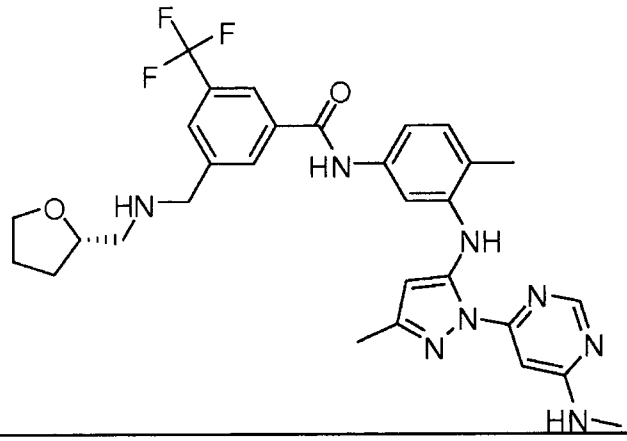
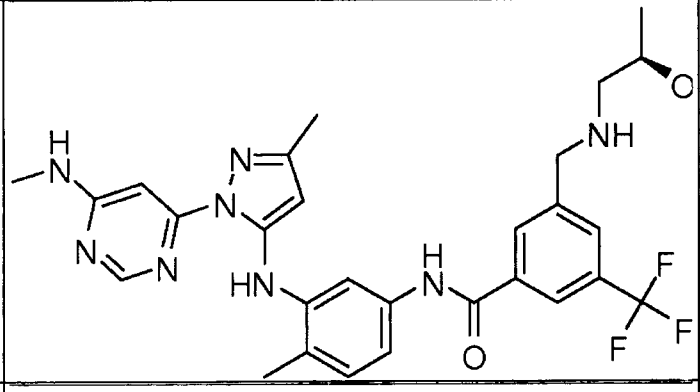
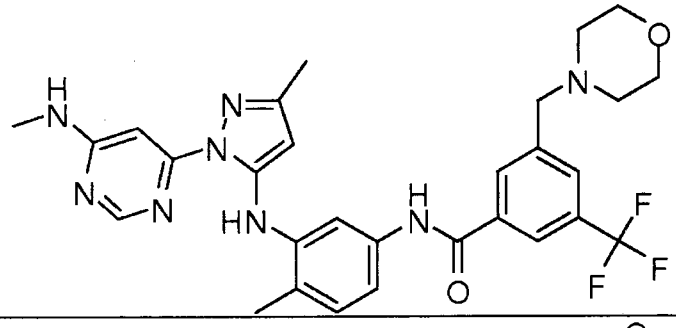
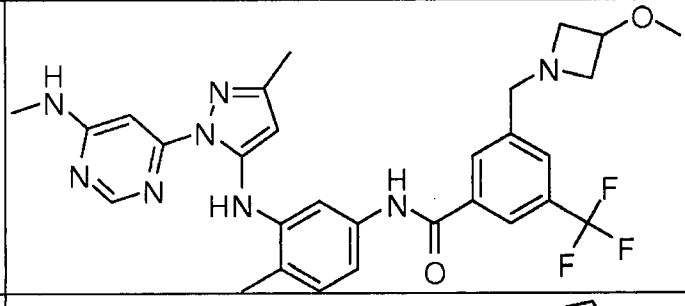
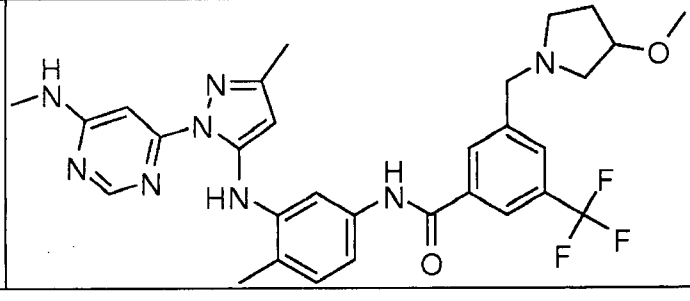
448		MS m/z 567.3 (M + 1)
449		MS m/z 605.3 (M + 1)
450		MS m/z 533.3 (M + 1)
451		MSm/z 511.2 (M + 1)
452		MS m/z 540.2 (M + 1)

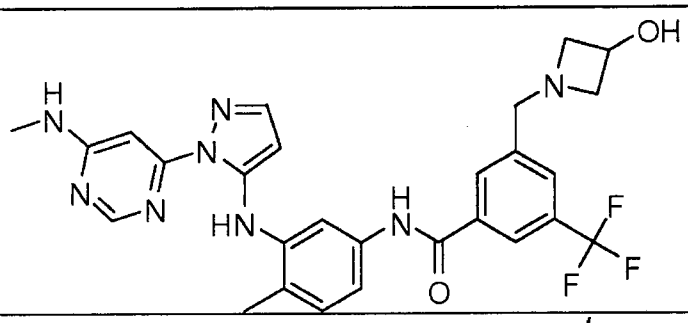
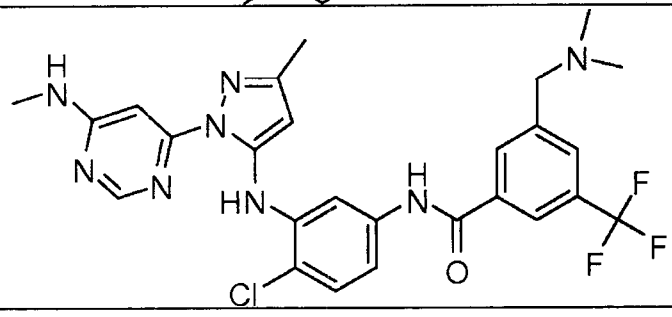
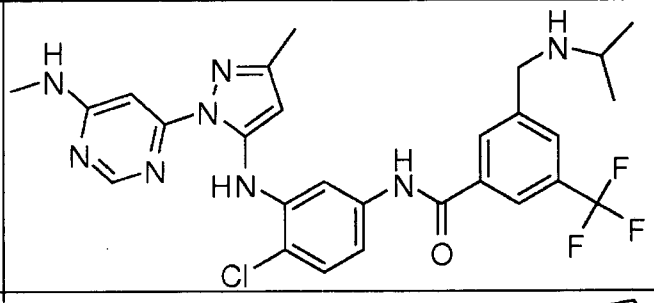
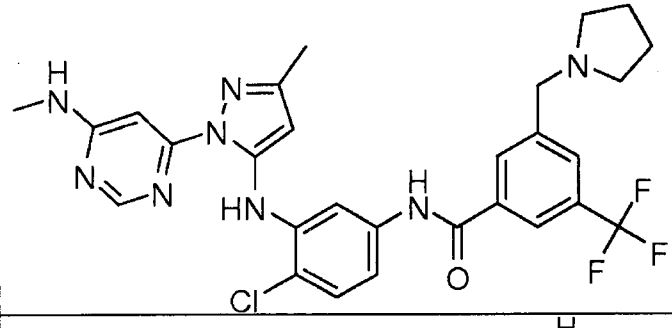
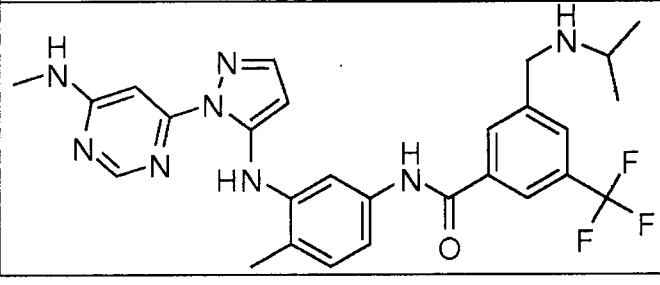
453		MS m/z 569.3 (M + 1)
454		MS m/z 542.2 (M + 1)
455		MS m/z 569.3 (M + 1)
456		MS m/z 569.3 (M + 1)
457		MSm/z 554.3 (M + 1)

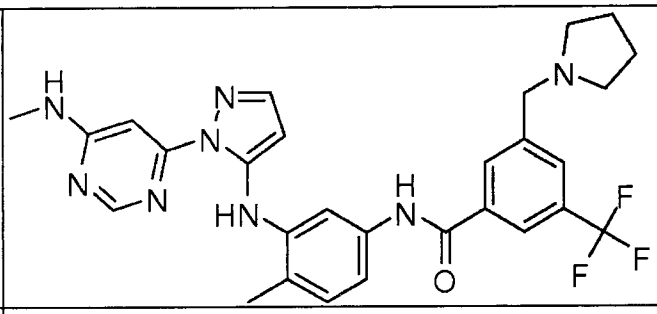
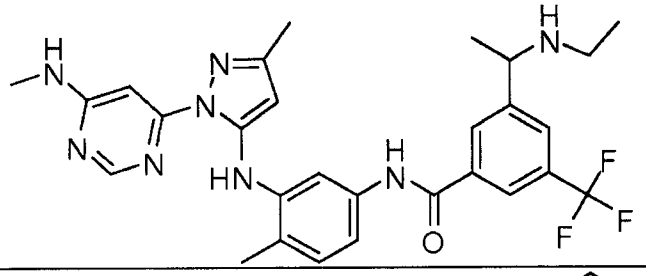
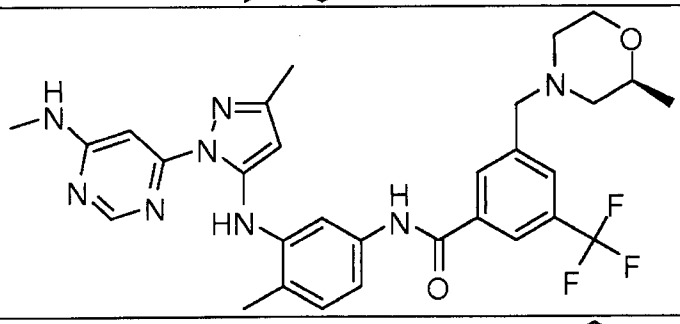
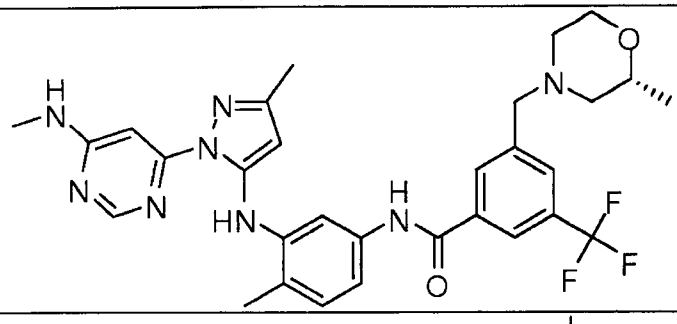
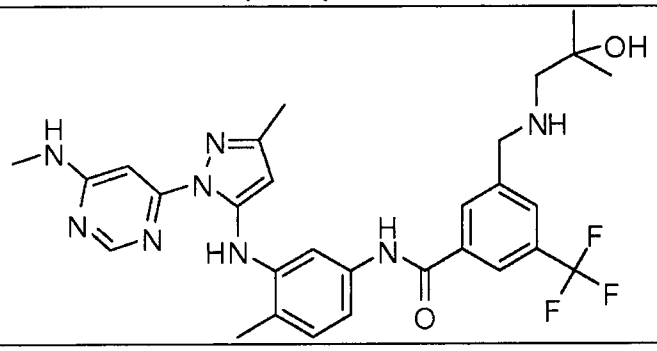
458		MS m/z 541.2 (M + 1)
459		MS m/z 527.2 (M + 1)
460		MS m/z 595.3 (M + 1)
461		MS m/z 569.3 (M + 1)
462		MSm/z 595.3 (M + 1)

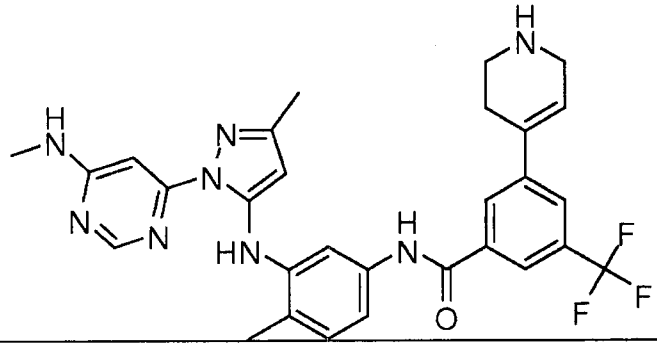
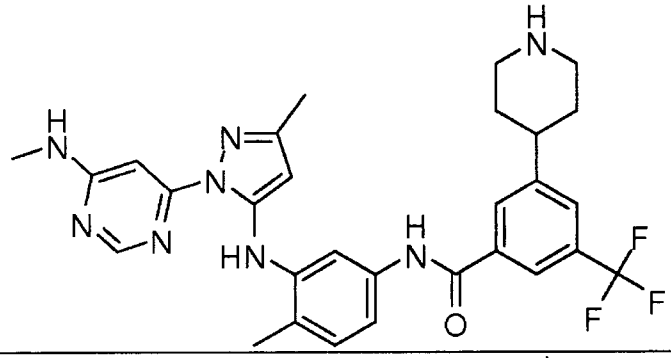
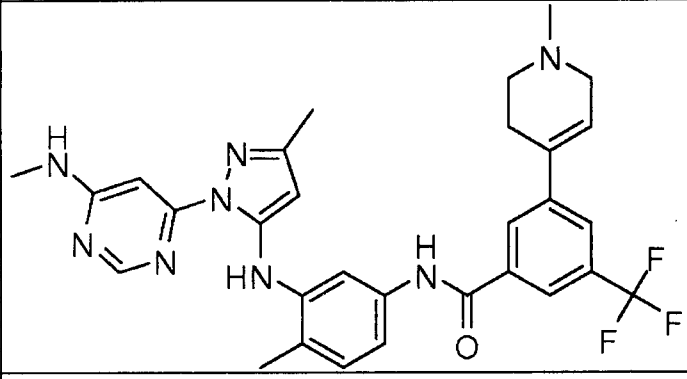
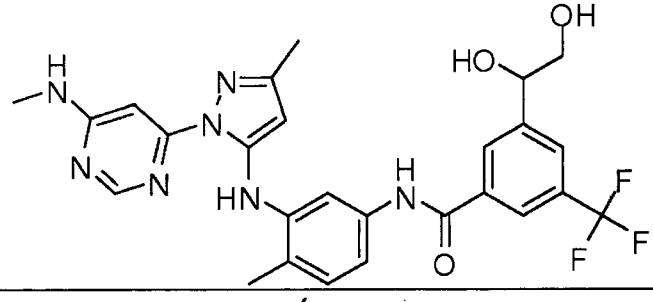
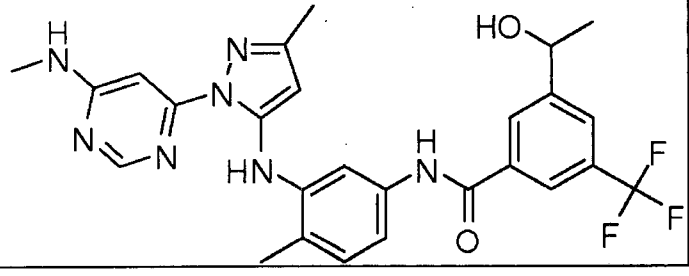
463		MS m/z 585.3 (M + 1)
464		MS m/z 585.3 (M + 1)
465		MS m/z 585.3 (M + 1)
466		MSm/z 583.3(M + 1)

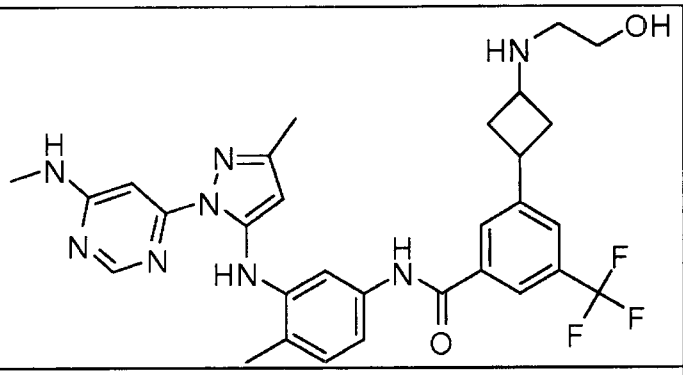
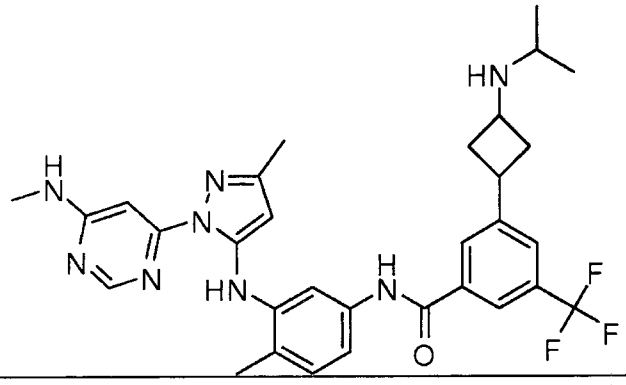
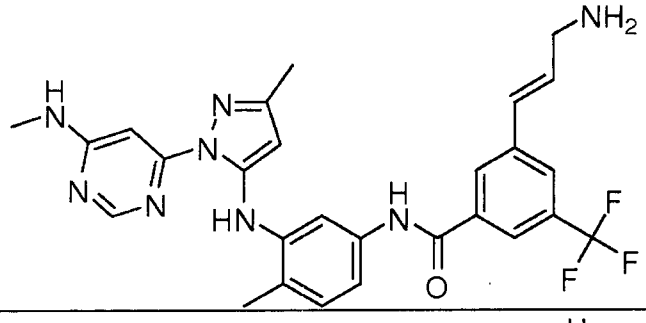
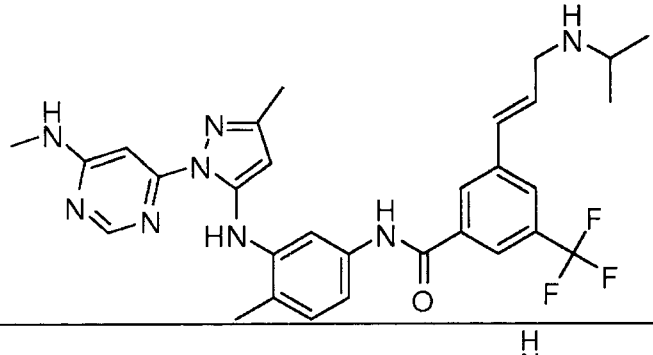
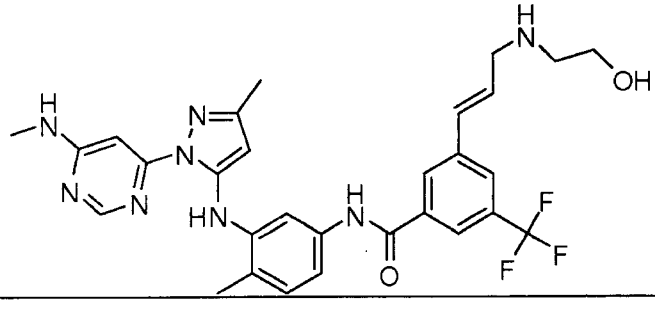
467		MS m/z 565.3 (M + 1)
468		MS m/z 525.2 (M + 1)
469		MS m/z 583.3 (M + 1)
470		MS m/z 595.3 (M + 1)

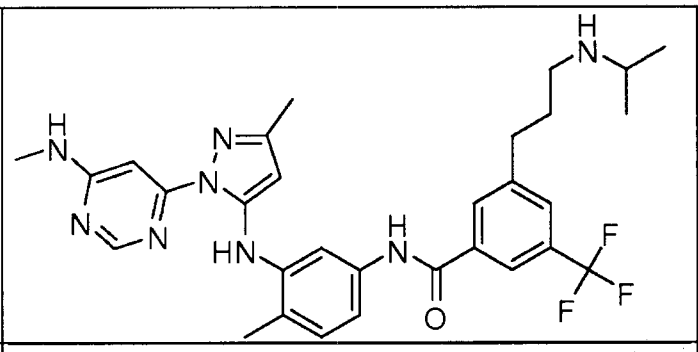
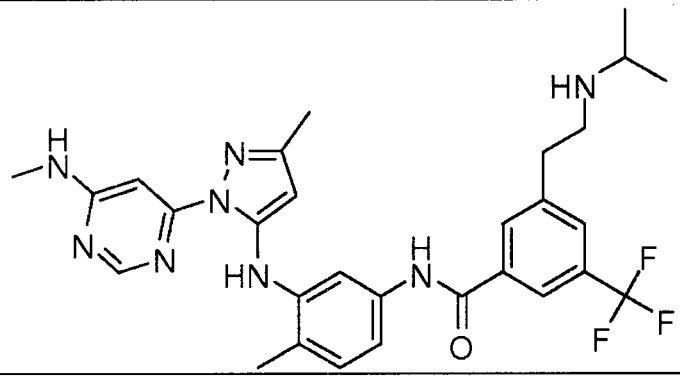
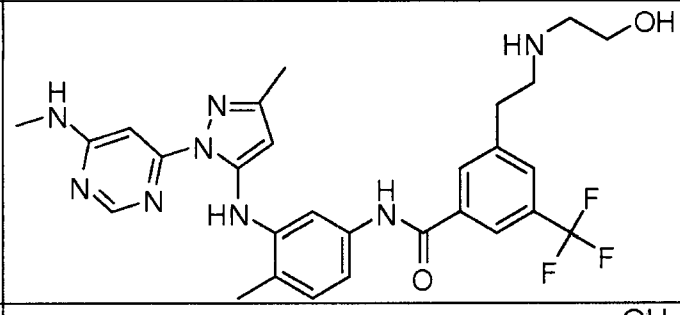
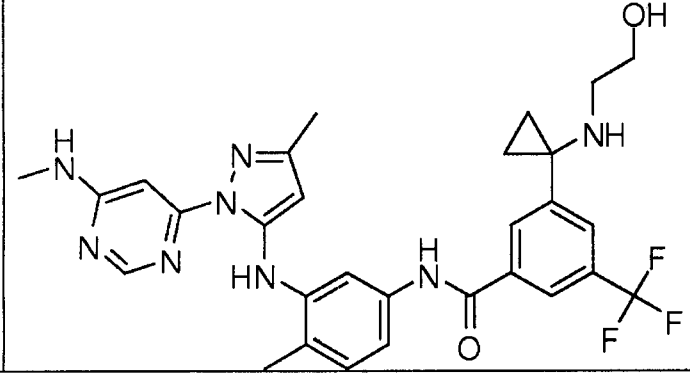
471		MSm/z 595.3 (M + 1)
472		MS m/z 569.3 (M + 1)
473		MS m/z 581.3 (M + 1)
474		MS m/z 581.3 (M + 1)
475		MS m/z 595.3 (M + 1)

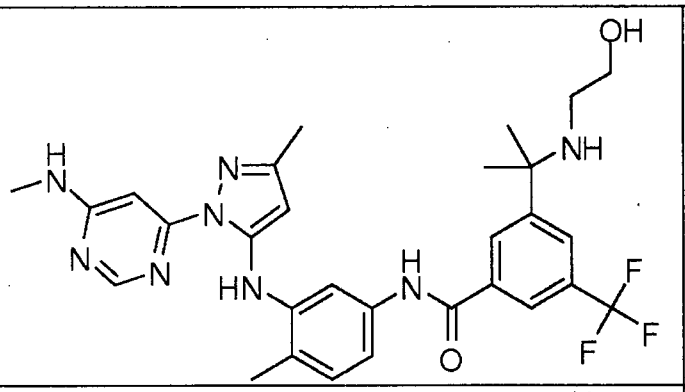
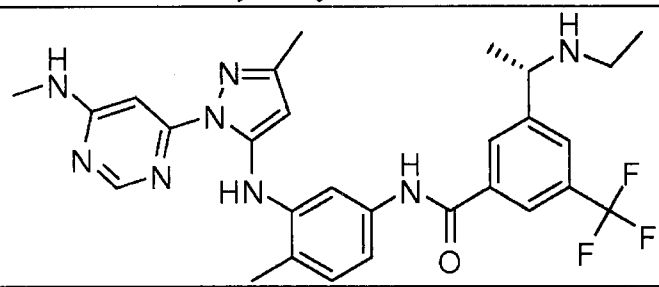
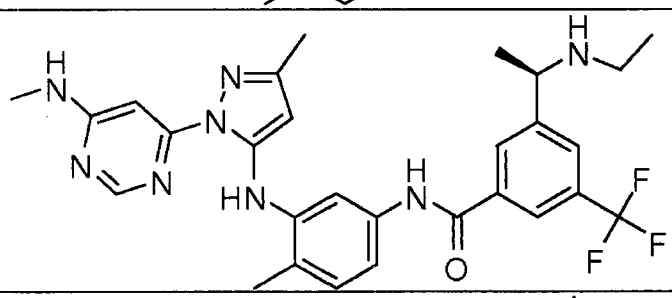
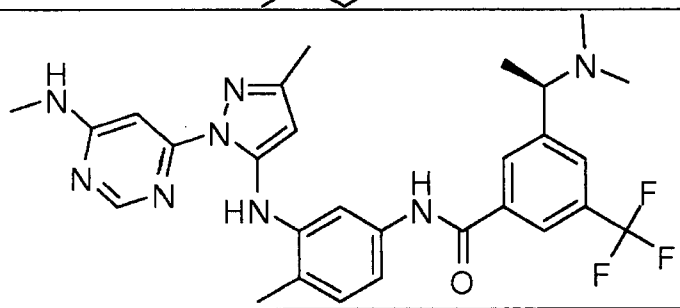
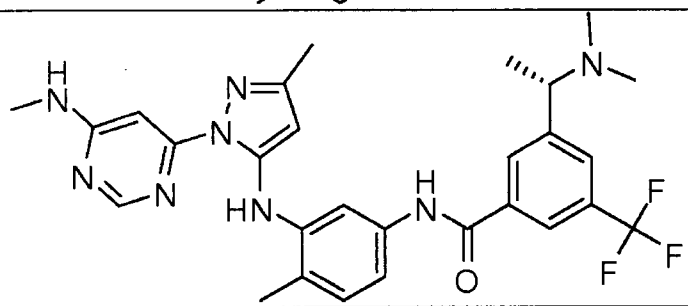
476		MSm/z 553.3 (M + 1)
477		MS m/z 559.2 (M + 1)
478		MS m/z 573.2 (M + 1)
479		MS m/z 585.2 (M + 1)
480		MS m/z 539.2 (M + 1)

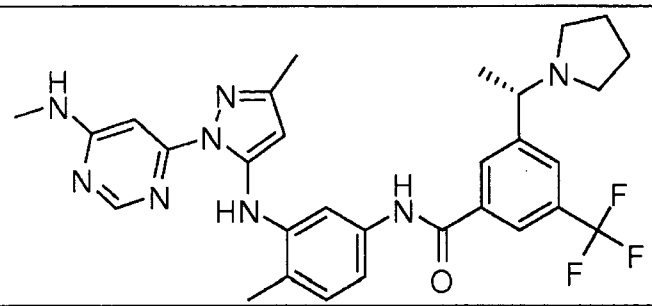
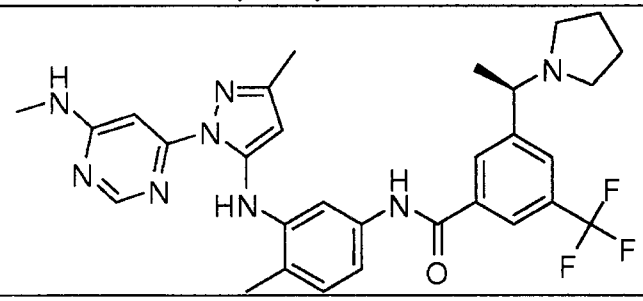
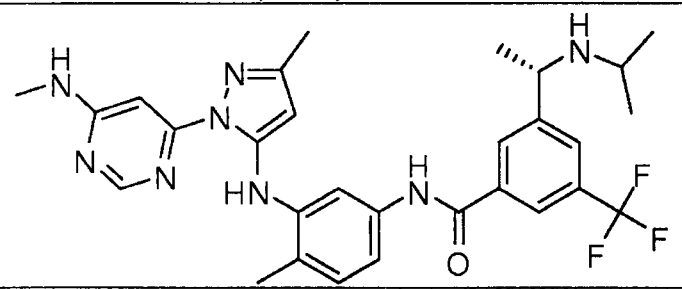
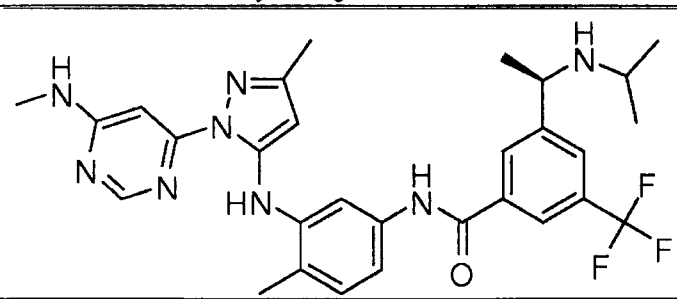
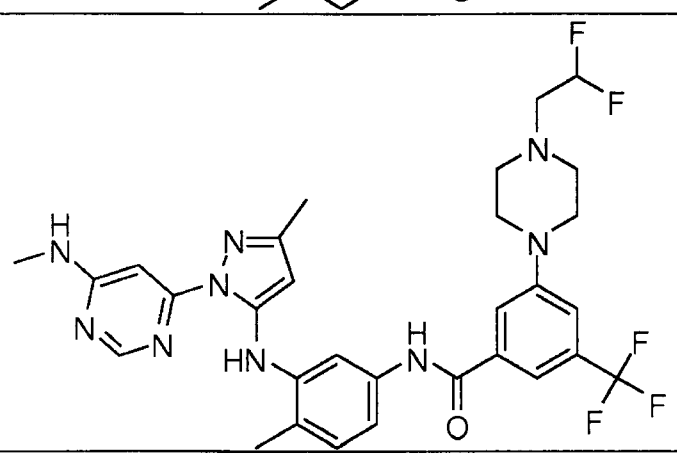
481		MS m/z 551.2 (M + 1)
482		MSm/z 553.3 (M + 1)
483		MS m/z 595.3 (M + 1)
484		MS m/z 595.3 (M + 1)
485		MS m/z 583.3 (M + 1)

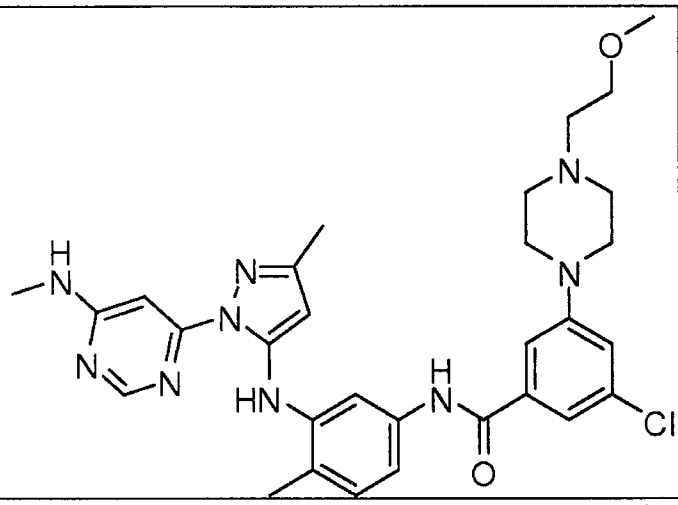
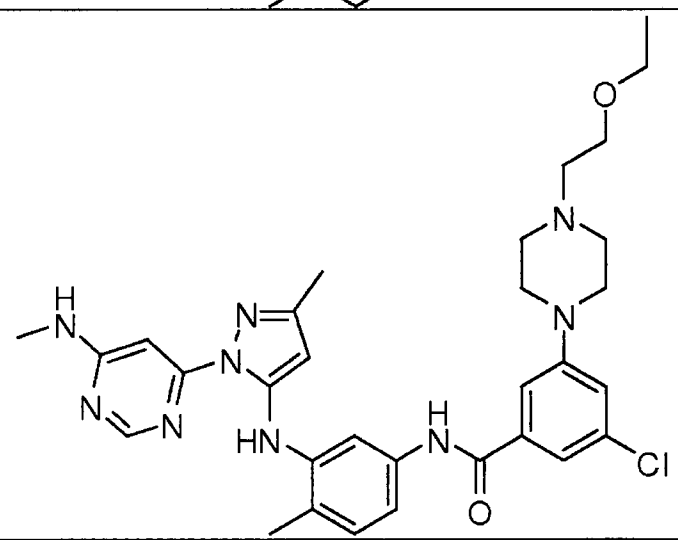
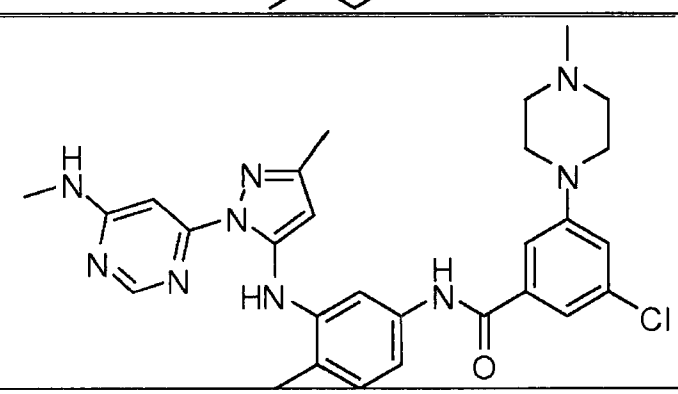
486		MS m/z 563.2 (M + 1)
487		MSm/z 565.3 (M + 1)
488		MS m/z 577.3 (M + 1)
489		MS m/z 542.2 (M + 1)
490		MS m/z 526.2 (M + 1)

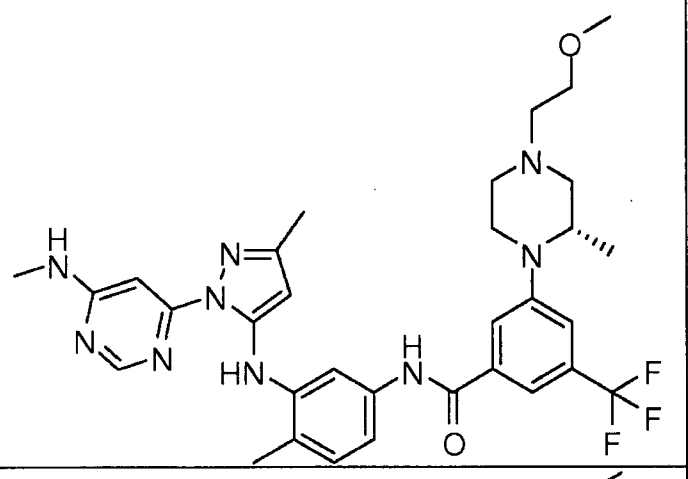
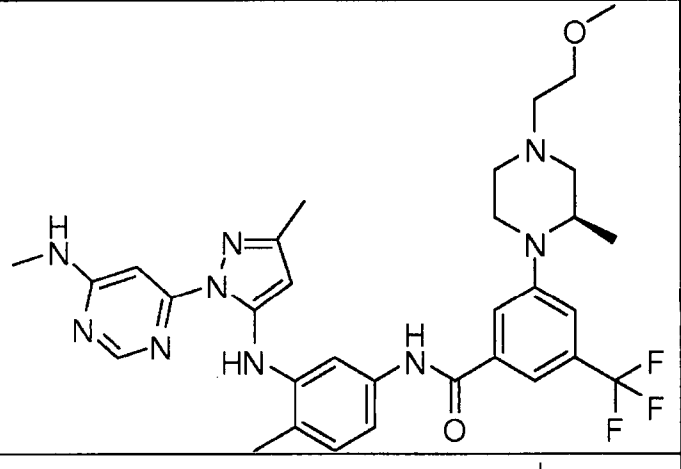
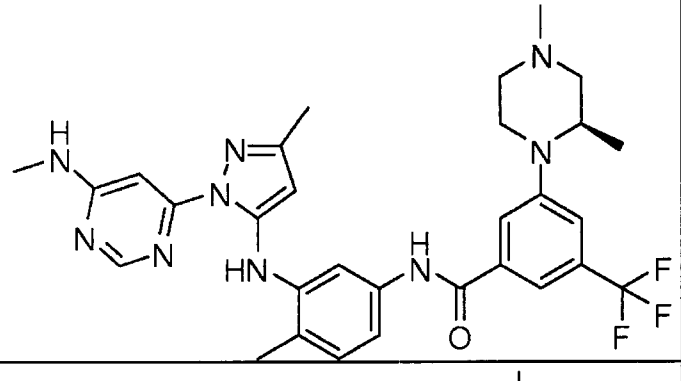
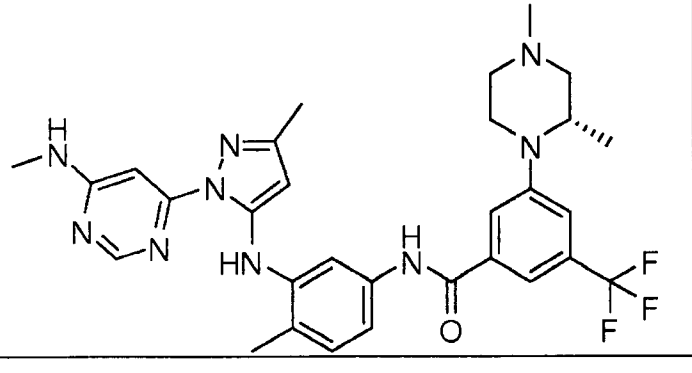
491		
492		
493		
494		
495		

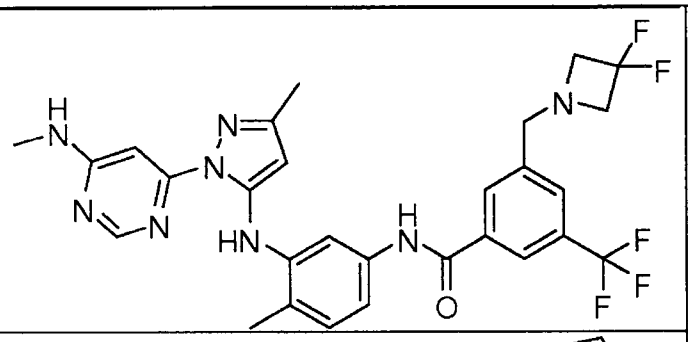
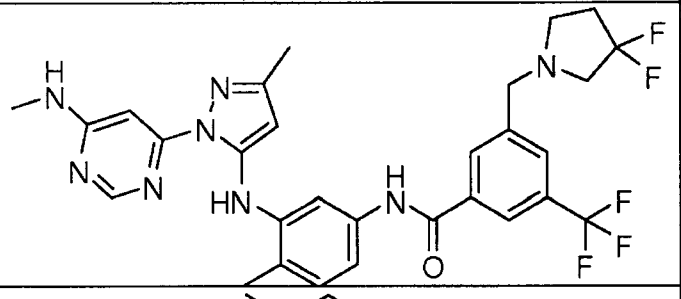
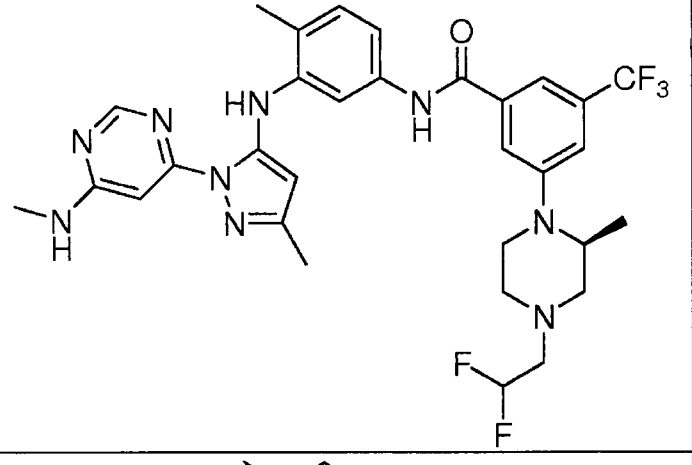
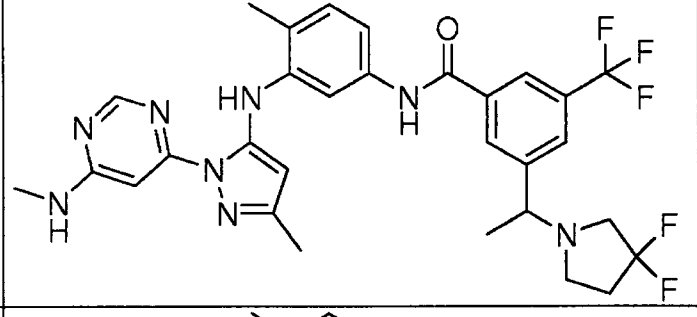
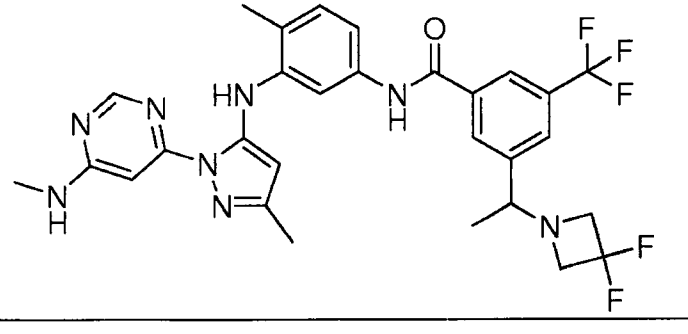
496		
497		
498		
499		

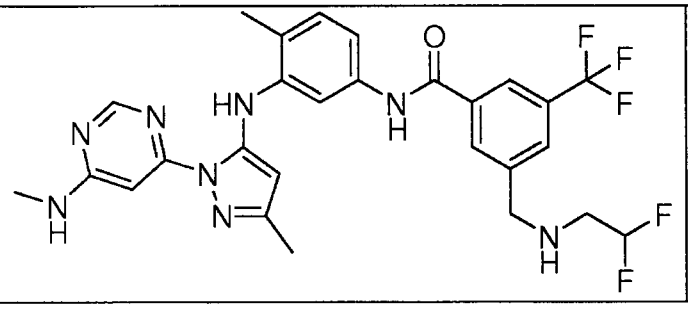
500		
501		
502		
503		
504		

505		
506		
507		
508		
509		MSm/z 630.3 (M + 1)

510		MS m/z 590.3 (M + 1)
511		MS m/z 604.3 (M + 1)
512		MSm/z 546.3 (M + 1)

513		MS m/z 638.3 (M + 1)
514		MS m/z 638.3 (M + 1)
515		MS m/z 594.3 (M + 1)
516		MSm/z 594.3 (M + 1)

517		
518		
519		
520		
521		

522		

Ensayos

Los compuestos del presente invento son probados para medir su capacidad para inhibir selectivamente la proliferación celular de células 32D expresando BCR- Abl (32D- p210) en comparación con células 32D parentales. Los compuestos que selectivamente inhiben la proliferación de estas células transformadas mediante BCR- Abl son probados para actividad anti- proliferativa sobre células Ba/F3 expresando bien sea formas tipo silvestre o mutantes de Bcr- abl. Además, los compuestos son probados para medir su capacidad para inhibir las quinasas Abl, ARG, BCR- Abl, BRK, EphB, Fms, Fyn, KDR, c- Kit, LCK, PDGF- R, b- Raf, c- Raf, SAPK2, Src, Tie2 y TrkB.

Inhibición de proliferación celular dependiente de BCR- Abl (Método de alto rendimiento)

La línea celular murina utilizada es la línea celular progenitora hemopoyetica 32D transformada con BCR- Abl cADN (32D- p210). Estas células son mantenidas en RPMI/10% suero de ternero fetal (RPMI/FCS) suplementado con penicilina 50 ug/mL, estreptomicina 50 ug/mL y L- glutamina 200 mM. Células 32D sin transformar son mantenidas de manera similar con la adición de 15% de Medio acondicionado con WEHI como una fuente de IL3.

50 ul de una suspensión de células 32D o 32D- p210 son sembradas en microplacas Greiner de 384 pozos (negras) a una densidad de 5000 células por pozo. Se agrega 50nl de compuesto de prueba (1 mM en Solución DMSO concentrada) a cada pozo (se incluye STI571 como un control positivo). Las células son incubadas durante 72 horas a 37 °C, 5% $C0_2$. Se agrega 10 ul de una solución de Azul Alamar al 60% (diagnósticos Tek) a cada pozo y la células son incubadas durante 24 horas más. La intensidad de fluorescencia (Excitación a 530 nm, Emisión a 580 nm) es cuantificada utilizando el sistema Acquest™ (Moleular Devices Corp.).

Inhibición de proliferación celular dependiente de BCR- Abl

Las células 32D- p210 son sembradas en placas TC de 96 pozos a una densidad de 15,000 células por pozo. Se agrega 50 uL de dos diluciones seriadas dobles del compuesto de prueba (C_{max} es 40 uM) a cada pozo (STI571 se incluye como un control positivo). Después de incubar las células durante 48 horas a 37 °C, 5% CO2, se agrega15 uL de MTT (Promega) a cada pozo y las células son incubadas durante 5 horas más. La densidad óptica a 570nm es cuantificada espectrofotométricamente y los valores IC50, la concentración del compuesto requerida para inhibición del 50%, se determinan a partir de una curva de respuesta de dosis.

Efecto sobre distribución de ciclo celular

Las células 32D y 32D- p210 son sembradas en placas TC de 6 pozos TC a $2.5x10^6$ células por pozo en 5 ml de medio y se agrega compuesto de prueba a 1 o 10 uM (STI571 se incluye como un control). Luego las células son incubadas durante 24 o 48 horas a 37 °C, 5% CO_2. 2 ml de suspensión celular es lavada con PBS, fijada en 70% EtOH durante 1 hora y tratada con PBS/EDTA/RNase A durante 30 minutos. Se agrega yoduro de propidio (Cf= 10 ug/ml) y la intensidad de fluorescencia es cuantificada mediante citometría de flujo sobre el sistema FACScalibur™ (BD Biosciences). Los compuestos de prueba del presente invento demuestran un efecto apoptótico sobre las células 32D- p210 pero no inducen apoptosis en las células parenterales 32D.

Efecto sobre autofosforilación Celular BCR- Abl

La autofosforilación BCR- Abl es cuantificada con Elisa de captura utilizando un anticuerpo de captura específico c- abl y un anticuerpo de antifosfotirosina. Las células 32D- p210 son sembradas en placas TC 96 pozos TC a $2x10^5$ células por pozo en 50 uL de medio. Se agregan 50 uL de dos diluciones seriales dobles de los compuestos de prueba ($C_{max}$is 10 uM) son a cada pozo (STI571 se incluye como control positivo). La células son incubadas durante 90 minutos a 37 °C, 5% CO_2. Luego, las células son tratadas durante 1 hora sobre hielo con 150 uL de amortiguador de lisis (50 mM Tris- HCl, pH 7.4, 150 mM NaCl, 5 mM EDTA, 1 mM EGTA y 1% NP- 40) conteniendo inhibidores de proteasa y fosfatasa. Se agrega 50 uL de lisado celular a optiplacas de 96 pozos previamente recubiertas con anticuerpo específico anti- abl y bloqueadas. Las placas son incubadas durante 4 horas a 4 °C. Después de lavar con amortiguador TBS-Tween 20, se agregó 50 uL de anticuerpo anti- fosfotirosina conjugado con fosfatasa alcalina y la

placa se incubó adicionalmente durante la noche a 4 °C. Después de lavar con amortiguador TBS- Tween 20, se agregó 90 uL de un substrato luminiscente y la luminiscencia es cuantificada utilizando el sistema Acquest™ (Moleular Devices Corp.). Los compuestos de prueba del invento que inhiben la proliferación de las células que expresan BCR- Abl, inhiben la autofosforilación celular de BCR- Abl en una forma dependiente de dosis.

Efecto sobre proliferación de células que expresan formas mutantes de Bcr- abl

Los compuestos del invento son probados para su efecto antiproliferativo sobre Células Ba/F3 expresando bien sea forma tipo silvestre o las formas mutantes de BCR- Abl (G250E, E255V, T315I, F317L, M351T) que confiere resistencia o sensibilidad disminuida a STI571. Los efectos antiproliferativo de estos compuestos sobre las células que expresan BCR-Abl mutante y sobre las células no transformadas se probaron a 10, 3.3, 1.1 y 0.37 uM como se describió anteriormente (en medios sin IL3). Los valores IC50 de los compuestos sin toxicidad sobre las células no transformadas fueron determinados a partir de la curva de respuesta de dosis obtenida como se describió anteriormente.

FGFR3 (Ensayo Enzimático)

El ensayo de actividad de quinasas con FGFR3 purificado, es realizado en un volumen final de 10 uL conteniendo 0.25 ug/mL de enzima en amortiguador de quinasa (30 mM Tris- HCl pH7.5, 15 mM $MgCl_2$, 4.5 mM $MnCl_2$, 15 uM Na_3V0_4 y 50 ug/mL BSA), y substratos (5 ug/mL biotin- poli- EY(Glu, Tyr) (CIS- US, Inc.) y 3 uM ATP). Se preparan dos soluciones: la primera solución de 5 μl contiene la enzima FGFR3 en amortiguador de quinasa fue primero dispensada en ProxiPlaca® (Perkin- Elmer) formato 384 seguido por la adición de 50 nL de compuestos disueltos en DMSO, luego 5 μl de la segunda solución contiene el substrato (poli-EY) y se agregó ATP en amortiguador de quinasa se agregó a cada uno de los pozos. Las reacciones son incubadas a temperatura ambiente durante hora, detenidas al agregar 10 uL de mezcla de detección de HTRF, la cual contiene 30 mM Tris- HCl pH7.5, 0.5 M KF, 50 mM ETDA, 0.2 mg/mL BSA, 15 ug/mL estreptavidina- XL665 (CIS- US, Inc.) y 150 ng/mL de anticuerpo anti- fosfotirosina conjugado con criptato (CIS- US, Inc.). Después de 1 hora de incubación a temperatura ambiente para permitir interacción de estreptavidina- biotina, las señales fluorescentes resultas en el tiempo son leídas sobre Analist GT (Moleular Devices Corp.

Corp.). Los valores IC50 son calculados mediante análisis de regresión lineal del porcentaje de inhibición de cada compuesto a 12 concentraciones (1:3 dilución desde 50 uM a 0.28 nM). En este ensayo, los compuestos del invento tienen un IC50 en el rango entre 10 nM y 2 uM.

FGFR3 (Ensayo Celular)

Los compuestos del invento se prueban para su capacidad de inhibir proliferación de células Ba/F3- TEL- FGFR3 transformadas, lo cual depende de la actividad de la quinasa celular FGFR3. Ba/F3- TEL- FGFR3 se cultivan hasta 800,000 células/mL en suspensión, con RPMI 1640 suplementada con 10% suero bovino fetal como el medio de cultivo. Las células se dispensan en placas de formato de 384 pozos a 5000 células/pozo en 50 uL de medio de cultivo 50. Los compuestos del invento se disuelven y diluyen en dimetilsufóxido (DMSO). Se preparan disoluciones seriales 1:3 de doce puntos en DMSO para crear gradientes de concentración típicamente en el rango entre 10 mM a 0.05 uM. Se agregan células con 50 nL de compuestos diluidos y se incuban durante 48 horas en incubador de cultivo de células. Se agrega AlamarBlue® (TREK Sistemas de Diagnóstico), el cual se puede utilizar para monitorear el ambiente reductor creado por las células proliferantes, a las células a concentración final de 10%. Después de cuatro horas más de incubación en un incubador de cultivo de células 37 °C, las señales fluorescentes a partir de AlamarBlue® reducido (Excitación a 530 nm, Emisión a 580 nm) son cuantificadas sobre un Analyst GT (Moleular Devices Corp.). Se calculan los valores IC50 mediante análisis de regresión lineal del porcentaje de inhibición de cada compuesto a 12 concentraciones.

FLT3 y PDGFR0 (Ensayo Celular)

Los efectos de los compuestos del invento sobre la actividad celular de FLT3 y PDGFR3 son conducidos utilizando métodos idénticos como se describió anteriormente para actividad celular de FGFR3, excepto que en vez de utilizar Ba/F3- TEL- FGFR3, se utilizan Ba/F3- FLT3- ITD y Ba/F3- Tel- PDGFR3 respectivamente.

b- Raf - Ensayo Enzimático

Los compuestos del invento se prueban para su capacidad de inhibir la actividad de b- Raf. El ensayo se realiza en placas de MaxiSorp de 384 pozos (NUNC) con

paredes negras y fondo claro. El sustrato, IκBoc se diluye en DPBS (1:750) y se agregan 15μl a cada pozo. La placas se incuban a 4°C durante la noche y se lavan 3 veces con TBST (25 mM Tris, pH 8.0, 150 mM NaCl y 0.05% Tween- 20) utilizando el lavador de placas EMBLA. Las placas se bloquean mediante Superblock (15 ul/pozo) durante 3 horas a temperatura ambiente, se lavan 3 veces con TBST y se secan mediante golpes suaves. Se agrega amortiguador de ensayo conteniendo 20 uM de ATP (10 μl) a cada pozo seguido por 100nl o 500nl de compuesto. B- Raf se diluye en el amortiguador de ensayo (1 μl en 25 μl) y se agrega 10μl de b- Raf diluido a cada pozo (0.4 μg/pozo). Las placas se incuban a temperatura ambiente durante 2.5 horas. La reacción de quinasa se detiene al lavar las placas 6 veces con TBST. Se diluye anticuerpo Fosf- lKBcc (Ser32/36) en Superblock (1:10,000) y se agrega 15 μl a cada pozo. Las placas se incuban a 4°C durante la noche y se lavan 6 veces con TBST. Se diluye IgG anti- ratón de cabra conjugado con AP en Superblock (1:1,500) y se agrega 15 μl a cada pozo. Las placas se incuban a temperatura ambiente durante 1 hora y se lavan 6 veces con TBST. Se agregan 15 μl de sustrato fluorescente Atofos AP (Promega) a cada pozo y las placas se incuban a temperatura ambiente durante 15 minutos. Las placas se leen sobre Acquest o Analist GT utilizando un Programa de Intensidad de Fluorescencia (Excitación 455 nm, Emisión 580 nm).

b- Raf - Ensayo Celular

Los Compuestos del invento se prueban en células A375 para su capacidad de inhibir fosforilación de MEK. La línea celular A375 (ATCC) se deriva de un paciente con melanoma humano y tiene una mutación V599E sobre el gen B- Raf. Los niveles de MEK fosforilado se elevan debido a la mutación de B- Raf. Las células A375 subconfluentes a confluentes se incuban con compuestos durante 2 horas a 37 °C en un medio sin suero. Luego las células se lavan una vez con PBS frío y se someten a lisis con el amortiguador de lisis conteniendo Triton X100 al 1%. Después de la centrifugación, los sobrenadantes se sujetan a SDS- PAGE, y luego se transfieren a membranas de nitrocelulosa. Luego la membranas se someten a western blotting con anticuerpo anti- fosfo- MEK (ser217/221) (Señalización celular). La cantidad de MEK fosforilado se monitorea mediante la densidad de bandas de fosfo- MEK sobre las membranas de nitrocelulosa.

Upstate QuinasaProfiler™ - Ensayo de Fijación de Filtro Radio-enzímatico

Los compuestos del invento son probados para su capacidad de inhibir miembros individuales del panel de quinasas. Los compuestos se prueban por duplicado a una concentración final de 10 μM siguiendo este protocolo genérico. Note que la composición de amortiguador de quinasa y los sustratos varían para las diferentes quinasas incluidas en el panel "Upstate QuinasaProfiler™". Se mezclan amortiguador de quinasa (2.5 μL, 10x - que contiene $MnCl_2$ cuando se requiere), quinasa activa (0.001- 0.01 Unidades; 2.5 μL), especifica o Poli(Glu4- Tyr) peptídica (5- 500 μM o .01mg/ml) en amortiguador de quinasa y amortiguador de quinasa (50 μM; 5 μL) en un eppendorf (tubo de microcentrífuga) sobre hielo. Una mezcla Mg/ATp (10 μL; 67.5 (o 33.75) mM $MgCl_2$, 450 (o 225) μM ATP y 1 μCi/ μl [y- ^{32}P]- ATP (3000Ci/mmol)) se agrega y la reacción se incuba a 30°C durante 10 minutos aproximadamente. La mezcla de la reacción es goteada (20 μL) en un cuadrado de papel de 2cm x 2cm P81 (fosfocelulosa, para sustratos peptídicos cargados positivamente) o Whatman No. 1 (para sustrato peptídico Poli (Glu4- Tyr)). Los cuadros de ensayo se lavan 4 veces, durante 5 minutos cada uno, con ácido fosfórico al 0.75% y una vez con acetona durante 5 minutos. Los cuadros de ensayo se transfieren a un tubito de centelleo, se agregá 5 ml de cóctel de centelleo y se cuantifica la incorporación ^{32}P (cpm) al sustrato péptidico con un contador Beckman de centelleo . El porcentaje inhibición se calcula para cada reacción.

Ensayo Anti-malaria utilizando SYBR Green I

Los compuestos del presente invento se pueden probar para medir su capacidad para inhibir la proliferación de parasitemia en glóbulos rojos sanguíneos infectados. La proliferación es cuantificada por adición del tinte SYBR Green I (Invitrogen)® el cual tiene una alta afinidad para ADN de doble hebra.

Para descartar fármacos, se dispensa 20μl de medio de descarte, sin contener suero humano, en 3 placas de ensayo. Luego se transfieren 50nl de cada uno de los compuestos del invento, incluyendo controles anti malaria (cloroquina y artimesinina), a las placas de ensayo. 50nl de DMSO es transferido a las placas de control de línea basal y de control de fondo. Luego 30μl de una suspensión de glóbulos rojos sanguíneos humanos infectados con P. *falciparum* en medio de descarte, se dispensa en las placas de ensayo y la placa de control de línea basal tal que el hematocrito final es 2.5% con una parasitemia final de 3%. Se dispensan glóbulos rojos sanguíneos no infectados a la placa de control de fondo tal que el hematocrito final es 2.5%. La

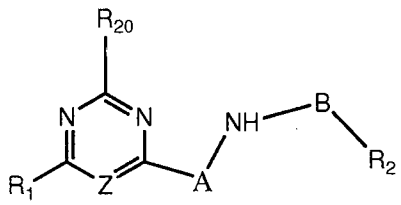
placas son colocadas en un incubador a 37°C durante 72 horas con una mezcla de 93% N_2, 4% $C0_2$, y 3% gas O_2 gas. 10 μl de una solución 10X solución SYBR Green I® es dispensada en la placas. La placas son selladas y colocadas en un congelador a - 80°C durante la noche para la lisis de los glóbulos rojos sanguíneos. La placas son descongeladas y dejadas a temperatura ambiente durante la noche para un teñido óptimo. La intensidad de fluorescencia es medida (excitación 497nm, emisión 520nm) utilizando el sistema Acquest (Moleular Devices Corp.). El porcentaje de inhibición es calculado para cada compuesto.

Los compuestos de la Formula I, en forma libre o en forma de sal farmacéuticamente aceptable, exhiben propiedades farmacológicas valiosas, por ejemplo, como se indicada por las pruebas *in vitro* descritas en esta solicitud.

Se entiende que los ejemplos y realizaciones descritos en la presente son para propósitos ilustrativos solamente y que varias modificaciones o cambios a la luz de los mismos serán indicadas a personas con experiencia en el estado de la técnica y se incluirán dentro del espíritu y competencia de esta solicitud y alcance de las reivindicaciones anexas. Todas las publicaciones, patentes, y solicitudes de patentes citadas en la presente se incorporan en la presente como referencia para todo propósito.

REIVINDICACIONES

1. Un compuesto de la Fórmula I:



I

en el cual :

A es un anillo no saturado o parcialmente saturado de 5 miembros que contiene 1 a 3 heteroátomos seleccionados a partir de - N=, - NR3- , - O- y - S- ; en donde R_3 se selecciona a partir de hidrógeno, halo, C_1- $_6$alquilo sustituido o no sustituido, C_2- $_6$alquenilo sustituido o no sustituido, C_2- $_6$ alquinilo sustituido o no sustituido, - XOR_{4a}, - XCN, - $XC(O)OR_{4a}$, - $XC(O)R_{4b}$, - $XNR_{4a}R4a$, - $XNR_{4a}XNR_{4a}R4_a$, - $XC(O)\ nR_{4a}XNR4_aR4_a$, - $XC(O)\ nR_{4a}XR4_b$, - $XC(O)\ nR_{4a}XNR4_aR_{4b}$, - $XC(O)\ nR_{4a}XOR4_a$, - $XNR_{4a}XNR_{4a}R_{4b}$, - $XNR_{4a}XOR4_a$, - $XNR_{4a}XCF_3$, - $XC(O)\ nR_{4a}R_{4a}$, y - XR_{4b}; en donde cada X es independientemente seleccionados a partir de un enlace y C_1- $_4$alquileno; R_{4a} se selecciona a partir de hidrógeno y C_1- $_6$alquilo sustituido o no sustituido, y dos R_{4a} sobre los mismos átomos o átomos adyacentes se pueden opcionalmente unir para formar un anillo de 5- 6 miembros que contiene hasta dos heteroátomos seleccionados a partir de N, O y S como miembros cíclicos; y R4b se selecciona a partir de C_6- $_{10}$arilo, C_1- $_{10}$heteroarilo, C_3- $_{10}$cicloalquilo y C_3- $_{10}$heterocicloalquilo; en donde cualquier cicloalquilo, heterocicloalquilo, arilo o heteroarilo de R_{4b} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de C_1- $_6$alquilo y –NR4cR4d; en donde cada R_{4c} y R4d es independientemente seleccionado a partir de hidrógeno y C_1- $_6$alquilo sustituido o no sustituido, y R4c y R_4d se pueden opcionalmente unir juntos para formar un anillo de 5- 6 miembros que contiene N y opcionalmente que contiene un heteroátomo adicional seleccionado a partir de N, O y S; con la condición que anillo A no sea imidazol;

en donde cualquier anillo A se puede opcionalmente sustituir por uno o dos radicales R3, con la condición que R3 no sea halo cuando se une directamente a un átomo de nitrógeno;

B es un anillo no saturado o parcialmente saturado de 5 o 6 miembros que contiene 0 a

3 heteroátomos seleccionados a partir de - N=, - NR21- , - O- y - S- ; en donde R_{21} se selecciona a partir de hidrógeno, C_1- $_6$alquilo, C_1- $_6$alquilo halo- sustituido y halo; en donde B se puede opcionalmente sustituir por 1 a 3 radicales independientemente seleccionados a partir de C_1- $_6$alquilo, C_1- $_6$alquilo halo- sustituido y halo;

Z se selecciona a partir de CH y N;

R1 se selecciona a partir de - XNR_5R_6, - $XNR_5XNR_5R_6$, - XNR5XR5, - XNR_5XOR_6, - $XNR_6XC(O)OR_5$, - $XNR_6XC(O)$ nR_6R_6, - XOR_5, - $XC(O)R_5$, - XR_5 y - $XS(O)_0$- $_2$R5; en donde X se selecciona a partir de un enlace y $_1$- $_4$alquileno opcionalmente sustituido por 1 a 2 radicales de C_1- $_6$alquilo; R5 se selecciona a partir de hidrógeno, C_1- $_6$alquilo sustituido o no sustituido, C_6- $_{10}$aril- C_0- $_4$alquilo, C_1- $_{10}$heteroaril- C_0- $_4$alquilo, C_3- $_{10}$cicloalquil- C_0- $_4$alquilo y C_3- $_{10}$heterocicloalquil- C_0- $_4$alquilo; y cada R6 es independientemente seleccionados a partir de hidrógeno y C_1- $_6$alquilo sustituido o no sustituido; o R5 y R6 junto con el nitrógeno al cual R5 y R6 están unidos forman heteroarilo o heterocicloalquilo que pueden contener un heteroátomo adicional seleccionados a partir de N, O y S como un miembro cíclico; o R1 junto con la N1 del anillo de pirimidina al cual R1 está fijado forma 2,3- dihidroimidazo[l,2- f]pirimidina;

en donde cualquier arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R5 o la combinación de R5 y R6 se puede opcionalmente sustituir por 1 a 3 radicales independientemente seleccionados a partir de halo, nitro, ciano, hidroxilo, C_1- $_6$alquilo, C_1- $_6$alcoxilo alquilo halo- sustituido, alcoxilo halo- sustituido - XNR_7R_8, - XOR_7, - $XNR_7S(O)_2R_8$, - $XNR_7S(O)R_8$, - XNR_7SR_8, - $XC(O)$ nR_7R_8, - $XC(O)$ $nR_7XNR_7R_8$, - $XNR_7C(O)$ nR_7R_8, - $XNR_7XNR_7R_8$, - XNR_7XOR_7, - $XNR_7C(=NR_7)$ nR_7R_8, - $XS(O)_2R_9$, - $XNR_7C(O)R_8$, - $XNR_7C(O)R_9$, - XR_9, - $XC(O)OR_8$, - $XS(O)_2NR_7R_8$, - $XS(O)$ nR_7R_8 y - $XSNR_7R_8$; en donde X es un enlace o C_1- $_4$alquileno; R_7 y R_8 son independientemente seleccionados a partir del grupo que consta de hidrógeno y C_1- $_4$alquilo sustituido o no sustituido, y en donde R_7 y R_8 sobre un nitrógeno pueden opcionalmente ciclar para formar un anillo de 5- 6 miembros que pueden contener un heteroátomo adicional seleccionados a partir de N, O y S como un miembro cíclico; y R9 se selecciona a partir de C_3- $_{10}$heterocicloalquilo y C_1- $_{10}$heteroarilo; en donde dicho heterocicloalquilo o heteroarilo de R9 es opcionalmente sustituido por una radical seleccionados a partir del grupo que consta de C_1- $_4$alquilo, - $XNR_7XNR_7R_7$, XNR_7XOR_7 y - XOR_7;

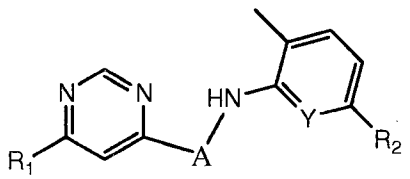
R_2 se selecciona a partir de $-R_{11}$, - CONR10R11, SO_2NR10R11, - NR10R11, - $NR10C(O)R_{11}$, - NR10S(O)0- 2R11 y $-NR10C(O)$ nR10R11; en donde R_{10} se selecciona a partir

de hidrógeno y C_{1-6}alquilo sustituido o no sustituido; R11 se selecciona a partir de C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde R10 y R_{11} sobre el mismo nitrógeno pueden opcionalmente ciclar para formar un anillo de 5- 6 miembros que pueden contener un heteroátomo adicional seleccionado a partir de N, O y S como un miembro cíclico, y cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R11 es opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halo, nitro, ciano, hidroxilo, C_{1-6}alquilo sustituido o no sustituido, C_{1-6}alcoxilo C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo ciano-sustituido, C_{1-6}alquilo hidroxi- sustituido, C_{1-6}alcoxilo halo- sustituido - X_2R_{13}, - $X_2NR_{12}C(O)R_{13}$, - $X_2NR_{12}C(O)$ $nR_{12}R_{13}$, - $X_2NR_{12}R_{12}$, - $X_2NR_{12}R_{13}$, - $X_2NR_{12}X_2R_{13}$, - $X_2NR_{12}NR_{12}R_{12}$, - $X_2NR_{12}X_2OR_{12}$, - $X_2C(O)$ $nR_{12}R_{13}$, - $X_2NR_{12}S(O)_{0-2}R_{13}$ y - $X_2S(O)0-2NR_{12}R_{13}$; en donde X_2 se selecciona a partir de un enlace, C_{1-4}alquileno y C_{2-4}alquenileno; R_{12} se selecciona a partir de hidrógeno, C_{1-6}alquilo y C_{1-6}alquilo hidroxi- sustituido; R_{13} se selecciona a partir de C_{1-6} alquilo sustituido o no sustituido, C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde dos grupos R_{12} o R_{12} y R_{13} sobre el mismo nitrógeno pueden opcionalmente ciclar para formar un anillo de 5- 6 miembros que puede contener un heteroátomo adicional seleccionados a partir de N, O y S como un miembro cíclico, cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, ciano, hidroxilo, nitro, amino, C_{1-6}alquilo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo hidroxi- sustituido, C_{1-6}alquilo ciano- sustituido, C_{1-6}alquilo hidroxi- sustituido, C_{1-6}alcoxilo C_{1-6}alcoxilo halo- sustituido - X_3NR7R8, - X_3NR7X_3OR7, C_{6-10}aril- C_{0-4}alquilo, C_{1-10}heteroaril- C_{0-4}alquilo, C_{3-10}cicloalquil- C_{0-4}alquilo, C_{3-10}heterocicloalquil- C_{0-4}alcoxilo y C_{3-10}heterocicloalquil- C_{0-4}alquilo; en donde X_3 se selecciona a partir de un enlace y C_{1-4}alquileno; R7 y R8 son como se describió anteriormente y en donde cualquier sustituyente arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es adicionalmente opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, hidroxilo, C_{1-6}alquilo, C_{1-6}alquilo halo-sustituido, C_{1-6}alquilo hidroxi- sustituido, C_{1-6}alcoxilo C_{3-10}heterocicloalquilo y C_{1-6}alcoxilo halo- sustituido;

R_{20} se selecciona a partir de hidrógeno, C_{1-6}alquilo sustituido o no sustituido, y $N(R_{21})_2$, en donde cada R_{21} es independientemente H o C_{1-6} alquilo sustituido o no sustituido, y en donde dos R_{21} sobre el mismo nitrógeno pueden ciclar para formar un anillo de 5- 6 miembros

que puede contener un heteroátomo adicional seleccionados a partir de N, O y S; y la sal farmacéuticamente aceptables de los mismos.

2. El compuesto de reivindicación 1 de la Fórmula Ia:



Ia

en el cual:

A es un anillo no saturado o parcialmente saturado de 5 miembros que contiene 1 a 3 heteroátomos seleccionados a partir de - N=, - NR3- , - O- y - S- ; en donde R3 se selecciona a partir de hidrógeno, halo, C_1- $_6$alquilo halo- sustituido, C_1- $_6$alquilo, - XOR_{4a}, - XCN, - $XC(O)OR_{4a}$, - $XC(O)R_{4b}$, - XNR_{4a}R4a, - XNR_{4a}R4b, - $XNR_{4a}XNR_{4a}R_{4a}$, - XC(O) $nR_{4a}XNR_{4a}R_{4a}$, - XC(O) $nR_{4a}XR_{4b}$, - XC(O) $nR_{4a}XNR_{4a}R4_b$, - XC(O) $nR_{4a}XOR4_a$, - $XNR_{4a}XNR_{4a}R_{4b}$, - $XNR_{4a}XOR_{4a}$,- $XNR_{4a}XCF_3$, - XC(O) $nR_{4a}R_{4a}$, y - XR_{4b}; en donde X se selecciona a partir de un enlace y C_1- $_4$alquileno; R_{4a} se selecciona a partir de hidrógeno y C_1- $_6$alquilo; y R_{4b} se selecciona a partir de C_6- $_{10}$arilo, C_1- $_{10}$heteroarilo, C_3- $_{10}$cicloalquilo y C_3- $_{10}$heterocicloalquilo; en donde cualquier cicloalquilo, heterocicloalquilo, arilo o heteroarilo de R_{4b} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de C_1- $_6$alquilo y –NR4cR4d; en donde cada R4c y R_4d es independientemente seleccionado a partir de hidrógeno y C_1- $_6$alquilo; con la condición que el anillo A no sea imidazol; en donde cualquier anillo A se puede opcionalmente sustituir por un radical R3;

R1 se selecciona a partir de - XNR_5R_6, - $XNR_5XNR_5R_6$, - XNR5XR5, - XNR_5XOR_6, - $XNR_6XC(O)OR_5$, - $XNR_6XC(O)$ nR_6R_6, - XOR_5, - $XC(O)R_5$, - XR_5 y - $XS(O)_0$- $_2$R5; en donde X se selecciona a partir de un enlace y C_1- $_4$alquileno opcionalmente sustituido por 1 a 2 radicales de C_1- $_6$alquilo; R5 se selecciona a partir de hidrógeno, C_1- $_6$alquilo, C_6- $_{10}$aril- C_0- $_4$alquilo, C_1- $_{10}$heteroaril- C_0- $_4$alquilo, C_3- $_{10}$cicloalquil- C_0- $_4$alquilo y C_3- $_{10}$heterocicloalquil- C_0- $_4$alquilo; y cada R6 es independientemente seleccionados a partir de hidrógeno y C_1- $_6$alquilo; o R5 y R6 junto con el nitrógeno al cual R5 y R6 están unidos forman heteroarilo o heterocicloalquilo; o R1 junto con el N1 del anillo de pirimidina al cual R1 está fijado forma 2,3- dihidroimidazo[1,2-

f]pirimidina;

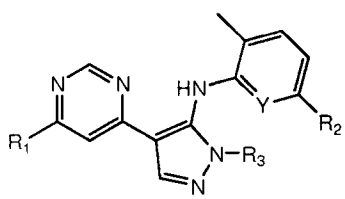
en donde cualquier arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R5 o la combinación de R5 y R6 se puede opcionalmente sustituir por 1 a 3 radicales independientemente seleccionados a partir de halo, nitro, ciano, hidroxilo, C_{1-6}alquilo, C_{1-6}alcoxilo alquilo halo-sustituido, alcoxilo halo- sustituido - XNR_7R_8, - XOR_7, - $XNR_7S(O)_2R_8$, - $XNR_7S(O)R_8$, - XNR_7SR_8, - $XC(O)nR_7R_8$, - $XC(O)nR_7XNR_7R_8$, - $XNR_7C(O)nR_7R_8$, - $XNR_7XNR_7R_8$, - XNR_7XOR_7, - $XNR_7C(=NR_7)nR_7R_8$, - $XS(O)_2R_9$, - $XNR_7C(O)R_8$, - $XNR_7C(O)R_9$, - XR_9, - $XC(O)OR_8$, - $XS(O)_2NR_7R_8$, - $XS(O)nR_7R_8$ y - $XSNR_7R_8$; en donde X es un enlace o C_{1-4}alquileno; R_7 y R_8 son independientemente seleccionados a partir del grupo que consta de hidrógeno y C_{1-4}alquilo; y R_9 se selecciona a partir de C_{3-10}heterocicloalquilo y C_{1-10}heteroarilo; en donde dicho heterocicloalquilo o heteroarilo de R_9 es opcionalmente sustituido por una radical seleccionados a partir del grupo que consta de C_{1-4}alquilo, - $XNR_7XNR_7R_7$, XNR_7XOR_7 y - XOR_7;

R_2 se selecciona a partir de $-R_{11}$, - CONR10R11, - SO_2NR10R11, - NR10R11, - NR10C(O)R_{11}, - NR10S(O)0- 2R11 y –NR10C(O) nR10R11; R10 se selecciona a partir de hidrógeno y C_{1-6}alquilo; R11 se selecciona a partir de C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R11 es opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halo, nitro, ciano, hidroxilo, C_{1-6}alquilo, C_{1-6}alcoxilo C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo ciano- sustituido, C_{1-6}alquilo hidroxi- sustituido, C_{1-6}alcoxilo halo- sustituido - X_2R_{13}, - $X_2NR_{12}C(O)R_{13}$, - $X_2NR_{12}C(O)nR_{12}R_{13}$, - $X_2NR_{12}R_{12}$, —$X_2NR_{12}R_{13}$, —$X_2NR_{12}X_2R_{13}$, —$X_2NR_{12}NR_{12}R_{12}$, —$X_2NR_{12}X_2OR_{12}$, — $X_2C(O)nR_{12}R_{13}$, - $X_2NR_{12}S(O)_{0-2}R_{13}$ y - $X_2S(O)_{0-2}NR_{12}R_{13}$; en donde R_{12} se selecciona a partir de hidrógeno, C_{1-6}alquilo y C_{1-6}alquilo hidroxi-sustituido; en donde X_2 se selecciona a partir de un enlace, C_{1-4}alquileno y C_{2-4}alquenileno; R_{13} se selecciona a partir de C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, ciano, hidroxilo, nitro, amino, C_{1-6}alquilo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo hidroxi- sustituido, C_{1-6}alquilo ciano- sustituido, C_{1-6}alquilo hidroxi- sustituido, C_{1-6}alcoxilo C_{1-6}alcoxilo halo-sustituido - $X3NR_7R_8$, - $X3NR_7X30R_7$, C_{6-10}aril- C_{0-4}alquilo, C_{1-10}heteroaril- C_{0-4}alquilo, C_{3-10}cicloalquil- C_{0-4}alquilo, C_{3-10}heterocicloalquil- C_{0-4}alcoxilo y C_{3-10}heterocicloalquil- C_{0-}

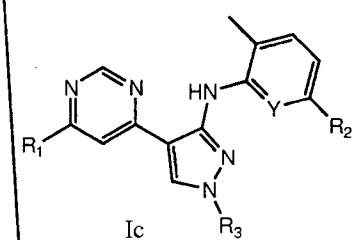
$_4$alquilo; en donde X3 se selecciona a partir de un enlace y C_1- $_4$alquileno; R_7 y R_8 son como se describió anteriormente y en donde cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo sustituyentes de R_{13} es adicionalmente opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, hidroxilo, C_1- $_6$alquilo, C_1- $_6$alquilo halo-sustituido, C_1- $_6$alquilo hidroxi- sustituido, C_1- $_6$alcoxilo C_3- $_{10}$heterocicloalquilo y C_1- $_6$alcoxilo halo- sustituido; y

Y se selecciona a partir de C y N.

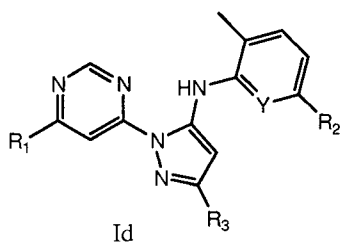
3. El compuesto de reivindicación 2 se selecciona a partir de las Fórmulas lb, Ic y Id:



Ib



Ic



Id

en el cual:

R1 se selecciona a partir de - XNR_5R_6, - $XNR_5XNR_5R_6$, - XNR5XR5, - XNR_5XOR_6, - $XNR_6XC(O)OR_5$, - $XNR_6XC(O)$ nR_6R_6, - XOR_5, - $XC(O)R_5$, - XR_5 y - $XS(O)_0$- $_2$R5; en donde X se selecciona a partir de un enlace y C_1- $_4$alquileno opcionalmente sustituido por 1 a 2 radicales de C_1- $_6$alquilo; R5 se selecciona a partir de hidrógeno, C_1- $_6$alquilo, C_6- $_{10}$aril- C_0- $_4$alquilo, C_1- $_{10}$heteroaril- C_0- $_4$alquilo, C_3- $_{10}$cicloalquil- C_0- $_4$alquilo y C_3- $_{10}$heterocicloalquil- C_0- $_4$alquilo; y cada R6 es independientemente seleccionados a partir de hidrógeno y C_1- $_6$alquilo; o R5 y R6 junto con el nitrógeno al cual R5 y R6 están unidos forman heteroarilo o heterocicloalquilo; o R1 junto con el N1 del anillo de pirimidina al cual R1 está fijado forma 2,3- dihidroimidazo[1,2-f]pirimidina;

en donde cualquier arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R5 o la combinación de R5 y R6 se puede opcionalmente sustituir por 1 a 3 radicales independientemente seleccionados a partir de halo, nitro, ciano, hidroxilo, C_1- $_6$alquilo, C_1- $_6$alcoxilo alquilo halo-sustituido, alcoxilo halo- sustituido - XNR_7R_8, - XOR_7, - $XNR_7S(O)_2R_8$, - $XNR_7S(O)R_8$, - XNR_7SR_8, - $XC(O)$ nR_7R_8, - $XC(O)$ $nR_7XNR_7R_8$, - $XNR_7C(O)$ nR_7R_8, - $XNR_7XNR_7R_8$, - XNR_7XOR_7, - $XNR_7C(=NR_7)$ nR_7R_8, - $XS(O)_2R_9$, - $XNR_7C(O)R_8$, - $XNR_7C(O)R_9$, - XR_9, - $XC(O)OR_8$, - $XS(O)_2NR_7R_8$, - $XS(O)$ nR_7R_8 y - $XSNR_7R_8$; en donde X es un enlace o C_1-

$_4$alquileno; cada R_7 y R_8 son independientemente seleccionados a partir del grupo que consta de hidrógeno y C_1- $_4$alquilo, o R_7 y R_8 junto con el nitrógeno al cual R_7 y R_8 están unidos forma heteroarilo o heterocicloalquilo;; y R_9 se selecciona a partir de C_3- $_{10}$heterocicloalquilo y C_1- $_{10}$heteroarilo; en donde dicho heterocicloalquilo o heteroarilo de R9 es opcionalmente sustituido por una radical seleccionados a partir del grupo que consta de C_1- $_4$alquilo, - XNR7XNR7R7, XNR7XOR7 y - XOR_7;

R_2 se selecciona a partir de $-R_{11}$, - CONR10R11, SO_2NR10R11, - NR10R11, - $NR_{10}C(O)R_{11}$, - NR10S(O)0- 2R11 y - $NR_{10}C(O)$ nR_{10}R11; en donde R_{10} se selecciona a partir de hidrógeno y C_1- $_6$alquilo; R11 se selecciona a partir de C_6- $_{10}$arilo, C_1- $_{10}$heteroarilo, C_3- $_{10}$cicloalquilo y C_3- $_{10}$heterocicloalquilo; en donde R10 y R11 junto con el nitrógeno al cual R10 y R11 están unidos pueden opcionalmente formar heteroarilo o heterocicloalquilo, y cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R11 es opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halo, nitro, ciano, hidroxilo, C_1- $_6$alquilo, C_1- $_6$alcoxilo C_1- $_6$alquilo halo- sustituido, C_1- $_6$alquilo ciano- sustituido, C_1- $_6$alquilo hidroxi- sustituido, C_1- $_6$alcoxilo halo- sustituido - X_2R_{13}, - $X_2NR_{12}C(O)R_{13}$, - $X_2NR_{12}C(O)$ $nR_{12}R_{13}$, - $X_2NR_{12}R_{12}$, - $X_2NR_{12}R_{13}$, - $X_2NR_{12}X_2R_{13}$, - $X_2NR_{12}NR_{12}R_{12}$, - $X_2NR_{12}X_2OR_{12}$, - $X_2C(O)$ $nR_{12}R_{13}$, - $X_2S(O)_0$- $_2R_{12}$, - $X_2NR_{12}S(O)_0$- $_2R_{13}$ y - $X_2S(O)0$- $2NR_{12}R_{13}$; en donde X_2 se selecciona a partir de un enlace, C_1- $_4$lquileno y C_2- $_4$alquenileno; R_{12} se selecciona a partir de hidrógeno, C_1- $_6$alquilo y C_1- $_6$alquilo hidroxi- sustituido; R_{13} se selecciona a partir de C_6- $_{10}$arilo, C_1- $_{10}$heteroarilo, C_3- $_{10}$cicloalquilo y C_3- $_{10}$heterocicloalquilo; en donde dos R_{12} de $NR_{12}R_{12}$ o R_{12} y R_{13} de $NR_{12}R_{13}$ junto con el nitrógeno al cual ambos están fijados opcionalmente forma heteroarilo o heterocicloalquilo, y cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_{13} es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, ciano, hidroxilo, nitro, amino, C_1- $_6$alquilo, C_1- $_6$alquilo halo- sustituido, C_1- $_6$alquilo hidroxi- sustituido, C_1- $_6$alquilo ciano- sustituido, C_1- $_6$alquilo hidroxi- sustituido, C_1- $_6$alcoxilo C_1- $_6$alcoxilo halo- sustituido - X3NR7R8, - X3NR7X3OR7, C_6- $_{10}$aril- C_0- $_4$alquilo, C_1- $_{10}$heteroaril- C_0- $_4$alquilo, C_3- $_{10}$cicloalquil- C_0- $_4$alquilo, C_3- $_{10}$heterocicloalquil- C_0- $_4$alcoxilo y C_3- $_{10}$heterocicloalquil- C_0- $_4$alquilo; en donde X3 se selecciona a partir de un enlace y C_1- $_4$alquileno; R7 y R_8 son como se describió anteriormente y en donde cualquier arilo, heteroarilo, cicloalquilo o heterocicloalquilo sustituyentes de R_{13} es adicionalmente opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de halo, hidroxilo, C_1- $_6$alquilo, C_1- $_6$alquilo

halo- sustituido, C_{1-6}alquilo hidroxi- sustituido, C_{1-6}alcoxilo C_{3-10}heterocicloalquilo y C_{1-6}alcoxilo halo- sustituido;

R3 se selecciona a partir de hidrógeno, halo, C_{1-6}alquilo halo- sustituido, C_{1-6}alquilo, - XOR4a, - XCN, - $XC(O)OR_{4a}$, - $XC(O)R_{4b}$, - $XNR_{4a}R4a$, - $XNR4_aR4b$, - XNR_4aXNR_4aR4a, - $XC(O)\ nR_{4a}XNR4aR4a$, - $XC(O)\ nR_4aXR_4b$, - $XC(O)\ nR_4aXNR_4aR4b$, - $XC(O)\ nR_4aXOR_4a$, - $XNR4aXNR_{4a}R4b$, - XNR_4aXOR_4a, - $XNR_{4a}XCF_3$, - $XC(O)\ nR_{4a}R4a$, y - XR_{4b}; en donde X es seleccionados a partir de un enlace y C_{1-4}alquileno; $R4_a$ se selecciona a partir de hidrógeno y C_{1-6}alquilo; y R4b se selecciona a partir de C_{6-10}arilo, C_{1-10}heteroarilo, C_{3-10}cicloalquilo y C_{3-10}heterocicloalquilo; en donde dos $R4_a$ de $NR4_aR4a$ junto con el nitrógeno al cual ambos están fijados opcionalmente forma heteroarilo o heterocicloalquilo, y cualquier cicloalquilo, heterocicloalquilo, arilo o heteroarilo de R4b es opcionalmente sustituido por 1 a 3 radicales independientemente seleccionados a partir de C_{1-6}alquilo y - $NR4_CR4d$; en donde cada $R4_C$ y R4d es independientemente seleccionados a partir de hidrógeno y C_{1-6}alquilo, y R4c y R4d de NRt_cR4d junto con el nitrógeno al cual $R4_C$ y R4d están fijados opcionalmente forma una heteroarilo o heterocicloalquilo; y

Y se selecciona a partir de CH y N.

4. El compuesto de la reivindicación 3 en el cual R3 se selecciona a partir de hidrógeno, metilo, morfolino- etilo, etoxi- carbonilo, cloro, trifluorometilo, (metil- piperidinil) (metil) amino- metilo, metil- amino- carbonilo, hidroxi- metilo, dimetil- amino- metilo, metil-amino- metilo, morfolino- metilo, dietil- amino- etil- amino- metilo, metil- piperazinil- metilo, metil- piperazinil- etil- amino- metilo, dimetil- amino- propil- amino- metilo, ((2- hidroxietil) (metil) amino) metilo, etil- amino- metilo, trifluorometil- amino- metilo, dimetil- amino- etil-amino- carbonilo, piperidinil- etil- amino- carbonilo, morfolino- etil- amino- carbonilo, morfolino- carbonilo, amino- carbonilo, dimetil- amino- carbonilo, dimetil- amino- pirrolidinil-metilo, dimetil- amino- pirrolidinil- carbonilo, tiomorfolino- metilo, metoxi- etil- piperazinil-metilo, metoxi- etil- amino- carbonilo, ciano- metilo, (2,6- dimetilmorfolino) metilo, (2,6-dimetil- piperidinil) etil- amino- carbonilo y ciclopropil- amino- carbonilo.

5. El compuesto de la reivindicación 4 en el cual R_1 se selecciona a partir de morfolino- etil- amino, metil- amino, metil- piperazinil- etil- amino, ciclopropil- amino, hidroxi-

etil- piperazinil- amino, isopropil- amino, dimetil- amino- etil- amino, metil- piperazinil- amino, amino, 2,6- dimetil- morfolino- etil- amino, hidroxi- piridinil- etil- amino, amino- etil- amino, 3-oxopiperazin- 1- il- etil- amino, hidroxi- etil- amino, hidroxi- propil- amino, metil- sulfanilo, metoxilo, sulfanilo, piridinil- etil- amino, piridinil- metil- amino, morfolino- metil- piridinil-amino, carboxi- propil- amino, carboxi- metil- amino, azetidin- 3- il- amino, azetidin- 3- il- metil-amino, carboxi- etil- amino y hidroxi- pirrolidinilo.

6. El compuesto de la reivindicación 5 en el cual R_2 se selecciona a partir de –R11, - $CONHR_{11}$, $S0_2NHR_{11}$, - NHR_{11}, - $NHC(O)R_{11}$, - $NHS(O)_0$- $_2$R11 y - NHC(O) nHR_{11}; en donde R11 se selecciona a partir de fenilo, piridinilo, tiazolilo, benzimidazolilo, isoxazolilo, 1,2,3,4-tetrahidronaftilo, benzotiazolilo, benzo[d][l,2,3]triazol, 2,3- dihidrobenzofurano y 2,3- dihidro-3,3- dimetilbenzofuran- 5- ilo; en donde dicho fenilo, piridinilo, tiazolilo, isoxazolilo y 2,3-dihidro- 3,3- dimetilbenzofuran- 5- ilo de R2 son opcionalmente sustituidos por 1 a 3 radicales independientemente seleccionados a partir de halo, isopropilo, metil- sulfonilo, hidroxilo, metil-sulfonil- amino, l- (2- hidroxietilamino) ciclopropilo, 3- (3- hidroxipropilamino) ciclobutilo, isopropil- amino- ciclobutilo, 2- (2- hidroxietilamino) propan- 2- ilo, 3- aminoprop- 1- enilo, isopropil- 3- aminoprop- 1- enilo, isopropil- amino- propilo, isopropil- amino- etilo, hidroxietil-3- aminoprop- 1- enilo, metil- amino, 1,2- dihidroxietilo, 2- hidroxi- etilo, (3- hidroxiazetidin- l-il) metilo, (3- metoxiazetidin- l- il) metilo, 2- metil- morfolino- metilo, (3- metoxipirrolidin- l- il) metilo, (2- hidroxi- 2- metilpropilamino) metilo, 1- metil- l,2,3,6- tetrahidropiridin- 4- ilo, l,2,3,6-tetrahidropiridin- 4- ilo, piperidin- 4- ilo, (4- etilpiperazin- l- il) metilo, pirrolidin- 1- il- metilo, l-(etilamino) etilo, 4- (2- hidroxipropil)- l- piperazinilo, 3- trifluorometil- 4- metil- l- piperazinilo, difluoro- metilo, 4- metil- 1 - imidazolilo, metil- sulfonil- etil- amino- carbonilo, hidroxi- propil-amino- carbonilo, 4- t- butoxi- carbonil- l- piperazinilo, 4- (l- carboxietil) piperazin- l- ilo, 4,7-diazaspiro[2.5]octan- 7- ilo, etoxilo, 4- (tert- butoxicarbonil)- 2- oxopiperazin- l- ilo, 4- metil- 2-oxopiperazin- 1- ilo, 2- oxopiperazin- l- ilo, metoxilo, etilo, pirazolilo, trifluorometilo, 2-cianobutan- 2- ilo, 1- cianociclopropilo, 2- hidroxipropan- 2- ilo, difluorometilo, 3- etilpentan- 3-ilo, metil- piperazinilo, etil- piperazinilo, t- butilo, t- butoxilo, 1,2- dihidroxipropilo, 2-hidroximetil- etilo, ciclopropil- 1- piperazinilo, 4- metil- sulfonil- etil- l- piperazinilo, 2- hidroxi-propil- amino- metilo, (tetrahidrofuran- 2- ilamino) metilo, (2,3- dihidroxipropilamino) metilo), (l,3- dihidroxipropan- 2- ilamino) metilo, (l- hidroxi- 2- metilpropan- 2- ilamino) metilo,

ciclobutil- amino- metilo, 4- hidroxi- piperidinilo, (1- hidroxipropan- 2- ilamino) metilo, dimetil- amino- amino- metilo, metoxi- amino- metilo, hidroxi- amino- metilo,2- hidroxi- metil- pirrolidin- 1- il- metilo, pirrolidinil- etoxilo, 3- hidroxi- pirrolidinilo, 3- hidroxiazetidin- l- ilo, 3- (metoxi- carbonil)- 4- metilpiperazin- 1- ilo, 4- metilpiperazin- l- ilo, 4- metil- 3- hidroximetil- piperazin- l- ilo, 4- metoxi- carbonil- piperidinilo, 4- carboxi- piperidinilo, piperazinilo, 4- (2,2,2- trifluoroetil) piperazin- l- ilo, 2- hidroxi- ciclopent- l- il- amino- metilo, amino- carbonil- metilo, dimetil- amino- propil(metil)- amino, (2- (dimetilamino) etil) (metil) amino, metoxi etil(metil) amino, dimetil- amino- etoxilo, nitro, l- metil- 4- piperidiniloxi, morfolino, 2- metil- morfolino, 4- etil- piperazin- l- il- metilo, etil- amino- metilo, ciclopropil- amino- metilo, dietil- amino- etilo, azetidin- 1- ilmetilo, 3- hidroxi- pirrolidin- l- il- metilo, hidroxi- etil- amino- metilo, propil- amino- metilo, 3- hidroxi- azetidin- l- ilmetilo, 4- metoxietil- 1- piperazinilo, metoxi- etil- amino- metilo, butil- amino- etilo, t- butil- amino- metilo, hidroxi- ciclohexil- amino- metilo, amino- metilo, hidroxi- propil- amino- metilo, hidroxi- etil(metil) amino- metilo, 4- hidroxipropil- 1 - piperazinilo, 4- carboxi- metil- piperazinilo, dimetil- amino- metilo, isopropil- amino- metilo, 4- dimetil- amino- carbonil- metil- 1 - piperazinilo, 4- (2- hidroxipropil) piperazin- 1 - ilo, hidroxi- etil- piperazinilo, metilo, ciclopropilo, halo, trifluorometoxilo, difluorometoxilo, 2- fluoropropan- 2- ilo, 2- metoxi- propan- 2- ilo, 1,1- difluoroetilo, 1- metil- 1- fluoroetilo, 1- metil- l- metoxi- etilo, 2- hidroxipropan- 2- ilo, 2- metoxipropan- 2- ilo, 2- cianopropan- 2- ilo, 3- cianopropan- 2- ilo, 2,3- difluoropropan- 2- ilo y ciano- ciclopropilo.

7. El compuesto de la reivindicación 1 seleccionado a partir de N- (4- Metil- 3- {2- metil- 4- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- (4- metil- 3- {1 - metil- 4- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 1H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- (4- metil- piperazin- 1 - il)- 5- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- [4- Metil- 3- (5- metil- 2- {6- [2- (4- metil- piperazin- l- il)- etilamino]- pirimidin- 4- il}- 2H- pirazol- 3- ilamino)- fenil]- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3-

trifluorometil- benzamida, N- {3- [4- (6- Ciclopropilamino- pirimidin- 4- il)- 2- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- [4- metil- 3- (2- metil- 4- {6- [2- (4- metil- piperazin- l- il)- etilamino]- pirimidin- 4- il}- 2H- pirazol- 3- ilamino)- fenil]- 3- trifluorometil- benzamida, N- (4- Metil- 3- {2- metil- 4- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- {3- [4- (6- Ciclopropilamino- pirimidin- 4- il)- l- metil- lH- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- [4- Metil- 3- (l- metil- 4- {6- [2- (4- metil- piperazin- l- il)- etilamino] - pirimidin- 4- il}- 1 H- pirazol- 3- ilamino)- fenil] - 3 - trifluorometil- benzamida, N- (4- metil- 3- {1 - metil- 4- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- (4- metil- piperazin- 1- il)- 5- trifluorometil- benzamida, N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- (4- metil- piperazin- 1 - il)- 5- trifluorometil- benzamida, N- {3- [2- (6- ciclopropilamino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3 - ilamino]- 4- metil- fenil}- 3- (4- etil- piperazin- 1- il)- 5- trifluorometil- benzamida, 3- (4- Etil- piperazin- 1- il)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3 - ilamino] - fenil}- 5- trifluorometil- benzamida, 3- (4- Etil- piperazin- l- il)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 5- trifluorometil- benzamida, N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino- fenil)- 3- (4- metil- piperazin- 1 - il)- 5- trifluorometil- benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3 - ilamino]- fenil}- 3- (4- metil- piperazin- 1- il)- 5- trifluorometil- benzamida, 3- (4- Etil- piperazin- l- il)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 5- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, (3- trifluorometil- fenil)- amida del ácido 5- metil- 6- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- piridina- 2- carboxílico, (3- trifluorometil- fenil)- amida del ácido 5- metil- 6- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- piridina- 2- carboxílico, (3- trifluorometil- fenil)- amida del ácido 5- metil- 6- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- piridina- 2- carboxílico, N- (4- Metil- 3 - {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino-

pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- amino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- (4- metil- piperazin- l- il)- 5- trifluorometil- benzamida, N- [3- (2- {6- [2- (2,6- Dimetil- morfolin- 4- il)- etilamino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- 3- trifluorometil- benzamida, N- [3- (2- {6- [2- (4- Hidroxi- piperidin- 1- il)- etilamino] - pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- 3- trifluorometil- benzamida, N- [4- Metil- 3 - (5- metil- 2- {6- [2- (3- oxo- piperazin- 1- il)- etilamino]- pirimidin- 4- il}- 2H- pirazol- 3- ilamino)- fenil] –3- trifluorometil- benzamida, N- (3 - {2- [6- (2- amino- etilamino)- pirimidin- 4- il]- 5- metil- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, 2- tert- butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- tert- Butil- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, N- {4- Metil- 3- [4- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [4- (6- metilamino- pirimidin- 4- il)- l- (2- morfolin- 4- il- etil)- lH- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [1- metil- 4- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- ilamino]- fenil}- 3- (4- metil- piperazin- l- il)- 5- trifluorometil- benzamida, 3- [4- (2- Hidroxi- etil)- piperazin- 1 - il]- N- {4- metil- 3- [1- metil- 4- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- ilamino]- fenil}- 5- trifluorometil- benzamida, N- {3- [4- (6- Ciclopropilamino- pirimidin- 4- il)- l- metil- lH- pirazol- 3- ilamino]- 4- metil- fenil}- 3- (4- metil- piperazin- 1- il)- 5- trifluorometil- benzamida, N- {3- [4- (6- Ciclopropilamino- pirimidin- 4- il)- 1- metil- 1H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- [4- (2- hidroxi- etil)- piperazin- l- il]- 5- trifluorometil- benzamida, N- (3- {2- [6- (2- Hidroxi- etilamino)- pirimidin- 4- il]- 5- metil- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, N- {4- metil- 3- [5- metil- 2- (6- metilsulfanil- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (2,3- Dihidro- imidazo[1,2- c]pirimidin- 7- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, 2- tert- butil- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, N- {3- [2- (6- Metoxi- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3-

trifluorometil- benzamida, N- {3- [2- (6- amino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- Mercapto- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (2- piridin- 3- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, ácido 4- (6- {3- Metil- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- pirazol- 1- il}- pirimidin- 4- ilamino)- butírico, ácido (6- {3- Metil- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino] - pirazol- 1- il}- pirimidin- 4- ilamino)- acético, N- (3 - {2- [6- (Azetidin- 3- ilamino)- pirimidin- 4- il]- 5- metil- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, ácido 3- (6- {3- Metil- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- pirazol- 1- il}- pirimidin- 4- ilamino)- propiónico, N- (3- {2- [6- (3- Hidroxi- pirrolidin- 1 - il)- pirimidin- 4- il]- 5- metil- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, N- [3- (2- {6- [(Azetidin- 3- ilmetil)- amino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- 3- trifluorometil- benzamida, N- [4- Metil- 3- (5- metil- 2- {6- [(piridin- 2- ilmetil)- amino]- pirimidin- 4- il}- 2H- pirazol- 3- ilamino)- fenil]- 3- trifluorometil- benzamida, 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- N- [3- (4- metil- piperazin- 1 - il)- 5- trifluorometil- fenil]- benzamida, éster tert- butílico del ácido(4- metil- 3- {5- metil- 2- [6- (5- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- carbámico, 5- Metil- N- (4- metil- 3- {5- metil- 2- [6- (5- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, (4- metil- 3- {5- metil- 2- [6- (5- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- amida del ácido 3- Ciclopropil- isoxazol- 5- carboxílico, 3,4- dicloro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- Fluoro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 5- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 4- trifluorometil- benzamida, 3,5- dicloro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- fluoro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, N- (4- Metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il-

etilamino)- pirimidin- 4- il] - 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometoxi- benzamida, 3- Bromo- 4- cloro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- difluorometoxi- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- Cloro- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (l- Hidroxi- l- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1 - Metoxi- 1 - metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 2- (Ciano- dimetil- metil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 3- (Ciano- dimetil- metil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1,1 - Difluoro- etil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1 - Ciano- ciclopropil)- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino }- fenil)- amida del ácido 3,3- Dimetil- 2,3- dihidro- benzofuran- 5- carboxílico, 4- Metil- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, 2- (Ciano- dimetil- metil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 3- (Ciano- dimetil- metil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino} - fenil)- benzamida, 3- (1 - Ciano- ciclopropil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 2- (1- ciano- ciclopropil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 3- (1,1- difluoro- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1 - Hidroxi- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1- metoxi- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, éster etílico del ácido 1- (6-

Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, metilamida del ácido l- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- hidroximetil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- dimetilaminometil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- ciclopropilamino- pirimidin- 4- il)- 5- metilaminometil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- (3- {2- (6- ciclopropilamino- pirimidin- 4- il)- 5- [(2- dietilamino- etilamino)- metil]- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- (4- metil- piperazin- l- ilmetil)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- [3- (2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- {[2- (4- metil- piperazin- 1- il)- etilamino]- metil}- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- 3- trifluorometil- benzamida, N- (3- {2- (6- ciclopropilamino- pirimidin- 4- il)- 5- [(3- dimetilamino- propilamino)- metil]- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- 3- trifluorometil- benzamida, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- etilaminometil- 2H- pirazol- 3 - ilamino] - 4- metil- fenil} - 3 - trifluorometil- benzamida, N- (3 - {2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [(2,2,2- trifluoro- etilamino)- metil]- 2H- pirazol- 3- ilamino- 4- metil- fenil)- 3- trifluorometil- benzamida, l- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- ácido carboxílico (2- dimetilamino- etil)- amida, éster etílico del ácido l- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, (2- morfolin- 4- il- etil)- amida del ácido 1- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1 H- pirazol- 3- carboxílico, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- (morfolina- 4- carbonil)- 2H- pirazol- 3- ilamino] - 4- metil- fenil} - 3 - trifluorometil- benzamida, amida del ácido1- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- ácido carboxílico, dimetilamida del ácido l- (6- ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- l H- pirazol- 3- carboxílico, N- {3- [2- (6- Ciclopropilamino- pirimidin- 4- il)- 5- (3- dimetilamino- pirrolidina- l- carbonil)- 2H- pirazol- 3- ilamino]- 4- metil-

fenil}- 3- trifluorometil- benzamida, (2- metoxi- etil)- amida del ácido 1- (6- Ciclopropilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, metilamida del ácido l- (6- metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, N- {4- Metil- 3- [5- metilaminometil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil- 3- trifluorometil- benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, metilamida del ácido 1 - (6- Metilamino- pirimidin- 4- il)- 5- {2- metil- 5- [3- (4- metil- piperazin- l- il)- 5- trifluorometil- benzoilamino]- fenilamino}- lH- pirazol- 3-carboxílico, metilamida del ácido l- (6- metilamino- 2- morfolin- 4- il- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (l,l- difluoro- etil)- benzo ilamino]- 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- 1 H- pirazol- 3 - carboxílico, metilamida del ácido 5- {5- [3- (Ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- l- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (1- Ciano- ciclopropil)- benzoilamino]- 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, N- {3- [5- Cianometil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, (2- morfolin- 4- il- etil)- amida del ácido l- (6- Metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- l H- pirazol- 3- carboxílico, ciclopropilamida del ácido 1- (6- Metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- ácido, 5- tert- Butil- N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, N- [5- (l- fluoro- l- metil- etil)- piridin- 3- il]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [5- (1- Metoxi- 1- metil- etil)- piridin- 3- il]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [5- (l- Fluoro- l- metil- etil)- piridin- 3- il]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- [5- (l- Metoxi- l- metil- etil)- piridin- 3- il]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il] - 2H- pirazol- 3- ilamino}-

benzamida, 4- Metil- 3 - {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- N- (4- trifluorometil- piridin- 2- il)- benzamida, N- (3- tert- butil- fenil)- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- (2- tert- butil- piridin- 4- il)- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- (3- tert- butil- fenil)- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [3- (Ciano- dimetil- metil)- fenil]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- N- (4- trifluorometil- piridin- 2- il)- benzamida, (6- {5- [5- (6- tert- Butil- lH- benzoimidazol- 2- il)- 2- metil- fenilamino]- 3- metil- pirazol- 1 - il}- pirimidin- 4- il)- (4- metil- piperazin- 1 - il)- amina, (6- {3- Metil- 5- [2- metil- 5- (6- trifluorometil- 1 H- benzoimidazol- 2- il)- fenilamino] - pirazol- 1 - il} - pirimidin- 4- il)- (4- metil- piperazin- l- il)- amina, N- [3- (l,l- difluoro- etil)- fenil]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- [3- (1,1 - difluoro- etil)- fenil] - 4- metil- 3 - {5- metil- 2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, 4- fluoro- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, 4- Fluoro- N- (4- metil- 3 - {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, metilamida del ácido 5- [5- (4- Fluoro- 3- trifluorometil- benzoilamino)- 2- metil- fenilamino]- l- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, metilamida del ácido 5- [5- (4- Fluoro- 3- trifluorometil- benzoilamino)- 2- metil- fenilamino]- l- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, (2- morfolin- 4- il- etil)- amida del ácido 5- [5- (4- Fluoro- 3- trifluorometil- benzoilamino)- 2- metil- fenilamino]- l- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, metilamida del ácido 5- [5- (2- tert- butil- piridin- 4- ilcarbamoil)- 2- metil- fenilamino] - 1 - [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il] - 1 H- pirazol- 3- carboxílico, (2- morfolin- 4- il- etil)- amida del ácido 5- {5- [3- (l,l- difluoro- etil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 1H- pirazol- 3- carboxílico, N- (4- metil- 3- {2- [6- (4- metil- piperazin- l- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, 3 - (1,1 - difluoro- etil)- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5-

morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (ciano- dimetil- metil)- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 2- tert- butil- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 5- tert- butil- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 2- (ciano- dimetil- metil)- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- (Ciano- dimetil- metil)- N- {3- [5- {[(2- hidroxi- etil)- metil- amino]- metil}- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- isonicotinamida, 3- (Ciano- dimetil- metil)- N- {3- [5- {[(2- hidroxi- etil)- metil- amino]- metil}- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- benzamida, 2- tert- butil- N- {3- [5- {[(2- hidroxi- etil)- metil- amino]- metil}- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- isonicotinamida, 2- tert- butil- N- {3- [5- [2- (2,6- dimetil- piperidin- 1- il)- etilcarbamoil]- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- isonicotinamida, 2- (ciano- dimetil- metil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 3- (Ciano- dimetil- metil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (1- Ciano- ciclopropil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 2- (1- ciano- ciclopropil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 3- (1- Ciano- 1- metil- propil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino] - fenil}- benzamida, 2- tert- butil- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 3- (1,1 - Difluoro- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (1- Hidroxi- 1- metil- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (1- metoxi- 1- metil- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 5- tert- butil- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- nicotinamida, 2- tert- butil- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, {4- metil- 3- [5-

metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- amida del ácido 2,2-dimetil- 2,3- dihidro- benzofuran- 7- carboxílico, 2- (l- Fluoro- 1- metil- etil)- N- (4- metil- 3- {5-metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)-isonicotinamida, 2- (1- Fluoro- 1- metil- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino-pirimidin- 4- il)- 2H- pirazol- 3 - ilamino]- fenil}- isonicotinamida, 2- (l- Fluoro- 1- metil- etil)-N- (4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3-ilamino}- fenil)- isonicotinamida, 2- (l- Metoxi- l- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6-(4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)-isonicotinamida, 2- (l- Metoxi- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4-il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- (1- metoxi- 1- metil- etil)- N- (4- metil-3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}-fenil)- isonicotinamida, 2- (1- Hidroxi- 1 - metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil-piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- (1-Hidroxi- 1- metil- etil)- N- {4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H-pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- (l- Hidroxi- l- metil- etil)- N- (4- metil- 3- {5-metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino- fenil)-isonicotinamida, 3- (l- Ciano- ciclopropil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)-2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (Ciano- dimetil- metil)- N- {4- metil- 3- [2- (6-metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 2- (Ciano- dimetil-metil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}-isonicotinamida, 2- (l- Ciano- ciclopropil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)-2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 3 - (1,1- difluoro- etil)- N- {4- metil- 3- [2- (6-metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 3- (l- Metoxi- l- metil-etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}-benzamida, 3- (1 - hidroxi- 1- metil- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)-2H- pirazol- 3- ilamino]- fenil}- benzamida, 2- (1- fluoro- 1- metil- etil)- N- {4- metil- 3- [2- (6-metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- (l- metoxi- l-metil- etil)- N- {4- metil- 3 - [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]-fenil}- isonicotinamida, 2- (l- hidroxi- l- metil- etil)- N- {4- metil- 3- [2- (6- metilamino-pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 5- tert- butil- N- {4- metil- 3-[2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- nicotinamida, N- [3-

(Ciano- dimetil- metil)- fenil]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- (2- tert- Butil- piridin- 4- il)- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- - ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, 5- (1- fluoro- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3 - ilamino} - fenil)- nicotinamida, 5- (1 - metoxi- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- (1- Hidroxi- 1- metil- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 2- (1,1- difluoro- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, N- {3- [2- (6- amino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- (1,1- difluoro- etil)- benzamida, 3 - (1,1- difluoro- etil)- N- (4- metil- 3- {5- metil- 2- [6- (5- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (1,1- difluoro- etil)- N- (4- metil- 3- {5- metil- 2- [6- (4- morfolin- 4- ilmetil- piridin- 2- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- benzamida, N- {3- [2- (6- amino- pirimidin- 4- il)- 5- metil- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 2- tert- butil- isonicotinamida, 2- tert- Butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- tert- butil- N- [3- (2- {6- [4- (2- hidroxi- etil)- piperazin- 1- ilamino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- isonicotinamida, 5- tert- Butil- N- [3- (2- {6- [4- (2- hidroxi- etil)- piperazin- 1- ilamino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- fenil]- nicotinamida, N- (2- tert- butil- piridin- 4- il)- 3- (2- {6- [4- (2- hidroxi- etil)- piperazin- 1- ilamino]- pirimidin- 4- il}- 5- metil- 2H- pirazol- 3- ilamino)- 4- metil- benzamida, N- (5- tert- Butil- piridin- 3- il)- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- [2- (1- metoxi- 1- metil- etil)- piridin- 4- il]- 4- metil- 3- {5- metil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, N- [3- (1,1- difluoro- etil)- fenil]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, N- [2- (ciano- dimetil- metil)- piridin- 4- il]- 4- metil- 3- [5- metil- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- benzamida, 5- (1- Fluoro- 1- metil- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- fenil}- nicotinamida, N- {3- [2- (6- Amino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 2- tert- butil- isonicotinamida,

3- (l,l- difluoro- etil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- benzamida, 2- tert- butil- N- (3- {2- [6- (2- dimetilamino- acetilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- 4- metil- fenil)- isonicotinamida, N- [2- (l,l- difluoro- etil)- piridin- 4- il]- 4- metil- 3- {5- metil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- benzamida, (2- morfolin- 4- il- etil)- amida del ácido 5- {5- [3- (l H- difluoro- etil)- benzoilamino]- 2- metil- fenilamino}- l- (6- metilamino- pirimidin- 4- il)- lH- pirazol- carboxílico, 5- tert- butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, metilamida del ácido 1 - (6- Metilamino- pirimidin- 4- il)- 5- {2- metil- 5- [3- (4- metil- piperazin- l- il)- 5- trifluorometil- benzoilamino]- fenilamino}- lH- pirazol- 3- carboxílico, metilamida del ácido l- (6- metilamino- 2- morfolin- 4- il- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (l,l- difluoro- etil)- benzo ilamino] - 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- 1 H- pirazol- 3 - carboxílico, metilamida del ácido 5- {5- [3- (ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- l- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5 - [3 - (1 - Ciano- ciclopropil)- benzoilamino]- 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, ciclopropilamida del ácido l- (6- metilamino- pirimidin- 4- il)- 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- lH- pirazol- 3- carboxílico, 2- (Ciano- dimetil- metil)- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- (ciano- dimetil- metil)- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, metilamida del ácido 5- {5- [3- (ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- l- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, 2- tert- butil- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- tert- butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- tert-

butil- N- {4- metil- 3- [2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- tert- Butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- metilcarbamoil- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- tert- butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, metilamida del ácido 5- [5- (3- tert- Butil- benzoilamino)- 2- metil- fenilamino]- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 1H- pirazol- 3- carboxílico, 2- cloro- 6- metoxi- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- cloro- 6- metoxi- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 2- Cloro- 6- metoxi- N- {4- metil- 3- [2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- Cloro- 6- metoxi- N- {4- metil- 3- [2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- Cloro- 6- metoxi- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- isonicotinamida, 2- Cloro- 6- metoxi- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, N- (4- Metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 2H- pirazol- 3 - ilamino}- fenil)- 6- pirazol- 1- il- nicotinamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- metilcarbamoil- 2H- pirazol- 3- ilamino]- fenil}- 6- pirazol- 1- il- nicotinamida, N- {4- Metil- 3 - [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- 6- pirazol- 1 - il- nicotinamida, N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1 - ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 6- pirazol- 1- il- nicotinamida, metilamida del ácido 5- [2- Metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 1H- pirazol- 3- carboxílico, N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometil- benzamida, (2- morfolin- 4- il- etil)- amida del ácido 5- [2- metil- 5- (3- trifluorometil- benzoilamino)- fenilamino]- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 1 H- pirazol- 3- carboxílico, metilamida del ácido 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- [2- metil- 5 - (3 - trifluorometil- benzoilamino)- fenilamino]- 1H- pirazol- 3 -

carboxílico, N- (4- Metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 6- trifluorometoxi- nicotinamida, N- {4- metil- 3- [2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- 6- trifluorometoxi- nicotinamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- metilcarbamoil- 2H- pirazol- 3- ilamino]- fenil}- 6- trifluorometoxi- nicotinamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- (2- morfolin- 4- il- etilcarbamoil)- 2H- pirazol- 3- ilamino]- fenil}- 6- trifluorometoxi- nicotinamida, N- (4- Metil- 3- {5- metilcarbamoil- 2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- 6- trifluorometoxi- nicotinamida, 2- (ciano- dimetil- metil)- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, metilamida del ácido 5- {5- [3- (1- Ciano- 1- metil- propil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- carboxílico, 3- (l- Ciano- l- metil- propil)- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, metilamida del ácido 5- {5- [3- (1 - Ciano- 1- metil- propil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 1 H- pirazol- 3 - carboxílico, metilamida del ácido 5- {5- [3- (l- ciano- l- metil- propil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 1H- pirazol- 3- carboxílico, metilamida del ácido 5- {5- [3- (l- Metoxi- l- metil- etil)- benzoilamino]- 2- metil- fenilamino}- 1- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 1H- pirazol- 3 - carboxílico, 3- (- metoxi- 1- metil- etil)- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- (ciano- dimetil- metil)- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 5- tert- butil- N- (4- metil- 3- {5- metilcarbamoil- 2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 5- tert- Butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il] - 5- morfolin- 4- ilmetil- 2H- pirazol- 3 - ilamino}- fenil)- nicotinamida, metilamida del ácido 5- {5- [3- (l,l- Difluoro- etil)- benzoilamino]- 2- metil- fenilamino}- l- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, 3- (1,1 - difluoro- etil)- N- (4- metil- 3 - {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, metilamida del ácido 5- {5- [3- (l,l- difluoro- etil)- benzo ilamino]- 2- metil-

fenilamino}- 1- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- lH- pirazol- 3- carboxílico, 2- tert- butil- N- (4- metil- 3- {5- metilcarbamoil-2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 4- tert- Butil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- Metanosulfonil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- Cloro- 3- metanosulfonil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- tert- Butoxi- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 4- Metoxi- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 3 - trifluorometil- benzamida, 3- tert- Butoxi- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- benzamida, 3- Metanosulfonil- N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino} - fenil)- benzamida, N- (4- metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 4- trifluorometoxi- benzamida, N- (4- Metil- 3- {2- [6- (2- morfolin- 4- il- etilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- 3- trifluorometoxi- benzamida, metilamida del ácido 5- {5- [3- (1,1- Difluoro- etil)- benzoilamino]- 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, (2- morfolin- 4- il- etil)- amida del ácido 5- {5- [3- (ciano- dimetil- metil)- benzoilamino]- 2- metil- fenilamino}- 1- (6- metilamino- pirimidin- 4- il)- lH- pirazol- 3- carboxílico, 5- tert- butil- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- nicotinamida, 2- tert- butil- N- (4- metil- 3- {2- [6- (4- metil- piperazin- 1- ilamino)- pirimidin- 4- il]- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino}- fenil)- isonicotinamida, 5- tert- Butil- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- nicotinamida, {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- amida del ácido 1- isopropil- 1H- benzotriazol- 5- carboxílico, {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- amida del ácido 5,5,8,8- Tetrametil- 5,6,7,8- tetrahidro- naftaleno- 2- carboxílico, {4- metil- 3- [2- (6-

metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- amida del ácido 2- metil- benzotiazol- 5- carboxílico, 3- (1,1- dietil- propil)- N- {4- metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- morfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- benzamida, N- {3- [5- (3- Dimetilamino- pirrolidin- l- ilmetil)- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [5- [4- (2- metoxi- etil)- piperazin- 1- ilmetil]- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino] - 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [5- (2,6- dimetil- morfolin- 4- ilmetil)- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {3- [5- (2,6- dimetil- morfolin- 4- ilmetil)- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- [4- Metil- 3- (2- (6- metilamino- pirimidin- 4- il)- 5- {[metil- (1- metil- piperidin- 4- il)- amino]- metil}- 2H- pirazol- 3- ilamino)- fenil]- 3- trifluorometil- benzamida, N- {3- [5- (1,1- dioxo- 116- tiomorfolin- 4- ilmetil)- 2- (6- metilamino- pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- fenil}- 3- trifluorometil- benzamida, N- {4- Metil- 3- [2- (6- metilamino- pirimidin- 4- il)- 5- tiomorfolin- 4- ilmetil- 2H- pirazol- 3- ilamino]- fenil}- 3- trifluorometil- benzamida, 5- tert- butil- N- (3- (3- (((2- hidroxietil) (metil) amino) metil)- 1- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil) nicotinamida, - (2- (2- fluoropropan- 2- il) piridin- 4- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 5- tert- butil- N- (3- (3- (((2- hidroxietil) (metil) amino) metil)- 1- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil) nicotinamida, 5- tert- butil- N- (3- (3- (2- (2,6- dimetilpiperidin- l- il) etilcarbamoil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil) nicotinamida, 5- (2- metoxipropan- 2- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) nicotinamida, 5- (2- fluoropropan- 2- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) nicotinamida, N- (4- tert- butiltiazol- 2- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- (2- fluoropropan- 2- il) piridin- 2- il)- 4- metil- 3- (3 - metil- 1 - (6- (4- metilpiperazin- 1- ilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, 5- (5- (2- tert- butilpiridin- 4- ilcarbamoil)- 2- metilfenilamino)- 1 - (6- (isopropilamino) pirimidin- 4- il)- N- metil- 1H- pirazol- 3- carboxamida, 5- (5- (2- tert- butilpiridin- 4- ilcarbamoil)- 2- metilfenilamino)- N- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 3- carboxamida, N- (2- tert- butilpiridin- 4- il)- 4- metil- 3- (l- (6- (metilamino)

pirimidin- 4- il)- 3- (morfolinometil)- lH- pirazol- 5- ilamino) benzamida, N- (2- tert- butil-piridin- 4- il)- 3- [5- (1,1 - dioxo- 1lambda*6*- tiomorfolin- 4- ilmetil)- 2- (6- metilamino-pirimidin- 4- il)- 2H- pirazol- 3- ilamino]- 4- metil- benzamida, 2- tert- butil- N- (3- (l- (6-(isopropilamino) pirimidin- 4- il)- 3- (metilcarbamoil)- lH- pirazol- 5- ilamino)- 4-metilfenil)isonicotinamida, N- (2- tert- butilpiridin- 4- il)- 3- (l- (6- (isopropilamino) pirimidin-4- il)- 3- (morfolinometil)- lH- pirazol- 5- ilamino)- 4- metilbenzamida, N- (2- tert- Butil- piridin-4- il)- 3- [5- (l,l- dioxo- lambda*6*- tiomorfolin- 4- ilmetil)- 2- (6- isopropilamino- pirimidin- 4-il)- 2H- pirazol- 3- ilamino]- 4- metil- benzamida, 2- tert- butil- N- (3- (l- (6- (isopropilamino) pirimidin- 4- il)- 3- (morfolinometil)- lH- pirazol- 5- ilamino)- 4- metilfenil)isonicotinamida, N-(4- (2- fluoropropan- 2- il) piridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4-il)- lH- pirazol- 5- ilamino) benzamida, N- (5- tert- butil- 4- metiltiazol- 2- il)- 4- metil- 3- (3-metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (5- tert- butil-4- metiltiazol- 2- il)- 4- metil- 3- (3- metil- l- (6- (4- metilpiperazin- l- ilamino) pirimidin- 4- il)-lH- pirazol- 5- ilamino) benzamida, N- (4- (2- cianopropan- 2- il) piridin- 2- il)- 4- metil- 3- (3-metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (2- (2-metoxipropan- 2- il) piridin- 4- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH-pirazol- 5- ilamino) benzamida, N- (4- tert- butiltiazol- 2- il)- 4- metil- 3- (3- metil- l- (6- (2-morfolinoetilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (5- tert- butil- 4-metiltiazol- 2- il)- 4- metil- 3- (3- metil- l- (6- (2- morfolinoetilamino) pirimidin- 4- il)- lH-pirazol- 5- ilamino) benzamida, - (4- (1,1- difluoroetil) piridin- 2- il)- 4- metil- 3- (3- metil- l- (6-(metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- (1,l- difluoroetil) piridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (4- metilpiperazin- l- ilamino) pirimidin- 4- il)- lH-pirazol- 5- ilamino) benzamida, N- (4- tert- butilpiridin- 2- il)- 4- metil- 3- (3- metil- l- (6-(metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- tert- butilpiridin- 2- il)-4- metil- 3- (3- metil- l- (6- (4- metilpiperazin- l- ilamino) pirimidin- 4- il)- lH- pirazol- 5-ilamino) benzamida, 3- (l- (6- aminopirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (5- tert- butil-4- metiltiazol- 2- il)- 4- metilbenzamida, 3- (l- (6- aminopirimidin- 4- il)- lH- pirazol- 5-ilamino)- N- (4- tert- butiltiazol- 2- il)- 4- metilbenzamida, N- (4- (2- metoxipropan- 2- il)piridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)benzamida, N- (4- (2- metoxipropan- 2- il) piridin- 2- il)- 4- metil- 3- (3- metil- l- (6- (4-metilpiperazin- l- ilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (6- metil- 5-

(3- metil- 1- (6- (4- metilpiperazin- 1- ilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) piridin- 3- il)- 3- (trifluorometil) benzamida, N- (6- metil- 5- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) piridin- 3- il)- 3- (trifluorometil) benzamida, 2- tert- butil- N- (6- metil- 5- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) piridin- 3- il)isonicotinamida, 2- tert- butil- N- (6- metil- 5- (3- metil- 1- (6- (4- metilpiperazin- 1- ilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) piridin- 3- il)isonicotinamida, N- (4- metil- 3- (1- (6- (metilamino) pirimidin- 4- il)- 3- (1- oxo- tiomorfolinometil)- 1H- pirazol- 5- ilamino) fenil)- 3- (trifluorometil) benzamida, N- (3- (1- (6- aminopirimidin- 4- il)- 3- metil- 1H- pirazol- 5- ilamino)- 4- metilfenil)- 3- (4- hidroxipiperidin- 1- il)- 5- (trifluorometil) benzamida, 3- (4- hidroxipiperidin- 1- il)- N- (4- metil- 3- (1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (4- hidroxipiperidin- 1- il)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il) - 1H- pirazol- 5 - ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- (1- metilpiperidin- 4- iloxi)- 5- (trifluorometil) benzamida, 3- (4- (2- hidroxietil) piperazin- 1- il)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- morfolino- 5- (trifluorometil) benzamida, (S)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- (2- metilmorfolino)- 5- (trifluorometil) benzamida, (R)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- (2- metilmorfolino)- 5- (trifluorometil) benzamida, 1- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- (3- (trifluorometil) fenil)urea, 1- (4- fluoro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)urea, 1- (4- cloro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)urea, 1- (3- (4- etilpiperazin- 1- il)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)urea, N- (4- metil- 3- (3- metil- 1 - (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- (1,1- dioxo- tiomorfolino)- 5- (trifluorometil) benzamida, (R)- 3- (3,4- dimetilpiperazin- 1- il)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (3,4- dimetilpiperazin- 1- il)- N- (4- metil- 3- (1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5 - y lamino) fenil)- 5-

(trifluorometil) benzamida, N- (3- (4- hidroxipiperidin- 1- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, N- (3- (2- (dimetilamino) etoxi)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino)- N- (3- (2- (pirrolidin- 1- il) etoxi)- 5- (trifluorometil) fenil) benzamida, N- (3- (3- hidroxipirrolidin- 1- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, N- (3- (3- hidroxiazetidin- 1- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, 2- (1,1- difluoroetil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)isonicotinamida, 1- metil- 4- (3- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamido)- 5- (trifluorometil) fenil) piperazina- 2- carboxilato de metilo, N- (3- ((2- metoxietil) (metil) amino)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, N- (3- ((2- (dimetilamino) etil) (metil) amino)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, 3- (1,1- difluoroetil)- N- (3- (3- (hidroximetil)- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino)- 4- metilfenil) benzamida, N- (3- (3- (hidroximetil)- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino)- 4- metilfenil)- 3- (4- hidroxipiperidin- 1- il)- 5- (trifluorometil) benzamida, 4- metil- 3- (1- (6- (metilamino) pirimidin- 4- il)- 3- (trifluorometil)- 1H- pirazol- 5- ilamino)- N- (3- (4- metilpiperazin- 1- il)- 5- (trifluorometil) fenil) benzamida, 1- (3- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamido)- 5- (trifluorometil) fenil) piperidina- 4- carboxilato de metilo, ácido 1- (3- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamido)- 5- (trifluorometil) fenil) piperidina- 4- carboxílico, N- (3- (3- (hidroximetil)- 4- metilpiperazin- 1- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, N- (3- ((2- hidroxietil) (metil) amino)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, N- (3- (4- (hidroximetil) piperidin- 1- il)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) benzamida, 1- (3- (1,1- difluoroetil) fenil)- 3- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)urea, 1- (2- (1,1- difluoroetil) piridin- 4- il)- 3- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4-

il)- lH- pirazol- 5- ilamino) fenil)urea, l- (3- (4- hidroxipiperidin- l- il)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, N- (3- fluoro- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (metilsulfonamido)- 5- (trifluorometil) fenil) benzamida, 2- metoxi- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 6- (trifluorometil)isonicotinamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (trifluorometil) fenil) benzamida, N- (4- cloro- 3- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, N- (4- fluoro- 3- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 3- ((3- (dimetilamino) propil) (metil) amino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- nitro- 5- (trifluorometil) benzamida, 3- amino- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((2- metoxietil) (metil) amino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, l- (4- bromo- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (6- metil- 5- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) piridin- 3- il)urea, 3- ((2- (dimetilamino) etil) (metil) amino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, l- (3- (4- (2- hidroxietil) piperazin- l- il)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (3- (3- (hidroximetil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil)urea, metil 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamido)- 5- (trifluorometil) benzoato, 3- (2- (dimetilamino) etoxi)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (3- (dimetilamino) propoxi)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- hidroxi- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5 - ilamino) fenil)- 5- (trifluorometil)

benzamida, 3- (l- (6- (2- (dimetilamino) etilamino) pirimidin- 4- il)- 3- metil- lH- pirazol- 5- ilamino)- 4- metil- N- (3- (trifluorometil) fenil) benzamida, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (3- (l- (6- (2- (dimetilamino) etilamino) pirimidin- 4- il)- 3- metil- lH- pirazol- 5- ilamino)- 4- metilfenil)urea, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (2- morfolinoetilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, 3- (l- (6- (3- hidroxipropilamino) pirimidin- 4- il)- 3- metil- lH- pirazol- 5- ilamino)- 4- metil- N- (3- (trifluorometil) fenil) benzamida, 3- (difluorometil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- (difluorometil)- N- (3- (3- (hidroximetil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil) benzamida, l- (3- (4- metil- lH- imidazol- l- il)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, 3- (4- metil- lH- imidazol- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (4- metil- lH- imidazol- l- il)- 5- (trifluorometil) fenil) benzamida, N- (3- metoxi- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (2- metil- 5- (trifluorometil) fenil) benzamida, l- (3- (l,l- difluoroetil) fenil)- 3- (3- (3- (hidroximetil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil)urea, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (2- (metilsulfonil) etilcarbamoil)- 5- (trifluorometil) fenil) benzamida, N- (3- (3- hidroxipropilcarbamoil)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- metil- 5- (trifluorometil) fenil) benzamida, l- (3- ((2- metoxietil) (metil) amino)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (3- ((2- (dimetilamino) etil) (metil) amino)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (4- cloro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- 3- (morfolinometil)- lH- pirazol- 5- ilamino) fenil)urea, 1- (4- cloro- 3- (trifluorometil) fenil)- 3- (3- (3- ((dimetilamino) metil)- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- 4- metilfenil)urea, 3- bromo- 5- (1,1 - difluoroetil)- N- (4- metil- 3 - (3- metil- 1 - (6- (metilamino)

pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, (R)- l- (4- cloro- 3- (trifluorometil) fenil)- 3- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- 3- ((2- metilmorfolino) metil)- lH- pirazol- 5- ilamino) fenil)urea, tert- butil 4- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5 - ilamino) fenilcarbamoil)- 5- (trifluorometil) fenil) piperazina- 1- carboxilato, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (piperazin- l- il)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4- (2,2,2- trifluoroetil) piperazin- l- il)- 5- (trifluorometil) benzamida, 3- (4- (2- amin0- 2- oxoetil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (4- (2- metoxietil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (4- (3- hidroxipropil) piperazin- 1- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, ácido 2- (4- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil- carbamoil)- 5- (trifluorometil) fenil) piperazin- 1- il)- acético, 3- (4- (2- (dimetilamino)- 2- oxoetil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (4- (2- hidroxipropil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4- (2- (metilsulfonil) etil) piperazin- l- il)- 5- (trifluorometil) benzamida, 3- (4- ciclopropilpiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5 - ilamino) fenil)- 5- (trifluorometil) benzamida, ácido (S)- 2- (4- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenilcarbamoil)- 5- (trifluorometil) fenil) piperazin- l- il) propanóico, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4,7- diazaspiro[2.5]octan- 7- il)- 5- (trifluorometil) benzamida, 2- etoxi- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 6- (trifluorometil)isonicotinamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (trifluorometil)- 5- (3- (trifluorometil) piperazin- l- il) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4- metil- 4,7- diazaspiro[2.5]octan- 7- il)- 5- (trifluorometil) benzamida, 4- (3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH-

pirazol- 5- ilamino) fenilcarbamoil)- 5- (trifluorometil) fenil)- 3- oxopiperazina- l- carboxilato tert- butílico, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (2- oxopiperazin- l- il)- 5- (trifluorometil) benzamida, 3- (4- metil- 2- oxopiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 2- (metilamino)- 6- (trifluorometil)isonicotinamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (4- metil- 3- (trifluorometil) piperazin- l- il)- 5- (trifluorometil) benzamida, 2- (2- (dimetilamino) etilamino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 6- (trifluorometil)isonicotinamida, 2- (2- hidroxietilamino)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 6- (trifluorometil)isonicotinamida, 3- (4- hidroxipiperidin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (4- (2- hidroxipropil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (4- (2- hidroxipropil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (3- ((4- etilpiperazin- l- il) metil)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino)- N- (3- (pirrolidin- l- ilmetil)- 5- (trifluorometil) fenil) benzamida, N- (3- ((dimetilamino) metil)- 5- (trifluorometil) fenil)- 4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) benzamida, 3- ((dimetilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (pirrolidin- l- ilmetil)- 5- (trifluorometil) benzamida, 3- ((isopropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5 - y lamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((metilamino) metil)- 5- (trifluorometil) benzamida, 1- (3- ((dimetilamino) metil)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)urea, l- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol-

5- ilamino) fenil)- 3- (3- (pirrolidin- 1- ilmetil)- 5- (trifluorometil) fenil)urea, 1- (3- ((4- etilpiperazin- 1- il) metil)- 5- (trifluorometil) fenil)- 3- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)urea, 3- ((etilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5 - y lamino) fenil)- 5- (trifluorometil) benzamida, 3- ((ciclopropilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (1,1- difluoroetil)- 5- ((isopropilamino) metil)- N- (4- metil- 3- (1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, 3- (1,1- difluoroetil)- 5- ((isopropilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, 3- ((dietilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (azetidin- 1- ilmetil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (azetidin- 1- ilmetil)- N- (4- metil- 3- (1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3- hidroxiazetidin- 1- il) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3- hidroxipirrolidin- 1- il) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((2- hidroxietilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- ((propilamino) metil)- 5- (trifluorometil) benzamida, 3- (1,1- difluoroetil)- 5- ((dimetilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, 3- ((ciclopropilamino) metil)- 5- (1,1- difluoroetil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, 3- ((3- hidroxipropilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (1,1- difluoroetil)- 5- ((etilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, 3- ((2- metoxietilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((butilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((tert- butilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin-

4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (1,1 - difluoroetil)- 5- ((4- hidroxiciclohexilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, 3- ((ciclopropilamino) metil)- 5- (1,1- difluoroetil)- N- (4- metil- 3- (1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, 3- (aminometil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 2- ((dimetilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 6- (trifluorometil)isonicotinamida, 3- (((2- hidroxietil) (metil) amino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (1,2- dihidroxietil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5 - ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((1- hidroxipropan- 2- ilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((1- hidroxipropan- 2- ilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((2,2- dimetilhidrazinil) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((metoxiamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il) - 1H- pirazol- 5 - ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((hidroxiamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- ((2- (hidroximetil) pirrolidin- 1- il) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- ((2- hidroxipropilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- (((tetrahidrofuran- 2- il) metilamino) metil)- 5- (trifluorometil) benzamida, (R)- 3- ((2,3- dihidroxipropilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- ((2,3- dihidroxipropilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((1,3- dihidroxipropan- 2- ilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((1- hidroxi- 2- metilpropan- 2- ilamino) metil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)-

lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((ciclobutilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5 - y lamino) fenil)- 5 - (trifluorometil) benzamida, 3- ((dimetilamino) metil)- N- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5 - y lamino) fenil)- 5- (trifluorometil) benzamida, 3- (((2- metoxietil) (metil) amino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (((lS,2R)- 2- hidroxiciclopentilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (((tetrahidrofuran- 2- il) metilamino) metil)- 5- (trifluorometil) benzamida, (R)- 3- ((2- hidroxipropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (morfolinometil)- 5- (trifluorometil) benzamida, 3- ((3- metoxiazetidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida 3- ((3- metoxipirrolidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5 - ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3- hidroxiazetidin- 1 - il) metil)- N- (4- metil- 3- (1 - (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- cloro- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((dimetilamino) metil)- 5- (trifluorometil) benzamida, N- (4- cloro- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((isopropilamino) metil)- 5- (trifluorometil) benzamida, N- (4- cloro- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (pirrolidin- l- ilmetil)- 5- (trifluorometil) benzamida, 3- ((isopropilamino) metil)- N- (4- metil- 3- (l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (1 - (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 3- (pirrolidin- l- ilmetil)- 5- (trifluorometil) benzamida, 3- (l- (etilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((2- metilmorfolino) metil)- 5- (trifluorometil) benzamida, (i?)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- ((2- metilmorfolino) metil)- 5- (trifluorometil) benzamida, 3- ((2- hidroxi- 2-

metilpropilamino) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (l,2,3,6- tetrahidropiridin- 4- il)- 5- (trifluorometil) benzamida, N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (piperidin- 4- il)- 5- (trifluorometil) benzamida, 3- (l- metil- l,2,3,6- tetrahidropiridin- 4- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (l,2- dihidroxietil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5 - y lamino) fenil)- 5- (trifluorometil) benzamida, 3- (l- hidroxietil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (3- (2- hidroxietilamino) ciclobutil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (3- (isopropilamino) ciclobutil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (E)- 3- (3- aminoprop- l- enil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5 - y lamino) fenil)- 5 - (trifluorometil) benzamida, (E)- 3- (3- (isopropilamino) prop- l- enil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (E)- 3- (3- (2- hidroxietilamino) prop- l- enil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (3- (isopropilamino) propil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1 H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (2- (isopropilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il) - 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (2- (2- hidroxietilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (l- (etilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, *(R)- 3* - (1 - (etilamino) etil)- N- (4- metil- 3- (3 - metil- 1- (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (l- (dimetilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (l- (dimetilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)-

N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (1 - (pirrolidin- 1 - il) etil)- 5- (trifluorometil) benzamida, (R)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 3- (l- (pirrolidin- l- il) etil)- 5- (trifluorometil) benzamida, (S)- 3- (l- (isopropilamino) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (1 - (isopropilamino) etil)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- (4- (2,2- difluoroetil) piperazin- 1 - il)- N- (4- metil- 3 - (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- cloro- 5- (4- (2- metoxietil) piperazin- 1- il)- N- (4- metil- 3 - (3 - metil- 1 - (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil) benzamida, 3- cloro- 5- (4- (2- etoxietil) piperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil) benzamida, 3- cloro- N- (4- metil- 3- (3 - metil- 1- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (4- metilpiperazin- l- il) benzamida, (S)- 3- (4- (2- metoxietil)- 2- metilpiperazin- 1- il)- N- (4- metil- 3- (3- metil- 1- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (4- (2- metoxietil)- 2- metilpiperazin- 1 - il)- N- (4- metil- 3 - (3- metil- 1 - (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (2,4- dimetilpiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (S)- 3- (2,4- dimetilpiperazin- l- il)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3,3- difluoroazetidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, 3- ((3,3- difluoropirrolidin- l- il) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, (R)- 3- (4- (2,2- difluoroetil)- 2- metilpiperazin- 1 - il)- N- (4- metil- 3 - (3 - metil- 1 - (6- (metilamino) pirimidin- 4- il)- 1H- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, rac- 3- (2- (3,3- difluoropirrolidin- l- il) etil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, *rac- 3* - (2- (3,3 - difluoroazetidin- 1 - il) etil)- N- (4- metil- 3 - (3 - metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5- (trifluorometil) benzamida, y 3- ((2,2- difluoroetil) metil)- N- (4- metil- 3- (3- metil- l- (6- (metilamino) pirimidin- 4- il)- lH- pirazol- 5- ilamino) fenil)- 5-

(trifluorometil) benzamida.

8. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de Reivindicación 1 en combinación con un excipiente farmacéuticamente aceptable.

9. Un método para tratar una enfermedad en un animal en el cual la inhibición de la actividad de la quinasa puede inhibir o aliviar la patología y/o sintomatología de la enfermedad mediada por quinasas, tal método comprende administrar al animal una cantidad terapéuticamente efectiva de un compuesto de la Reivindicación 1.

10. El método de reivindicación 9 en el cual la quinasa se selecciona a partir del grupo que consta de Abl, ARG, BCR- Abl, BRK, EphB, Fms, Fyn, KDR, c- Kit, LCK, PDGF- R, b- Raf, c- Raf, SAPK2, Src, Tie2 y TrkB.

11. El uso de un compuesto de reivindicación 1 en la fabricación de un medicamento para tratar una enfermedad en un animal en la cual la actividad de quinasas Abl, ARG, BCR- Abl, BRK, EphB, Fms, Fyn, KDR, c- Kit, LCK, PDGF- R, b- Raf, c- Raf, SAPK2, Src, Tie2 y TrkB contribuye a la patología y/o sintomatología de la enfermedad.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/079340

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D403/04 C07D403/14 C07D405/14 C07D417/14
A61K31/506 A61P35/00

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

B. FIELDS SEARCHED

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

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/123719 A (IRM LLC [US]; REN PINGDA [US]; WANG XIA [US]; ZHANG GUOBAO [US]; DING) 29 December 2005 (2005-12-29) claims 6-9; examples	1-11
X	WO 2005/013982 A (VERTEX PHARMA [US]; ARNOST MICHAEL J [US]; BEMIS GUY W [US]; DAVIES RO) 17 February 2005 (2005-02-17) claims 77-80; example 3	1-11

☐ 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
8 February 2008	15/02/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beyss-Kahana,Ellen

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/079340

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9, 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/079340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005123719 A	29-12-2005	AR 049511 A1	09-08-2006
		AU 2005254982 A1	29-12-2005
		BR PI0511978 A	22-01-2008
		CA 2567662 A1	29-12-2005
		CN 1960988 A	09-05-2007
		EP 1758892 A1	07-03-2007
WO 2005013982 A	17-02-2005	AU 2004263148 A1	17-02-2005
		CA 2534921 A1	17-02-2005
		EP 1663211 A1	07-06-2006
		JP 2007501257 T	25-01-2007
		US 2005261268 A1	24-11-2005

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE
PCT

PATENTE DE INVENCIÓN [ ] MODELO DE UTILIDAD [ ]

- ◇ Indicación de que se solicita la concesión de una patente [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Descripción de la invención [ ]
- ◇ Dibujos de ser estos pertinentes [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- ◇ Indicación de que se solicita el registro de Diseño Industrial [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- ◇ Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica del esquema trazado [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Fecha

No. 09-034040- -00000-0000
Fecha: 2009-04-02 11:31:42 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 424

Carrera 13 No. 27-00 Piso 5,7y10
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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC
NOVARTIS AG

REFERENCIA	Radicación No.	9 34040
	Solicitud internacional	PCT/US2007/079340
	Fecha inicio fase nacional	02/05/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	5643

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.

Continua en la página siguiente...

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación No.:9 34040

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 15 MAYO 2009
adpa11