

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

08-117545

SOLICITUD DE PATENTE DE

INVENCION

TITULO: COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA
SENDA DE HEDGEHOG

SOLICITANTE: IRM LLC

DIRECCIÓN: Hurst Holme, 12 Trott Road, Hamilton, HM 11, Bermudas.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 4 de Noviembre 2008

OLARTE RAISBECK



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-117545- -00000-0000

Fecha: 2008-11-04 16:57:24 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYI Eve: 378 FASENACIONAL
Act. 411 PRESENTACION Folios: 184

PETITORIO - FORMULARIO ÚNICO PATENTE PC

ENTRADA EN FASE NACIONAL

P2008/000185

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: IRM LLC

Dirección: Hurts Holme, 12 Trot Road,
Hamilton, HM 11 Bermudas

Nacionalidad o Domicilio: Bermudas

Lugar de Constitución: Bermudas

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C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

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Número 79782747Bta

TP 74.295

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5

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Solicitud Internacional No. PCT/US2007/068292

Fecha Mayo 4, 2007

Publicación Internacional No. WO 2007/131201

Fecha Noviembre 15, 2007

6

**Título (54) COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA
SENDA DE HEDGEHOG**

Clasificación Internacional (51) C07D 213/75, C07D 401/04, C07D 405/12, C07D
409/12, C07D 413/04, C07D 295/135, C07D 295/26, C07D 239/49, A61K 31/4433,
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US

(32) Fecha

Mayo 5, 2006

(31) Número de
Solicitud

60/797,949

9

Comprobante de pago No. 08-

Fecha Noviembre 4 de 2008

10

ANEXOS☒

Comprobante de pago de la tasa de presentación de la solicitud.

☒

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso. Ver expediente No. 06-122179. Adjunto copia simple.

☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones.

☒

Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

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.

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTEFIRMA: C.C. 79.782.747 Btá T.P. 74.295

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PCT/US2007/068292



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4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 86,613
FECHA : NOVIEMBRE 4 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 411 PRESENTACION Folios: 184

***** C O N S *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	81240762	04/11/2008	2,519,000.00

***** 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	501,000.00
		TOTAL :	\$ 501,000.00

SDN: QUINIENTOS UN MIL PESOS

RESPONSABLE :

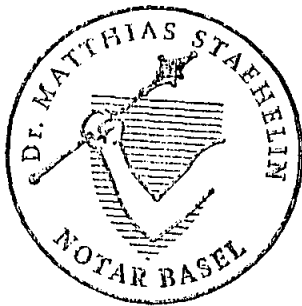
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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.

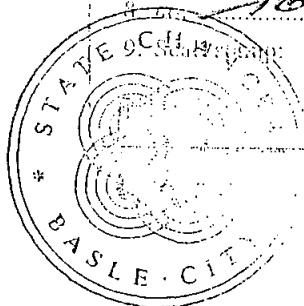
BASEL, this 20th (twentieth) day of November 2006 (twothousandandsix).



M. Staehelin, Notar

Leg.Prot.Nr. 1571 /2006

APOSTILLE (Hague Convention of October 5th, 1961)	
1. Country: Switzerland (CH) (Switzerland)	This official document is
2. signed by <i>Dr. Hillebrand</i>	
3. in his/her function <i>off. 1200</i>	
4. and certified <i>Staehelin</i>	
Certified 20. NOV. 2006	
5. in Basel (Basle)	6. on
7. by the State Chancery of the Canton of Basel-Stadt	
8. <i>10.11.2006/17894</i>	10. Signature: <i>Heidi Fischer</i>
	Heidi Fischer



OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

33842-CO-PCT

Power of Attorney

The undersigned,

domiciled in

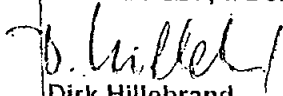
IRM LLC, a Delaware Limited Liability Company

'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.

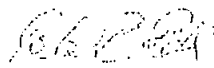
IRM LLC, a Delaware Limited Liability Company

Signature/Firma:



Dirk Hillebrand

Group Head Patents, MCD



Peter Roth

Snr. Patent Attorney

Date/Fecha: 08 November 2006

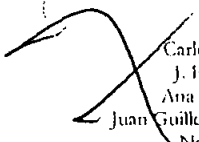
City/Country/Ciudad,País: Basel, CH

Poder

El suscrito,

domiciliado en

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.


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

6

APOSTILLA:	
(Convention de La Haye du 5 octobre 1961)	
1. País:	Suiza
<u>El presente documento público</u>	
2. Ha sido firmado por:	Dr. M. Staehelin
3. Actuando en calidad de:	Notario
4. Lleva el sello/estampilla de:	(Ilegible).
<u>Certificado</u>	
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 Ministerio de Justicia

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, Bermudà, 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

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C07D 295/135 (2006.01)

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

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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

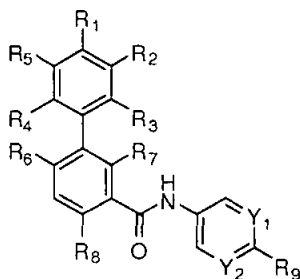
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(54) Title: COMPOUNDS AND COMPOSITIONS AS HEDGEHOG PATHWAY MODULATORS



I

(57) Abstract: The invention provides a method for modulating the activity of the hedgehog signaling pathway. In particular, the invention provides a method for inhibiting aberrant growth states resulting from phenotypes such as Ptc loss-of-function, hedgehog gain-of-function, smoothened gain-of-function or Gli gain-of-function, comprising contacting a cell with a sufficient amount of a compound of Formula I.

COMPOUNDS AND COMPOSITIONS AS HEDGEHOG PATHWAY MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Number 60/797,949, filed 5 May 2006. The full disclosure of this application is incorporated herein by reference in its entirety and for all purposes.

BACKGROUND

Field of the Invention

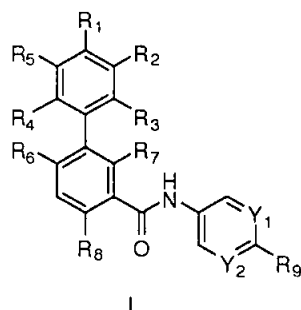
[0002] The invention provides a method for modulating the activity of the hedgehog signaling pathway. In particular, the invention provides a method for inhibiting aberrant growth states resulting from phenotypes such as Ptc loss-of-function, hedgehog gain-of-function, smoothened gain-of-function or Gli gain-of-function, comprising contacting a cell with a sufficient amount of a compound of Formula I.

Background of the Invention

[0002] During embryonic development, the hedgehog signaling pathway is essential for numerous processes such as the control of cell proliferation, differentiation and tissue patterning. The aberrant activity of the hedgehog signaling pathway, for example, as a result of enhanced activation, however may have pathological consequences. In this regard, activation of the hedgehog pathway in adult tissues can result in specific types of cancer that include, but are not limited to, cancers of the brain, muscle and skin, prostate, medulloblastoma, pancreatic adenocarcinomas and small-cell lung carcinomas. Enhanced activation of the hedgehog signaling pathway contributes to the pathology and/or symptomology of a number of diseases. Accordingly, molecules that modulate the activity of the hedgehog signaling pathway are useful as therapeutic agents in the treatment of such diseases.

Summary of the Invention

[0003] In one aspect, the present invention provides compounds of Formula I:



[0004] in which

[0005] Y_1 and Y_2 are independently selected from N and CR₁₀; wherein R₁₀ is selected from hydrogen, halo, C₁₋₆alkyl, halosubstituted-C₁₋₆alkyl, C₁₋₆alkoxy, halosubstituted-C₁₋₆alkoxy and -OXNR_{10a}R_{10b}; wherein R_{10a} and R_{10b} are independently selected from hydrogen and C₁₋₆alkyl;

[0006] R₁ is selected from cyano, halo, C₁₋₆alkyl, halosubstituted-C₁₋₆alkyl, C₁₋₆alkoxy, halosubstituted-C₁₋₆alkoxy, C₆₋₁₀aryl, dimethyl-amino, C₁₋₆alkyl-sulfanyl and C₃₋₆heterocycloalkyl optionally substituted with up to 2 C₁₋₆alkyl radicals;

[0007] R₂ and R₅ are independently selected from hydrogen, cyano, halo, C₁₋₆alkyl, halosubstituted-C₁₋₆alkyl, C₁₋₆alkoxy, halosubstituted-C₁₋₆alkoxy and dimethylamino;

[0008] R₃ and R₄ are independently selected from hydrogen, halo, cyano, C₁₋₆alkyl, halosubstituted-C₁₋₆alkyl, C₁₋₆alkoxy and halosubstituted-C₁₋₆alkoxy; or either R₁ and R₂ or R₁ and R₅ together with the phenyl to which they are both attached form C₅₋₁₀heteroaryl;

[0009] R₆ and R₇ are independently selected from hydrogen, C₁₋₆alkyl, halosubstituted-C₁₋₆alkyl, C₁₋₆alkoxy and halosubstituted-C₁₋₆alkoxy; with the proviso that R₆ and R₇ are not both hydrogen;

[0010] R₈ is selected from halo, C₁₋₆alkyl, halosubstituted-C₁₋₆alkyl, C₁₋₆alkoxy and halosubstituted-C₁₋₆alkoxy;

A

[0011] R_9 is selected from $-S(O)_2R_{11}$, $-C(O)R_{11}$, $-OR_{11}$, $-NR_{12a}R_{12b}$ and $-R_{11}$; wherein R_{11} is selected from aryl, heteroaryl, cycloalkyl and heterocycloalkyl; R_{12a} and R_{12b} are independently selected from C_{1-6} alkyl and hydroxy-substituted- C_{1-6} alkyl;

[0012] wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_9 can be optionally substituted with 1 to 3 radicals independently selected from C_{1-6} alkyl, halosubstituted- C_{1-6} alkyl, C_{1-6} alkoxy, halosubstituted- C_{1-6} alkoxy, C_{6-10} aryl- C_{0-4} alkyl, C_{5-10} heteroaryl- C_{0-4} alkyl, C_{3-12} cycloalkyl and C_{3-8} heterocycloalkyl;

[0013] wherein said aryl-alkyl substituent of R_9 is optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6} alkyl, halosubstituted- C_{1-6} alkyl, C_{1-6} alkoxy, halosubstituted- C_{1-6} alkoxy and methyl-piperazinyl; 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.

[0014] 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.

[0015] In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of the hedgehog pathway 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.

[0016] 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 hedgehog pathway activity, contributes to the pathology and/or symptomology of the disease.

[0017] 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.

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Definitions

[0018] "Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be either straight-chained or branched. C₁₋₄-alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0019] "Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl may be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group.

[0020] "Heteroaryl" is as defined for aryl above where one or more of the ring members is a heteroatom. For example C₅₋₁₀heteroaryl is a minimum of 5 members as indicated by the carbon atoms but that these carbon atoms can be replaced by a heteroatom. Consequently, C₅₋₁₀heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalyl, quinolyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc.

[0011] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C₃₋₁₀cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

[0012] "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, C₁₋₄alkyl or a nitrogen protecting group. For example, C₃₋₈heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, pyrrolidinyl-2-one, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxo-8-aza-spiro[4.5]dec-8-yl, thiomorpholino, sulfanomorpholino, sulfonomorpholino, etc.

[0013] "Halogen" (or halo) preferably represents chloro or fluoro, but may also be bromo or iodo.



[0014] "Hedgehog gain-of-function" refers to an aberrant modification or mutation of a Ptc gene, hedgehog gene, or smoothened gene, or a decrease (or loss) in the level of expression of such a gene, which results in a phenotype which resembles contacting a cell with a hedgehog protein, e.g., aberrant activation of a hedgehog pathway. The gain-of-function may include a loss of the ability of the Ptc gene product to regulate the level of expression of Gli genes, e.g., Gli1, Gli2, and Gli3. The term 'hedgehog gain-of-function' is also used herein to refer to any similar cellular phenotype (e.g., exhibiting excess proliferation) which occurs due to an alteration anywhere in the hedgehog signal transduction pathway, including, but not limited to, a modification or mutation of hedgehog itself. For example, a tumor cell with an abnormally high proliferation rate due to activation of the hedgehog signaling pathway would have a 'hedgehog gain-of-function' phenotype, even if hedgehog is not mutated in that cell.

[0015] "Patched loss-of-function" refers to an aberrant modification or mutation of a Ptc gene, or a decreased level of expression of the gene, which results in a phenotype which resembles contacting a cell with a hedgehog protein, e.g., aberrant activation of a hedgehog pathway. The loss-of-function may include a loss of the ability of the Ptc gene product to regulate the level of expression of Gli genes, e.g., Gli1, Gli2 and Gli3.

[0016] "Gli gain-of-function" refers to an aberrant modification or mutation of a Gli gene, or an increased level of expression of the gene, which results in a phenotype which resembles contacting a cell with a hedgehog protein, e.g., aberrant activation of a hedgehog pathway.

[0017] "Smoothened gain-of-function" refers to an aberrant modification or mutation of a Smo gene, or an increased level of expression of the gene, which results in a phenotype which resembles contacting a cell with a hedgehog protein, e.g., aberrant activation of a hedgehog pathway.

[0018] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

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[0019] The present invention relates to the discovery that signal transduction pathways regulated by hedgehog, patched (Ptc), gli and/or smoothened can be modulated by compounds of Formula I.

Description of Preferred Embodiments

[0020] In one embodiment, with respect to compounds of Formula I, Y_1 and Y_2 are selected from N and CR_{10} ; wherein R_{10} is selected from hydrogen, methyl, fluoro, chloro, bromo, dimethylamino-ethoxy and trifluoromethyl; R_6 and R_7 are independently selected from hydrogen methyl, chloro, fluoro, bromo, trifluoromethyl and methoxy; with the proviso that R_6 and R_7 are not both hydrogen; and R_8 is selected from fluoro, chloro, methyl and trifluoromethyl.

[0020] In another embodiment, R_1 is selected from cyano, chloro, fluoro, methyl, ethyl, t-butyl, propyl, isobutyl, isopropyl, isopropoxy, butoxy, methoxy, dimethyl-amino, ethoxy, methyl-sulfanyl, phenyl, trifluoromethyl, trifluoromethoxy and piperazinyl optionally substituted with up to 2 methyl radicals; R_2 and R_5 are independently selected from hydrogen, chloro, fluoro, cyano, methyl, trifluoromethyl, isopropoxy, methoxy, ethoxy, trifluoromethoxy and dimethylamino; and R_3 and R_4 are independently selected from hydrogen, chloro, methyl, methoxy and cyano; or either R_1 and R_2 or R_1 and R_5 together with the phenyl to which they are both attached form quinoxaliny.

[0021] In another embodiment, R_9 is selected from $-S(O)_2R_{11}$, $-OR_{11}$, $-C(O)R_{11}$, $-NR_{12a}R_{12b}$ and $-R_{11}$; wherein R_{11} is selected from thiomorpholino, sulfonmorpholino, sulfanomorpholino, morpholino, cyclohexyl, phenyl, azepan-1-yl, 2-oxopiperazin-1-yl, 1,4-oxazepan-4-yl, piperidin-1-yl, tetrahydro-2H-pyran-4-yl, piperidin-3-yl, piperazinyl, pyrrolidinyl and 1,4-diazepan-1-yl; R_{12a} and R_{12b} are independently selected from isobutyl and hydroxy-ethyl; wherein said thiomorpholino, sulfonmorpholino, sulfanomorpholino, morpholino, cyclohexyl, phenyl, azepan-1-yl, 2-oxopiperazin-1-yl, 1,4-oxazepan-4-yl, piperidin-1-yl, tetrahydro-2H-pyran-4-yl, piperidin-3-yl, piperazinyl, pyrrolidinyl or 1,4-diazepan-1-yl of R_9 can be optionally substituted with 1 to 3 radicals independently selected from methyl, ethyl, methoxy, benzyl, thienyl-methyl, pyridinyl-methyl, benzo[d][1,3]dioxol-6-yl and 2,3-dihydrobenzo[b][1,4]dioxin-7-yl; wherein said phenyl or benzyl substituent of R_9 is

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optionally substituted with 1 to 3 radicals independently selected from methoxy, ethoxy, methyl-piperazinyl, methyl, trifluoromethoxy, chloro, fluoro and trifluoromethyl.

[0022] Preferred compounds of Formula I are selected from 4'-cyano-6-methyl-biphenyl-3-carboxylic acid [4-(morpholine-4-sulfonyl)-phenyl]-amide, 4'-cyano-6-methyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Methoxy-2-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Methoxy-2-methyl-biphenyl-3-carboxylic acid (4-cyclohexyl-phenyl)-amide, 4'-Methoxy-2-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Dimethylamino-2-methyl-biphenyl-3-carboxylic acid (4-cyclohexyl-phenyl)-amide, 4'-Dimethylamino-2-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 6-Chloro-4'-dimethylamino-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 6-Chloro-4'-dimethylamino-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 6-Chloro-4'-dimethylamino-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Chloro-4'-methoxy-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 6-Chloro-4'-methoxy-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 6-Chloro-4'-methoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Chloro-4'-methoxy-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Dimethylamino-6-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Dimethylamino-6-methyl-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 4'-Dimethylamino-6-methyl-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Ethoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-4'-methylsulfanyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-

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Dimethylamino-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-[1,1';4',1'']terphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Chloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 2',4'-Dichloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 2'-Chloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Chloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3',4'-Dichloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Chloro-6-methyl-4'-trifluoromethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6,4'-Dimethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Ethyl-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-tert-Butyl-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-4'-propyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Isobutyl-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Isopropyl-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6,2',6'-Trimethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6,2',3'-Trimethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-4'-trifluoromethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-3'-trifluoromethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-3', 5'-bistrifluoromethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Isopropoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Ethoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 2',6'-Dimethoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-3'-trifluoromethoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 3'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-(2-Dimethylamino-ethoxy)-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 3'-Dimethylamino-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-Fluoro-6-methyl-biphenyl-3-

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carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 3'-Fluoro-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 2'-Fluoro-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4-Methyl-N-(4-morpholin-4-yl-phenyl)-3-quinoxalin-6-yl-benzamide, 6-Methyl-4'-(4-methyl-piperazin-1-yl)-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 2'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 3'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3-bromo-4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3-methyl-4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-3-trifluoromethyl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-cyclohexyl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid biphenyl-4-ylamide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4'-methoxy-biphenyl-4-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [4-(4-benzyl-piperazin-1-yl)-phenyl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [4-(pyrrolidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-methoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Cyano-2-methoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Fluoro-4'-methoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Isopropoxy-6-methyl-

biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Butoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Chloro-4'-methoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Methoxy-6,3'-dimethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-fluoro-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 6-Bromo-4'-cyano-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-benzyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-thiophen-3-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Methoxy-2-methyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 2-Methyl-4'-trifluoromethyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-2-fluoro-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-trifluoromethyl-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-4-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-3-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2,6-dimethoxy-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-ethoxy-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (6-{4-[2-(4-methyl-piperazin-1-yl)-benzyl]-[1,4]diazepan-1-yl]-pyridin-3-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-methoxy-2,3-dimethyl-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-2-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic



acid [6-(4-benzo[1,3]dioxol-4-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-trifluoromethoxy-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-dimethylamino-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-chloro-5-trifluoromethyl-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2,3-difluoro-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-chloro-4-fluoro-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2,6-difluoro-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 2-Chloro-4'-cyano-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-trifluoromethyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 2-Chloro-4'-cyano-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-ethyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(3-fluoro-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-trifluoromethoxy-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(3-chloro-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-isobutyl-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-tert-butyl-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(7-methoxy-benzo[1,3]dioxol-5-ylmethyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-benzyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-3-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-difluoromethoxy-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-cyano-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-quinolin-5-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-4-ylmethyl-piperazin-1-yl)-

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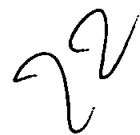
pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-2-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-imidazol-1-yl-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(3-cyano-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-isoquinolin-5-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-amide, (R)-2-methyl-N-(6-(2-methylmorpholino)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 4'-cyano-2-methyl-N-(6-sulfonylmorpholinopyridin-3-yl)biphenyl-3-carboxamide, (S)-4'-cyano-2-methyl-N-(6-(2-methylmorpholino)pyridin-3-yl)biphenyl-3-carboxamide, (R)-6-chloro-N-(6-(2-methylmorpholino)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 4'-cyano-2-methyl-N-(6-sulfinylmorpholinopyridin-3-yl)biphenyl-3-carboxamide, 4'-cyano-N-(6-(diisobutylamino)pyridin-3-yl)-2-methylbiphenyl-3-carboxamide, 4'-cyano-N-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-2-methylbiphenyl-3-carboxamide, N-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-2-methyl-4'-(trifluoromethyl)biphenyl-3-carboxamide, N-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, N-(2-(bis(2-hydroxyethyl)amino)pyrimidin-5-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(tetrahydro-2H-pyran-4-yloxy)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, N-(5-chloro-6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, N-(6-((2R,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, N-(6-(4-ethylpiperazine-1-carbonyl)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(2-oxopiperazin-1-yl)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(2-oxo-4-(pyridin-4-ylmethyl)piperazin-1-yl)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(1-(pyridin-4-ylmethyl)piperidin-3-yl)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, N-(6-(1-ethylpiperidin-3-yl)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-

carboxamide and N-(6-((2R,6S)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide.

[0023] It is, therefore, specifically contemplated that compounds of Formula I which interfere with aspects of hedgehog, Ptc, or smoothened signal transduction activity will likewise be capable of inhibiting proliferation (or other biological consequences) in normal cells and/or cells having a patched loss-of-function phenotype, a hedgehog gain-of-function phenotype, a smoothened gain-of-function phenotype or a Gli gain-of-function phenotype. Thus, it is contemplated that in certain embodiments, these compounds may be useful for inhibiting hedgehog activity in normal cells, e.g., which do not have a genetic mutation that activates the hedgehog pathway. In preferred embodiments, the compounds are capable of inhibiting at least some of the biological activities of hedgehog proteins, preferably specifically in target cells.

[0024] Thus, the methods of the present invention include the use of compounds of Formula I which agonize Ptc inhibition of hedgehog signaling, such as by inhibiting activation of smoothened or downstream components of the signal pathway, in the regulation of repair and/or functional performance of a wide range of cells, tissues and organs, including normal cells, tissues, and organs, as well as those having the phenotype of Ptc loss-of-function, hedgehog gain-of-function, smoothened gain-of-function or Gli gain-of-function. For instance, the subject method has therapeutic and cosmetic applications ranging from regulation of neural tissues, bone and cartilage formation and repair, regulation of spermatogenesis, regulation of smooth muscle, regulation of lung, liver and other organs arising from the primitive gut, regulation of hematopoietic function, regulation of skin and hair growth, etc. Moreover, the subject methods can be performed on cells which are provided in culture (in vitro), or on cells in a whole animal (in vivo).

[0025] In another embodiment, the subject method can be to treat epithelial cells having a phenotype of Ptc loss-of-function, hedgehog gain-of-function, smoothened gain-of-function or Gli gain-of-function. For instance, the subject method can be used in treating or preventing basal cell carcinoma or other hedgehog pathway-related disorders.



[0026] In certain embodiments, a compound of Formula I can inhibit activation of a hedgehog pathway by binding to smoothened or its downstream proteins. In certain embodiments, a subject antagonist may inhibit activation of a hedgehog pathway by binding to patched.

[0027] In another preferred embodiment, the subject method can be used as part of a treatment regimen for malignant medulloblastomas and other primary CNS malignant neuroectodermal tumors.

[0028] In another aspect, the present invention provides pharmaceutical preparations comprising, as an active ingredient, a hedgehog signaling modulator such as a compound of Formula I, a Ptc agonist, a smoothened antagonist, or downstream hedgehog pathway protein antagonist such as described herein, formulated in an amount sufficient to inhibit, in vivo, proliferation or other biological consequences of Ptc loss-of-function, hedgehog gain-of-function, smoothened gain-of-function or Gli gain-of-function.

[0029] The subject treatments using a compound of Formula I, patched agonists, smoothened antagonists, or downstream hedgehog pathway protein antagonists can be effective for both human and animal subjects. Animal subjects to which the invention is applicable extend to both domestic animals and livestock, raised either as pets or for commercial purposes. Examples are dogs, cats, cattle, horses, sheep, hogs, and goats.

Pharmacology and Utility

[0030] The present invention makes available methods and compounds for inhibiting activation of the hedgehog signaling pathway, e.g., to inhibit aberrant growth states resulting from phenotypes such as Ptc loss-of-function, hedgehog gain-of-function, smoothened gain-of-function or Gli gain-of-function, comprising contacting the cell with a compound of Formula I, in a sufficient amount to agonize a normal Ptc activity, antagonize a normal hedgehog activity, antagonize smoothened activity, or antagonize Gli activity e.g., to reverse or control the aberrant growth state.

[0031] Members of the Hedgehog family of signaling molecules mediate many important short- and long-range patterning processes during vertebrate development. Pattern formation is the activity by which embryonic cells form



ordered spatial arrangements of differentiated tissues. The physical complexity of higher organisms arises during embryogenesis through the interplay of cell-intrinsic lineage and cell-extrinsic signaling. Inductive interactions are essential to embryonic patterning in vertebrate development from the earliest establishment of the body plan, to the patterning of the organ systems, to the generation of diverse cell types during tissue differentiation. The effects of developmental cell interactions are varied: responding cells are diverted from one route of cell differentiation to another by inducing cells that differ from both the uninduced and induced states of the responding cells (inductions). Sometimes cells induce their neighbors to differentiate like themselves (homeogenetic induction); in other cases a cell inhibits its neighbors from differentiating like itself. Cell interactions in early development may be sequential, such that an initial induction between two cell types leads to a progressive amplification of diversity. Moreover, inductive interactions occur not only in embryos, but in adult cells as well, and can act to establish and maintain morphogenetic patterns as well as induce differentiation.

[0032] The vertebrate family of hedgehog genes includes three members that exist in mammals, known as Desert (Dhh), Sonic (Shh) and Indian (Ihh) hedgehogs, all of which encode secreted proteins. These various Hedgehog proteins consist of a signal peptide, a highly conserved N-terminal region, and a more divergent C-terminal domain. Biochemical studies have shown that autoproteolytic cleavage of the Hh precursor protein proceeds through an internal thioester intermediate which subsequently is cleaved in a nucleophilic substitution. It is likely that the nucleophile is a small lipophilic molecule which becomes covalently bound to the C-terminal end of the N-peptide, tethering it to the cell surface. The biological implications are profound. As a result of the tethering, a high local concentration of N-terminal Hedgehog peptide is generated on the surface of the Hedgehog producing cells. It is this N-terminal peptide which is both necessary and sufficient for short- and long-range Hedgehog signaling activities.

[0033] An inactive Hedgehog signaling pathway is where the transmembrane protein receptor Patched (Ptc) inhibits the activity of Smoothened (Smo), a seven transmembrane protein. The transcription factor Gli, a downstream

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component of Hh signaling, is prevented from entering the nucleus through interactions with cytoplasmic proteins, including Fused and Suppressor of fused (Sufu). As a consequence, transcriptional activation of Hedgehog target genes is repressed. Activation of the pathway is initiated through binding of any of the three mammalian ligands (Dhh, Shh or Ihh) to Ptc. Ligand binding results in a reversal of the repression of Smo, thereby activating a cascade that leads to the translocation of the active form of the transcription factor Gli to the nucleus. Nuclear Gli activates target gene expression, including Ptc and Gli itself.

[0034] Increased levels of Hedgehog signaling are sufficient to initiate cancer formation and are required for tumor survival. These cancers include, but are not limited to, prostate cancer ("Hedgehog signalling in prostate regeneration, neoplasia and metastasis", Karhadkar SS, Bova GS, Abdallah N, Dhara S, Gardner D, Maitra A, Isaacs JT, Berman DM, Beachy PA., Nature. 2004 Oct 7;431(7009):707-12; "Inhibition of prostate cancer proliferation by interference with SONIC HEDGEHOG-GLI1 signaling", Sanchez P, Hernandez AM, Stecca B, Kahler AJ, DeGuentie AM, Barrett A, Beyna M, Datta MW, Datta S, Ruiz i Altaba A., Proc Natl Acad Sci U S A. 2004 Aug 24;101(34):12561-6), breast cancer ("Hedgehog signaling pathway is a new therapeutic target for patients with breast cancer", Kubo M, Nakamura M, Tasaki A, Yamanaka N, Nakashima H, Nomura M, Kuroki S, Katano M., Cancer Res. 2004 Sep 1;64(17):6071-4), medulloblastoma ("Medulloblastoma growth inhibition by hedgehog pathway blockade", Berman DM, Karhadkar SS, Hallahan AR, Pritchard JJ, Eberhart CG, Watkins DN, Chen JK, Cooper MK, Taipale J, Olson JM, Beachy PA., Science. 2002 Aug 30;297(5586):1559-61), basal cell carcinoma ("Identification of a small molecule inhibitor of the hedgehog signaling pathway: effects on basal cell carcinoma-like lesions", Williams JA, Guicherit OM, Zaharian BI, Xu Y, Chai L, Wichterle H, Kon C, Gatchalian C, Porter JA, Rubin LL, Wang FY., Proc Natl Acad Sci U S A. 2003 Apr 15;100(8):4616-21; "Activating Smoothed mutations in sporadic basal-cell carcinoma", Xie J, Murone M, Luoh SM, Ryan A, Gu Q, Zhang C, Bonifas JM, Lam CW, Hynes M, Goddard A, Rosenthal A, Epstein EH Jr, de Sauvage FJ., Nature. 1998 Jan 1;391(6662):90-2), pancreatic cancer ("Hedgehog is an early and late mediator

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[0035] 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:

[0036] 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.

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[0037] 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.

[0038] 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 immunomodulatory or anti-inflammatory substances or other anti-tumor therapeutic agents. 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.

[0039] 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.

[0040] 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.

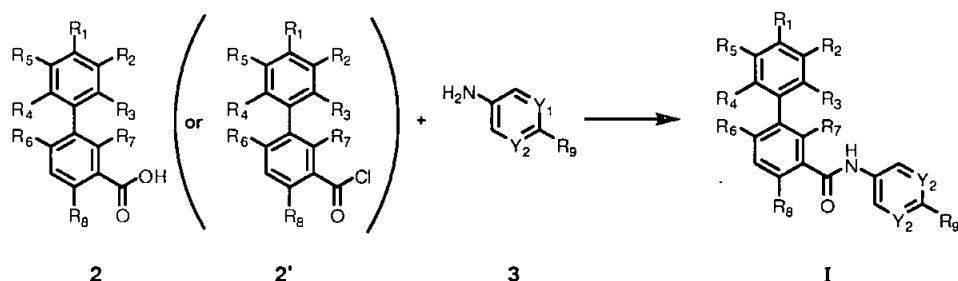
[0041] The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a 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

[0042] 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.

[0043] Compounds of Formula I can be prepared by proceeding as in the following Reaction Scheme I:

Reaction Scheme I:



in which Y_1 , Y_2 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are as defined for Formula I in the Summary of the Invention. A compound of Formula I can be prepared by reacting a compound of formula 2 (or 2') with a compound of formula 3 in the presence of a suitable solvent (e.g., dichloromethane, *N,N*-dimethylformide or the like), in a temperature range of about -20 to about 100°C. The reaction can take up to about 20 hours to complete.

[0044] Detailed examples of the synthesis of compounds of Formula I can be found in the Examples, *infra*.

Additional Processes for Making Compounds of the Invention

[0045] 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.

[0046] Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

[0047] 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 form, 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.).

[0048] 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.

[0049] 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).

[0050] 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.

[0051] 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.

[0052] 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.

[0053] In summary, the compounds of Formula I can be made by a process, which involves:

- (a) those of reaction scheme I; and
- (b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;
- (c) optionally converting a salt form of a compound of the invention to a non-salt form;
- (d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;
- (e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;
- (f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

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(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.

[0055] 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.

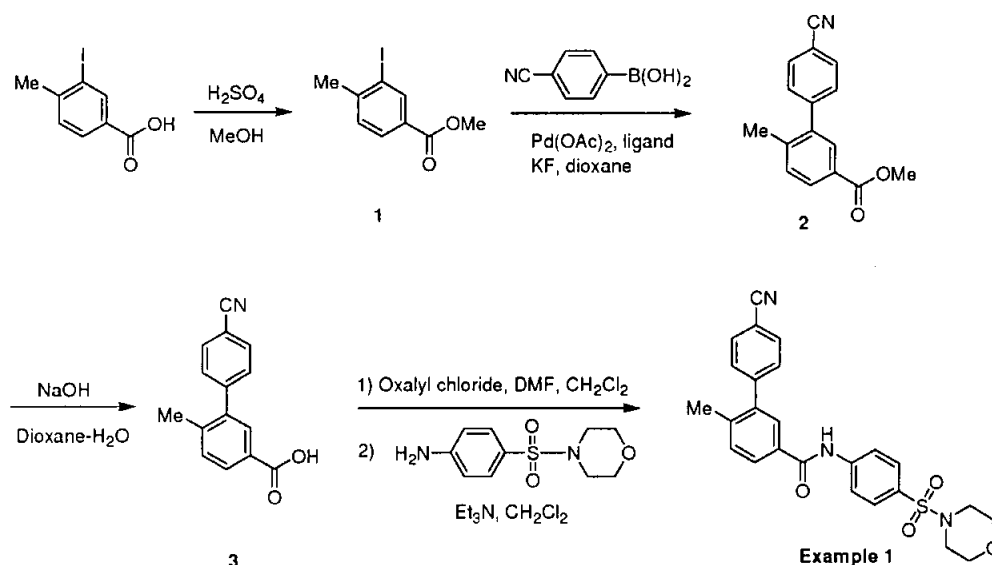
[0056] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

[0057] The present invention is further exemplified, but not limited, by the following example that illustrates the preparation of compounds of Formula I according to the invention.

Example 1

4'-cyano-6-methyl-biphenyl-3-carboxylic acid [4-(morpholine-4-sulfonyl)-phenyl]-amide



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[0058] Step 1: To a solution of 3-iodo-4-methyl-benzoic acid (10.0 g, 38.2 mmol) in methanol (70 ml) is added concentrated sulfuric acid (0.5 ml). The reaction mixture is heated at 70°C for 48 hours, cooled to room ambient temperature and then concentrated. After that, ethyl acetate (100 ml) and aqueous NaHCO₃ (saturated, 100 ml) solution are added to the residue. The organic layer is separated and washed again with aqueous NaHCO₃ (saturated, 100 ml) solution. The organic layer is separated, dried over anhydrous Na₂SO₄ and concentrated to yield 3-iodo-4-methyl-benzoic acid methyl ester 1. It is used without further purification in the next step. ¹H NMR (400 MHz, DMSO-d₆) δ 8.31 (s, 1 H), 7.87 (d, 1 H, J = 8.4 Hz), 7.48 (d, 1 H, J = 8.4 Hz), 3.85 (s, 3 H), 3.35 (s, 3H); LC-MS m/z: 277.0 (M+1).

[0059] Step 2: To a round-bottom flask containing 3-iodo-4-methyl-benzoic acid methyl ester (1.38 g, 5.00 mmol), 4-cyanophenylboronic acid (1.10 g, 7.48 mmol), palladium acetate (168 mg, 0.748 mmol), 2-(dicyclohexylphosphino)biphenyl (0.526 g, 1.50 mmol) and potassium fluoride (0.870 g, 15.0 mmol) is added anhydrous 1,4-dioxane (15 ml). The flask is purged with argon and sealed. The mixture is stirred at 130°C for 18 hours, cooled to ambient temperature and then water (20 ml) and ethyl acetate (20 ml) are added. Solid is removed under vacuum filtration. The filtrate is extracted with EtOAc (20 ml x 2). The organic layers are combined, washed with aqueous HCl (5%, 20 ml) and saturated NaHCO₃ (20 ml). It is dried over MgSO₄, and concentrated. The residue is purified by silica gel column chromatography (EtOAc/Hexane, gradient) to give 4'-cyano-6-methyl-biphenyl-3-carboxylic acid methyl ester 2; LC-MS m/z: 252.1 (M+1).

[0060] Step 3: To a solution of 4'-cyano-6-methyl-biphenyl-3-carboxylic acid methyl ester 2 (2.56 g, 10.3 mmol) in 1,4-dioxane-H₂O (1:1 mixture, 20 ml) is added NaOH (1.22 g, 30.2 mmol). The reaction is stirred at ambient temperature for 24 hours. To this mixture is added aqueous HCl (1 N, 36 ml) and it is then extracted with ethyl acetate (40 ml x 3). The organic layers are combined, dried over anhydrous Na₂SO₄. The solvent is removed. The solid obtained is washed with small amount of

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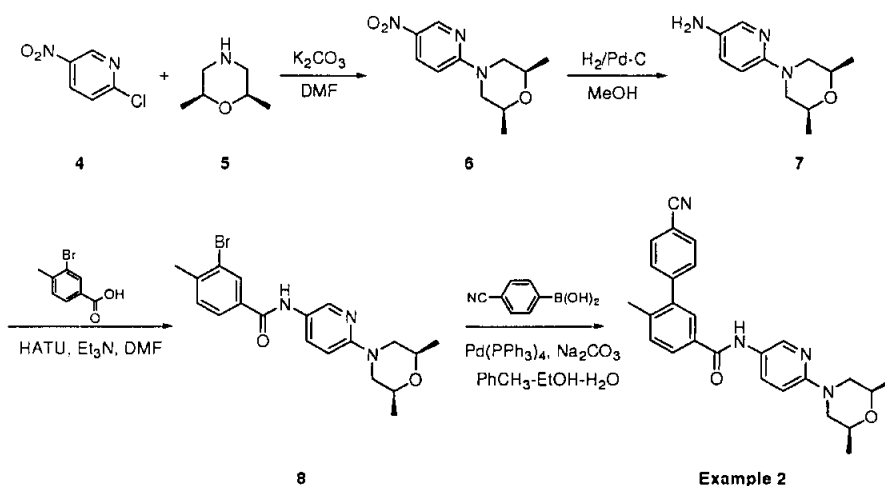
acetonitrile and air dried to give 4'-cyano-6-methyl-biphenyl-3-carboxylic acid 3: ^1H NMR (DMSO- d_6) δ 7.94 (d, 2 H, $J = 8.0$ Hz), 7.84 (dd, 1 H, $J_1 = 8.4$ Hz, $J_2 = 1.2$ Hz), 7.75 (d, 1 H, $J = 1.2$ Hz), 7.61 (d, 2 H, $J = 8.0$ Hz), 7.48 (d, 1 H, $J = 8.4$ Hz), 2.29 (s, 3 H); LC-MS m/z 238.1 (M+1).

[0061] Step 4: To a suspension of 4'-cyano-6-methyl-biphenyl-3-carboxylic acid 3 (40 mg, 0.17 mmol) in anhydrous methylene chloride (5 ml) is added 2 drops of DMF. Then oxalyl chloride (32 mg, 22 μl , 0.25 mmol) is added. The mixture is stirred at ambient temperature until it turns clear. After that, it is concentrated, re-dissolved in anhydrous methylene chloride (3 ml), and added to a solution of 4-(morpholine-4-sulfonyl)-phenylamine (61 mg, 0.25 mmol) and triethylamine (34 mg, 47 μl , 0.33 mmol) in methylene chloride (2 ml). The mixture is stirred for 2 hours, concentrated and the residue is purified by preparative mass triggered HPLC (C_{18} column, eluted with $\text{CH}_3\text{CN-H}_2\text{O}$ containing 0.05% TFA) to give 4'-cyano-6-methyl-biphenyl-3-carboxylic acid [4-(morpholine-4-sulfonyl)-phenyl]-amide: ^1H NMR (DMSO- d_6) δ 10.64 (s, 1 H), 8.07 (d, 2 H, $J = 8.8$ Hz), 7.97 (d, 2 H, $J = 8.4$ Hz), 7.95 (d, 1 H, $J = 8.8$ Hz), 7.89 (s, 1 H), 7.43 (d, 2 H, $J = 8.4$ Hz), 7.67 (d, 2 H, $J = 8.8$ Hz), 7.53 (d, 2 H, $J = 8.8$ Hz), 3.63 (m, 4 H), 2.84 (m, 4 H) 2.32 (s, 3 H); LC-MS m/z : 462.1 (M+1).

Example 2

4'-cyano-6-methyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide

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[0062] Step 1: To a solution of 2-chloro-5-nitro-pyridine **4** (2.38 g, 15 mmol) and *cis*-2,6-dimethylmorpholine (1.73 g, 15 mmol) is added K_2CO_3 (4.14 g, 30 mmol). The mixture was heated at 50°C overnight. After concentration, the residue is partitioned between EtOAc and water. The EtOAc layer is dried over anhydrous Na_2SO_4 and concentrated to give crude product **6** as a yellow solid. The crude product is used directly in next step without further purification. LC-MS m/z : 238.1 (M+1).

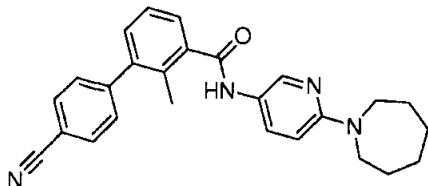
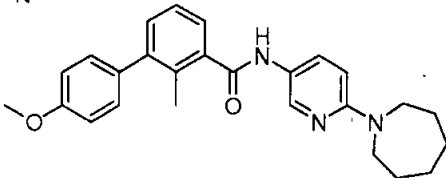
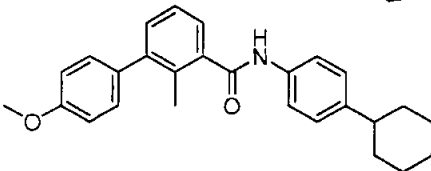
[0063] Step 2: The above crude material **6** is hydrogenated in the presence of Pd-C (0.2 g) in MeOH (100 mL) under hydrogen over 10 h. The suspension is filtered through celite and the filtrate is concentrated to give the crude product **7** as a dark brown oil which is used directly in the next step without further purification. LC-MS m/z : 208.1 (M+1).

[0064] Step 3: To a solution of 3-bromo-4-methyl benzoic acid (108 mg, 0.5 mmol), 6-(2,6-Dimethyl-morpholin-4-yl)-pyridin-3-ylamine **7** (104 mg, 0.5 mmol), and HATU (190 mg, 0.5 mmol) in dry DMF (5 mL) is added triethylamine (139 μ L, 1.0 mmol) dropwise. The resulting mixture is stirred at room temperature for 2 h. After concentration, the residue is partitioned between EtOAc and water. The organic layer is dried and concentrated to give the crude product. The final compound is purified by flash column chromatography using 50% EtOAc in hexane as eluent to give **8** as a white solid. LC-MS m/z : 404.1 (M+1).

35

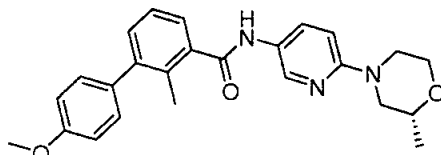
[0065] Step 4: A mixture of 4-cyanophenyl boronic acid (18 mg, 0.12 mmol), 3-bromo-N-[6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-4-methyl-benzamide **8** (40 mg, 0.1 mmol), Pd(PPh₃)₄ (11 mg, 0.01 mmol), and Na₂CO₃ (42 mg, 0.4 mmol) in a combined solvent system of toluene (0.2 mL) and water (0.2 mL) and ethanol (0.05 mL) is heated at 140°C under microwave irradiation for 30 min. The reaction mixture is diluted with EtOAc and water. The aqueous layer is extracted with EtOAc. The combined organic layer is washed with brine and concentrated to give the crude product which is purified by preparative mass triggered HPLC (C₁₈ column, eluted with CH₃CN-H₂O containing 0.05% TFA) to give 4'-cyano-6-methyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide. LC-MS *m/z*: 427.2 (M+1).

[0066] 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.

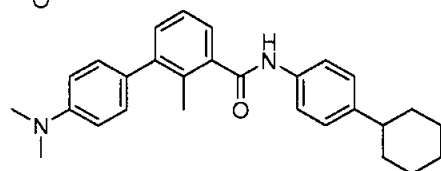
Table 1		
Compound Number	Structure	Physical Data
3		MS (<i>m/z</i>) LC-MS <i>m/z</i> 411.2 (M+1).
4		LC-MS <i>m/z</i> 416.2 (M+1).
5		LC-MS <i>m/z</i> 400.2 (M+1).

36

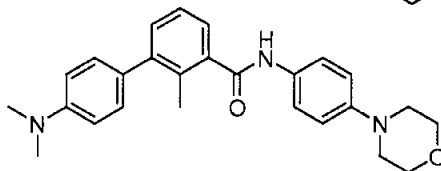
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LC-MS m/z
418.2 (M+1).

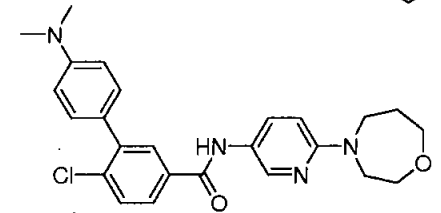
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LC-MS m/z
413.2 (M+1).

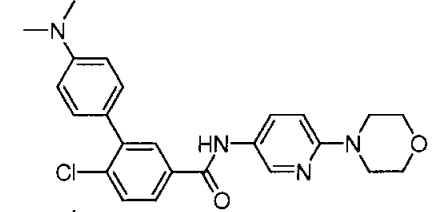
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LC-MS m/z
416.2 (M+1).

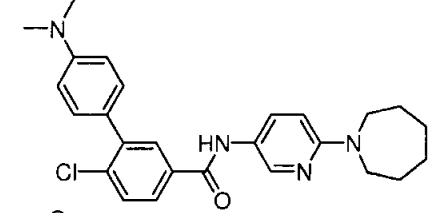
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LC-MS m/z
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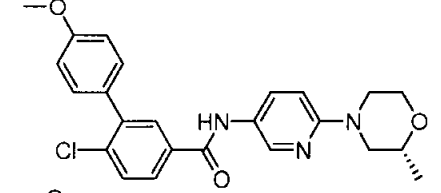
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437.2 (M+1).

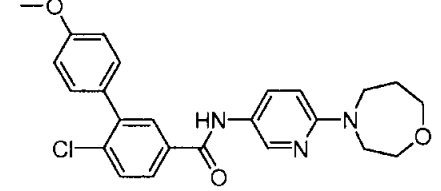
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LC-MS m/z
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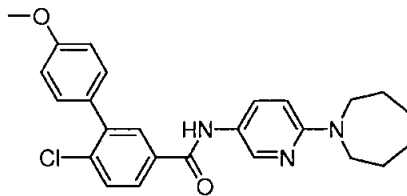
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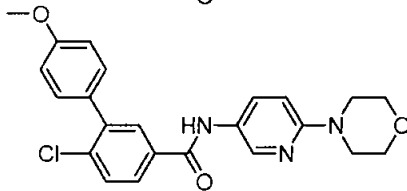
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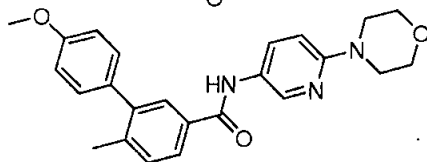
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436.2 (M+1).

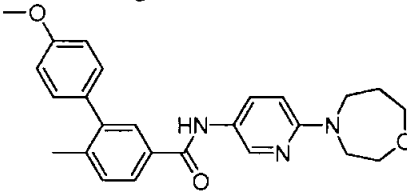
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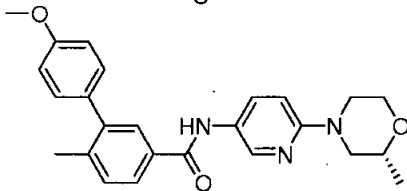
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LC-MS m/z
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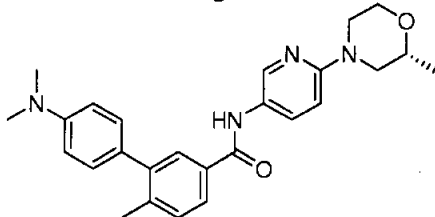
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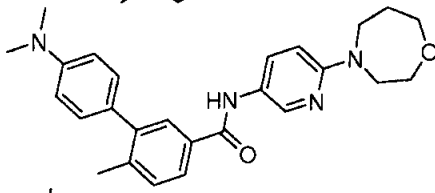
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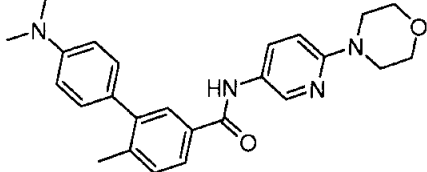
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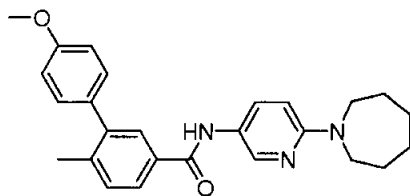
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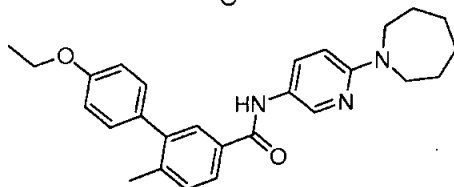
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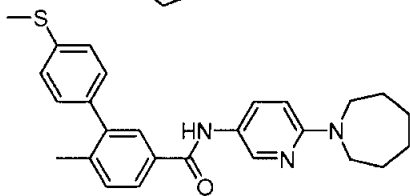
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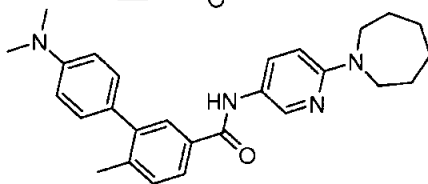
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LC-MS m/z
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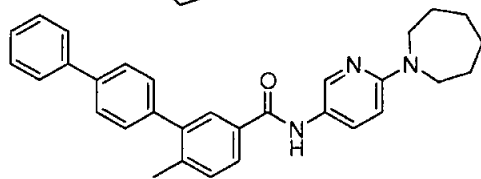
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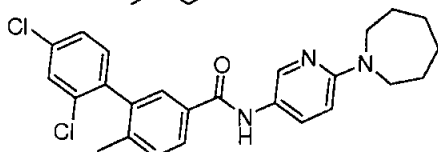
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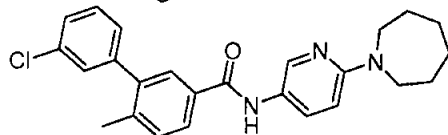
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LC-MS m/z
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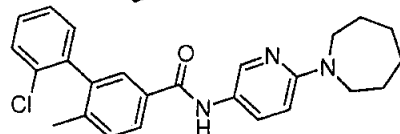
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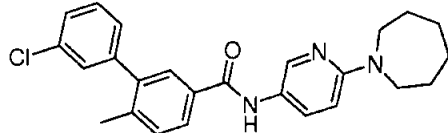
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LC-MS m/z
420.2 (M+1).

29

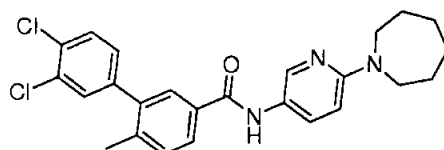
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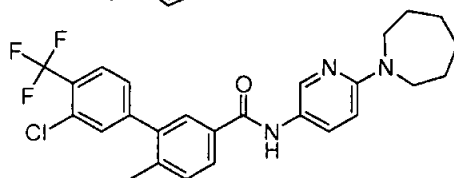
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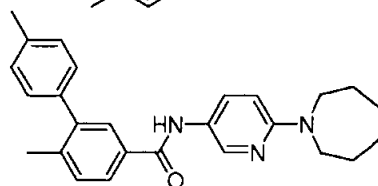
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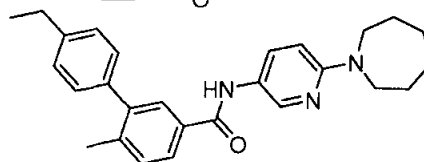
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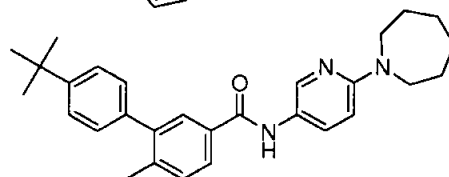
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LC-MS m/z
400.2 (M+1).

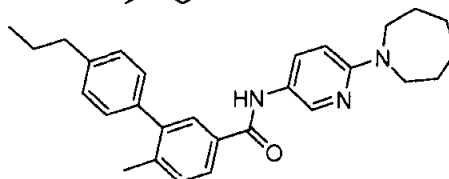
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LC-MS m/z
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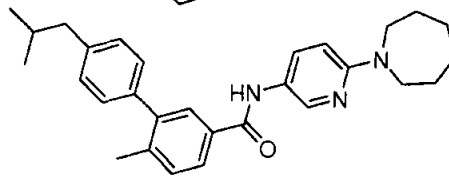
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LC-MS m/z
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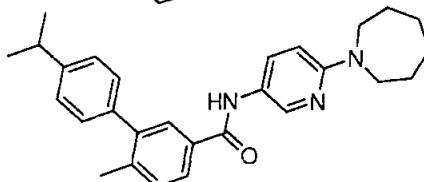
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LC-MS m/z
428.2 (M+1).

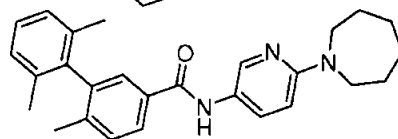
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LC-MS m/z
442.2 (M+1).

38

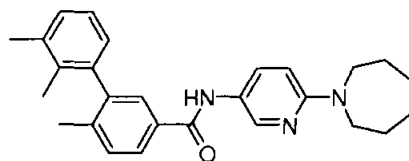
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428.2 (M+1).

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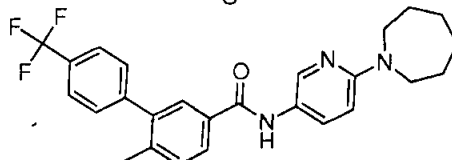
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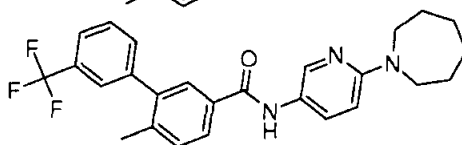
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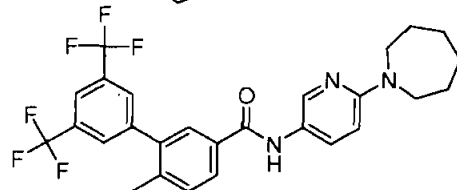
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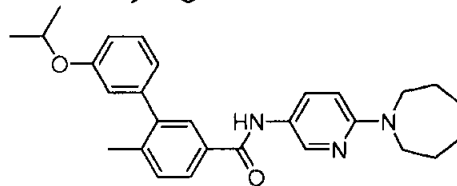
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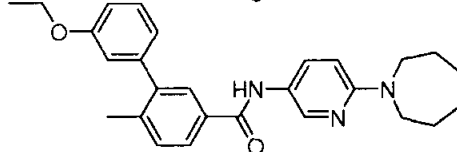
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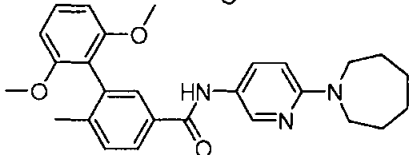
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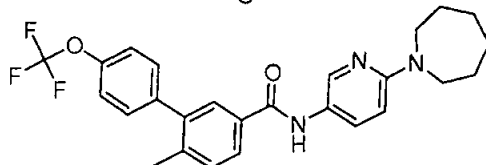
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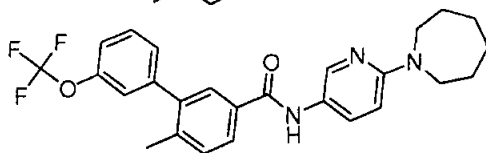
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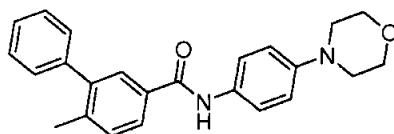
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LC-MS m/z
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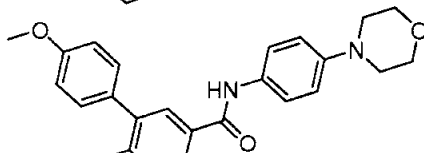
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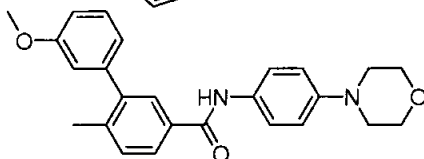
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LC-MS m/z
373.2 (M+1).

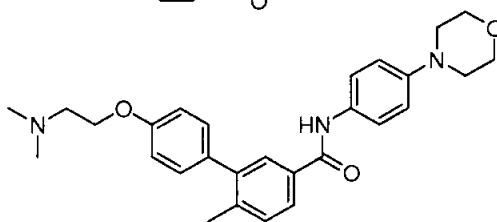
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403.2 (M+1).

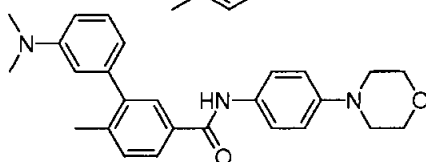
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403.2 (M+1).

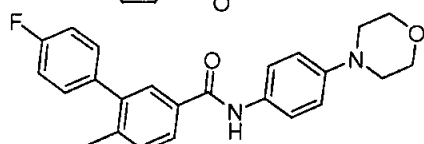
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LC-MS m/z
460.2 (M+1).

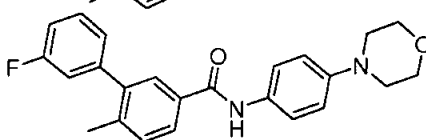
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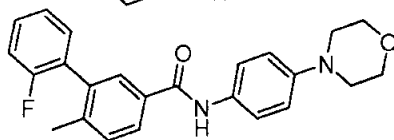
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391.2 (M+1).

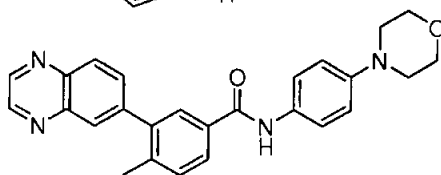
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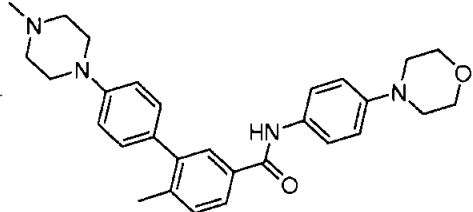
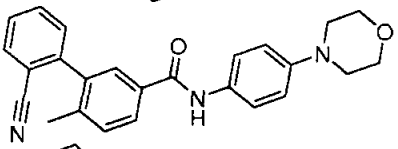
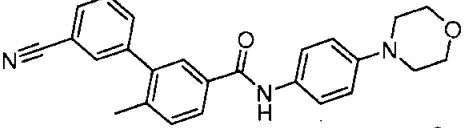
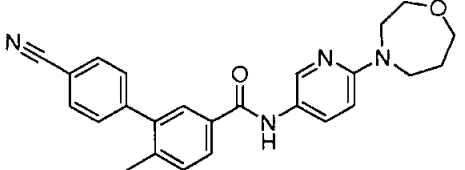
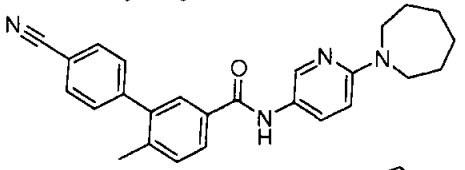
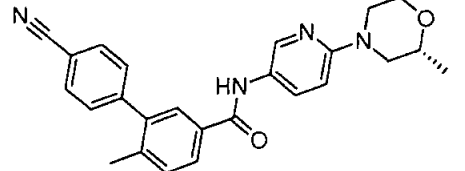
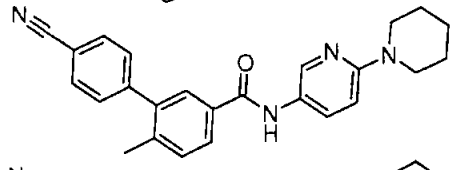
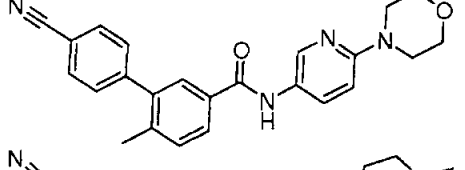
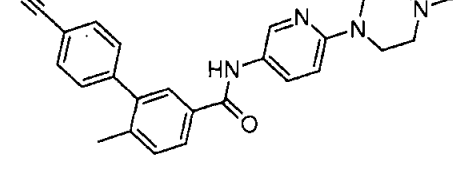
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LC-MS m/z
391.2 (M+1).

57

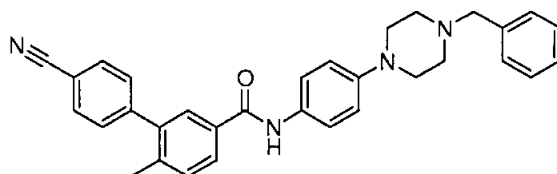
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H92

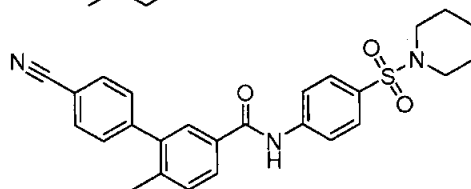
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62		LC-MS m/z 411.2 (M+1).
63		LC-MS m/z 413.2 (M+1).
64		LC-MS m/z 397.2 (M+1).
65		LC-MS m/z 399.2 (M+1).
66		LC-MS m/z 412.2 (M+1).

67		LC-MS <i>m/z</i> 398.2 (M+1).
68		LC-MS <i>m/z</i> 416.2 (M+1).
69		LC-MS <i>m/z</i> 432.1 (M+1).
70		LC-MS <i>m/z</i> 476.1 (M+1).
71		LC-MS <i>m/z</i> 412.2 (M+1).
72		LC-MS <i>m/z</i> 466.2 (M+1).
73		LC-MS <i>m/z</i> 385.2 (M+1).
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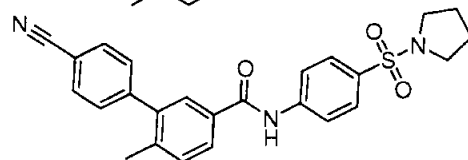
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LC-MS m/z
487.2 (M+1).

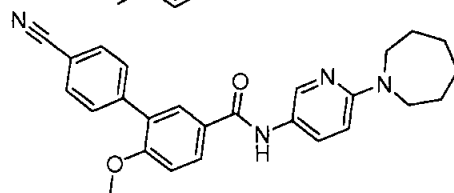
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LC-MS m/z
460.2 (M+1).

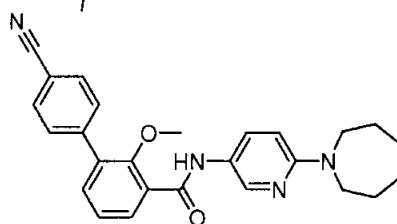
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LC-MS m/z
446.1 (M+1).

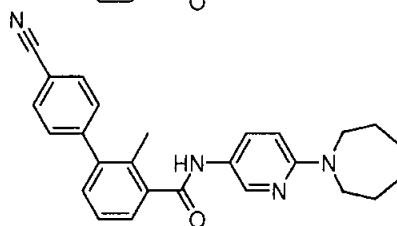
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LC-MS m/z
427.2 (M+1).

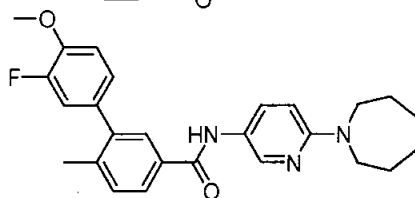
80

LC-MS m/z
427.2 (M+1).

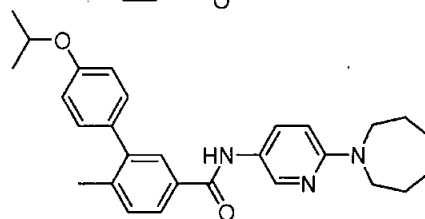
81

LC-MS m/z
411.2 (M+1).

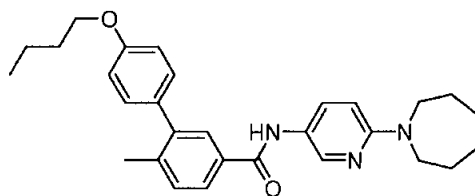
82

LC-MS m/z
434.2 (M+1).

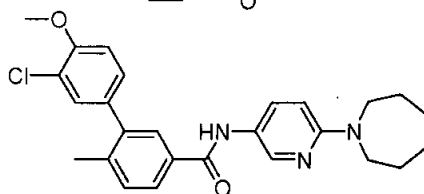
83

LC-MS m/z
444.3 (M+1).

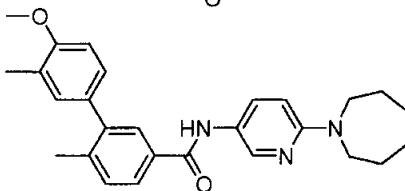
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LC-MS m/z
458.3 (M+1)

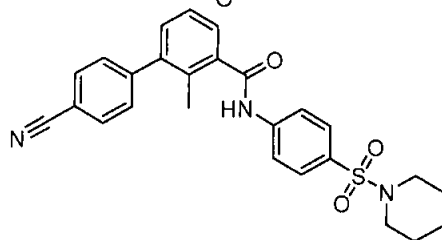
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LC-MS m/z
450.2 (M+1)

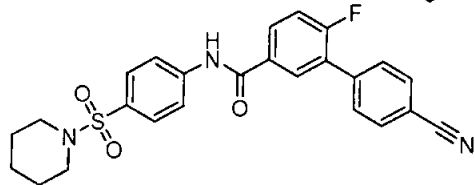
86

LC-MS m/z
430.2 (M+1)

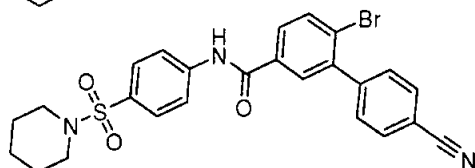
87

LC-MS m/z
460.2 (M+1)

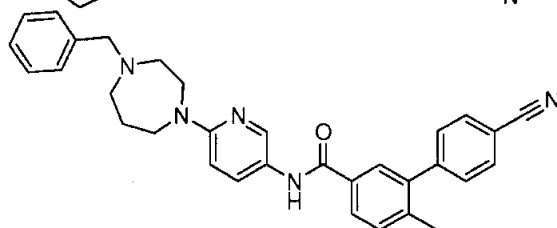
88

LC-MS m/z
464.1 (M+1)

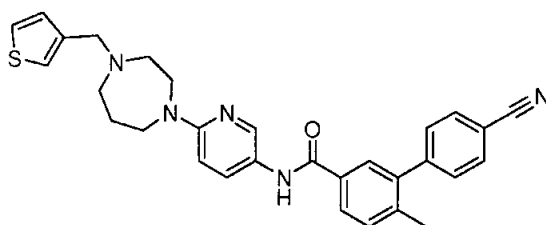
89

LC-MS m/z
524.1 (M+1)

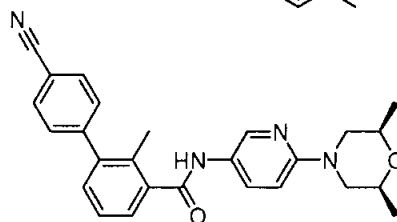
90

LC-MS m/z
502.3 (M+1)

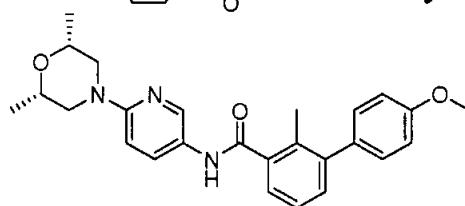
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LC-MS m/z
508.2 (M+1)

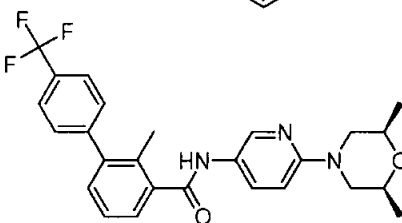
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LC-MS m/z
427.2 (M+1)

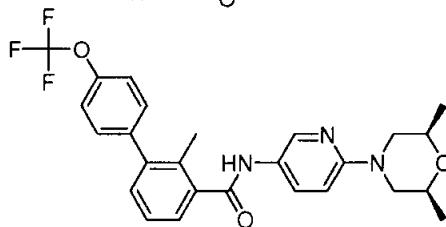
93

LC-MS m/z
432.2 (M+1)

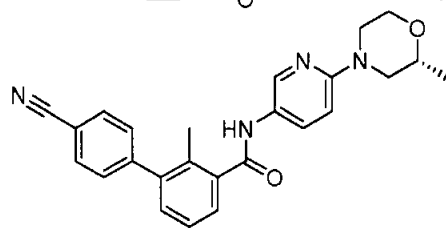
94

LC-MS m/z
470.2 (M+1)

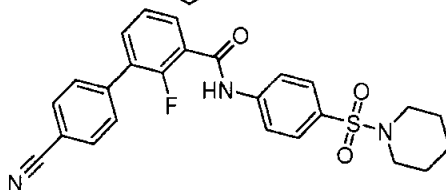
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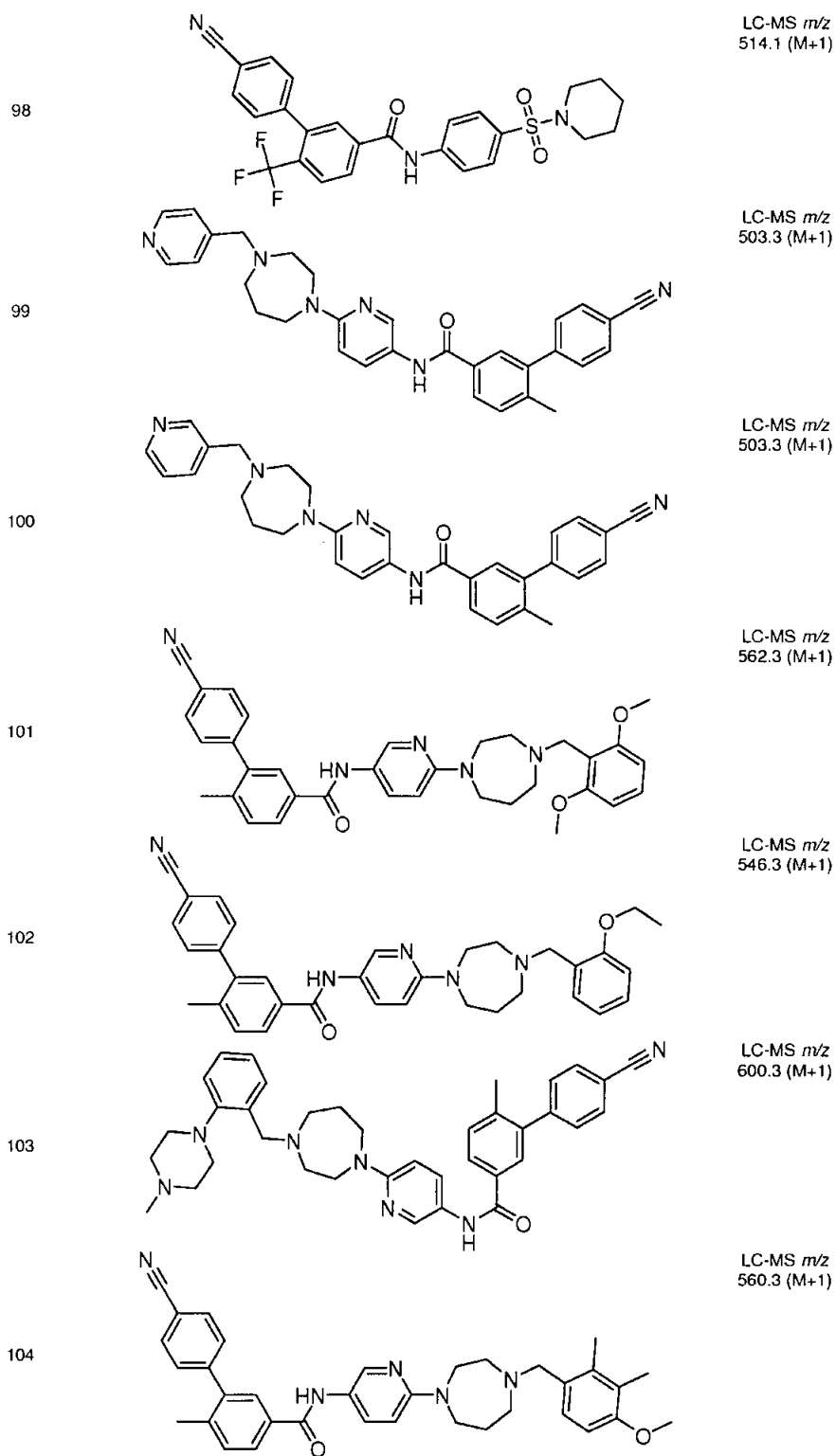
LC-MS m/z
486.2 (M+1)

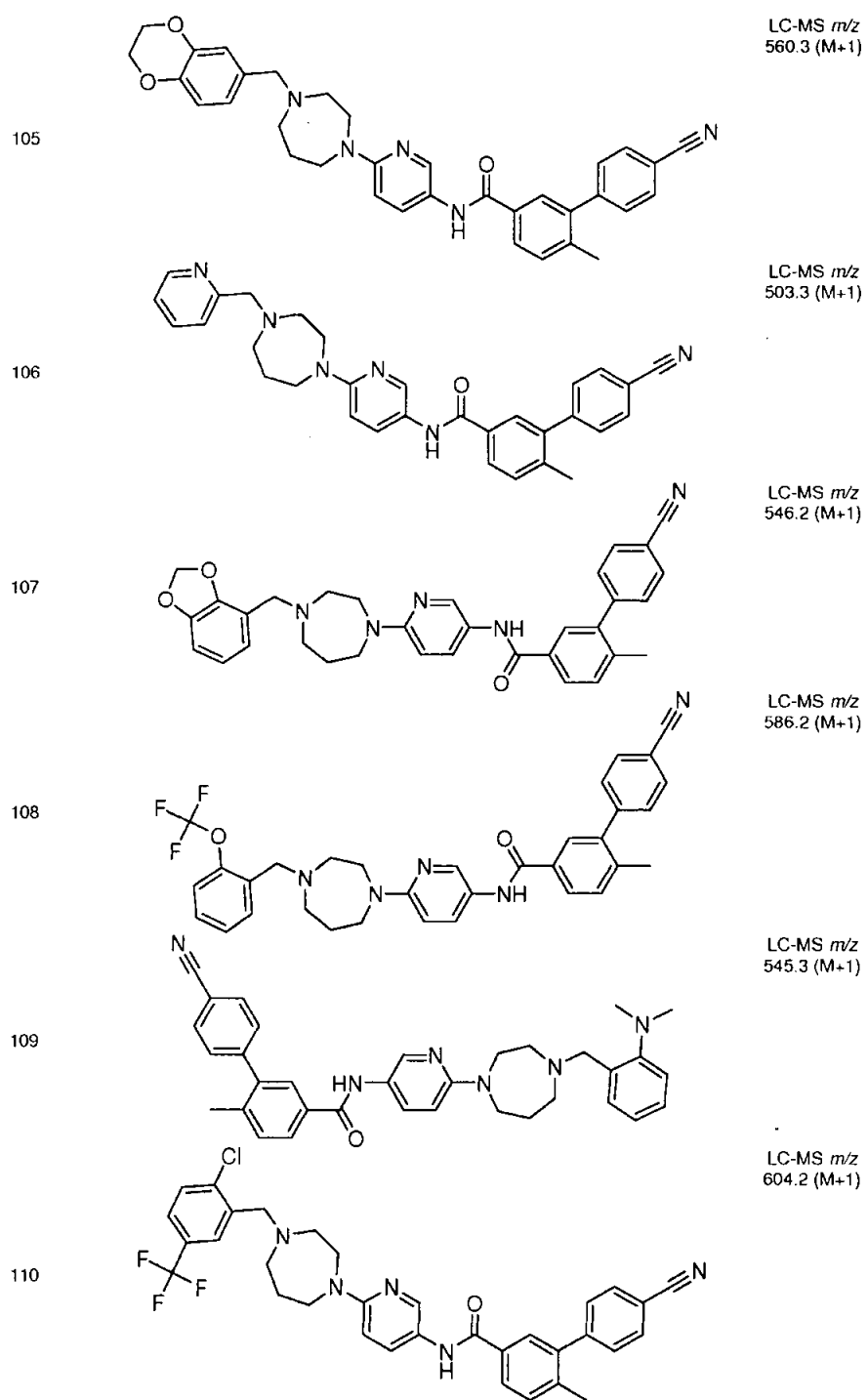
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LC-MS m/z
413.2 (M+1)

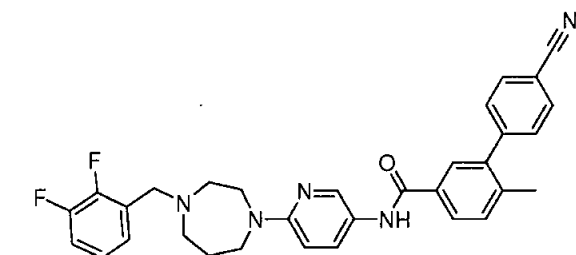
97

LC-MS m/z
464.1 (M+1)

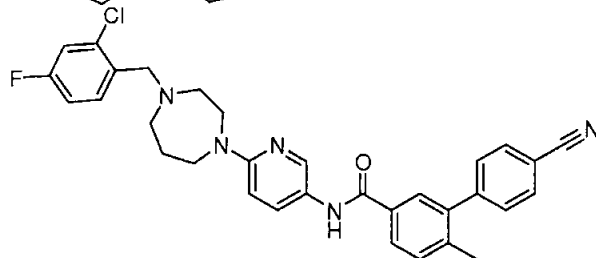




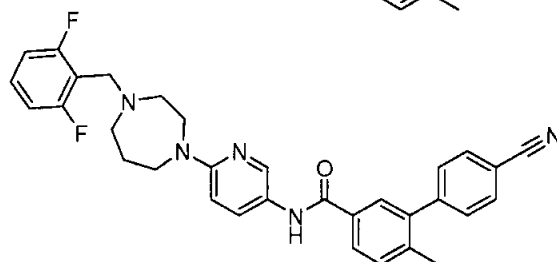
111

LC-MS m/z
538.2 (M+1)

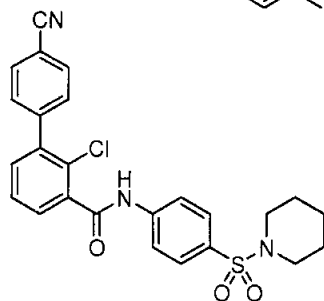
112

LC-MS m/z
554.2 (M+1)

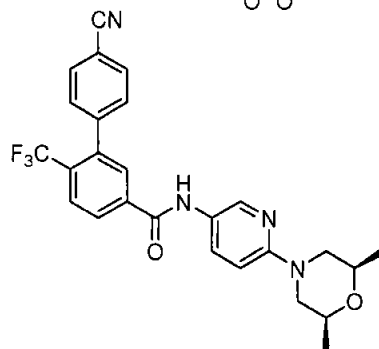
113

LC-MS m/z
538.2 (M+1)

114

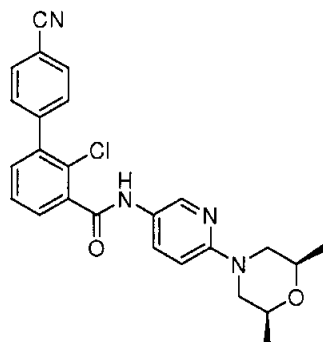
LC-MS m/z
480.1 (M+1)

115

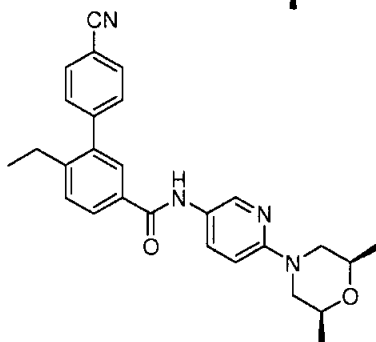
LC-MS m/z
481.2 (M+1)



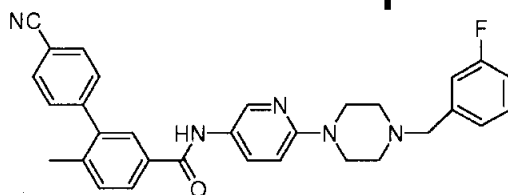
116

LC-MS m/z
447.2 (M+1)

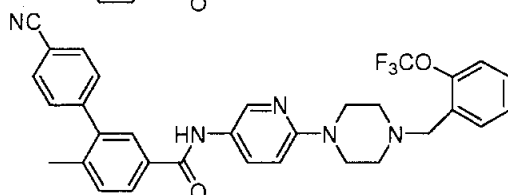
117

LC-MS m/z
441.2 (M+1)

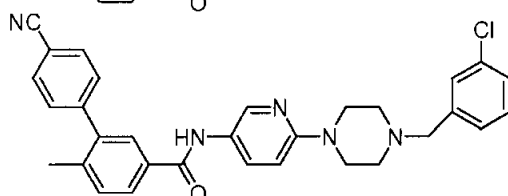
118

LC-MS m/z
506.2 (M+1)

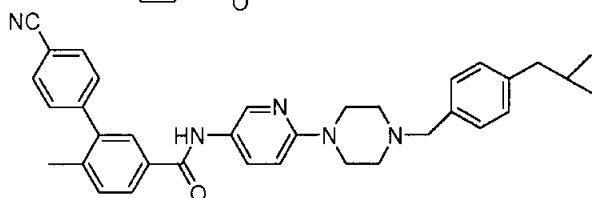
119

LC-MS m/z
572.2 (M+1)

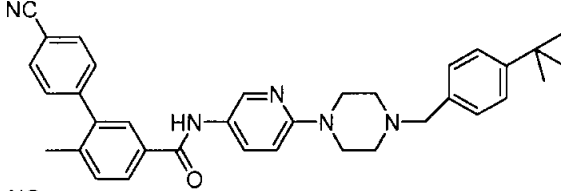
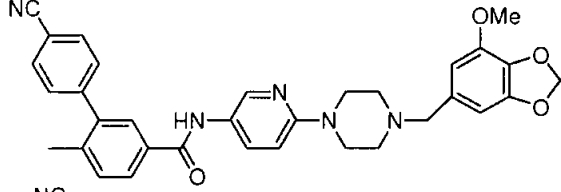
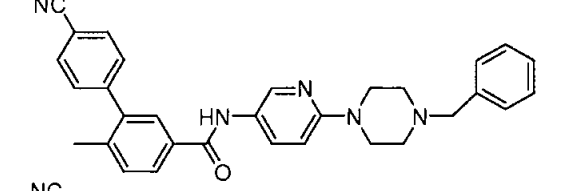
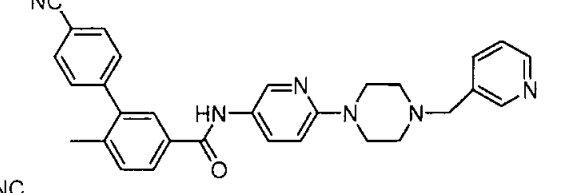
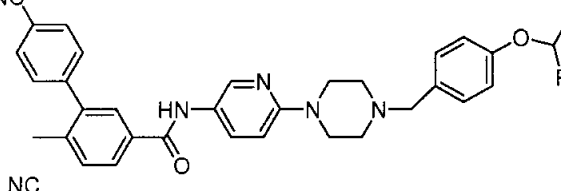
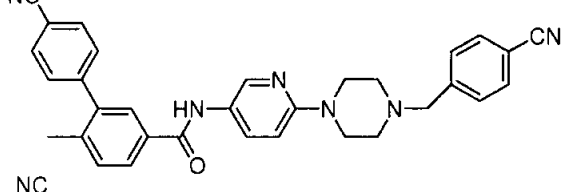
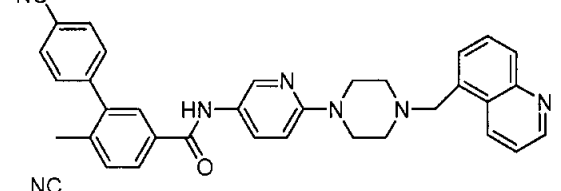
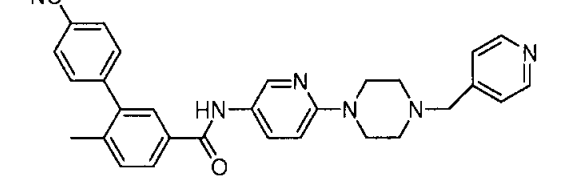
120

LC-MS m/z
522.2 (M+1)

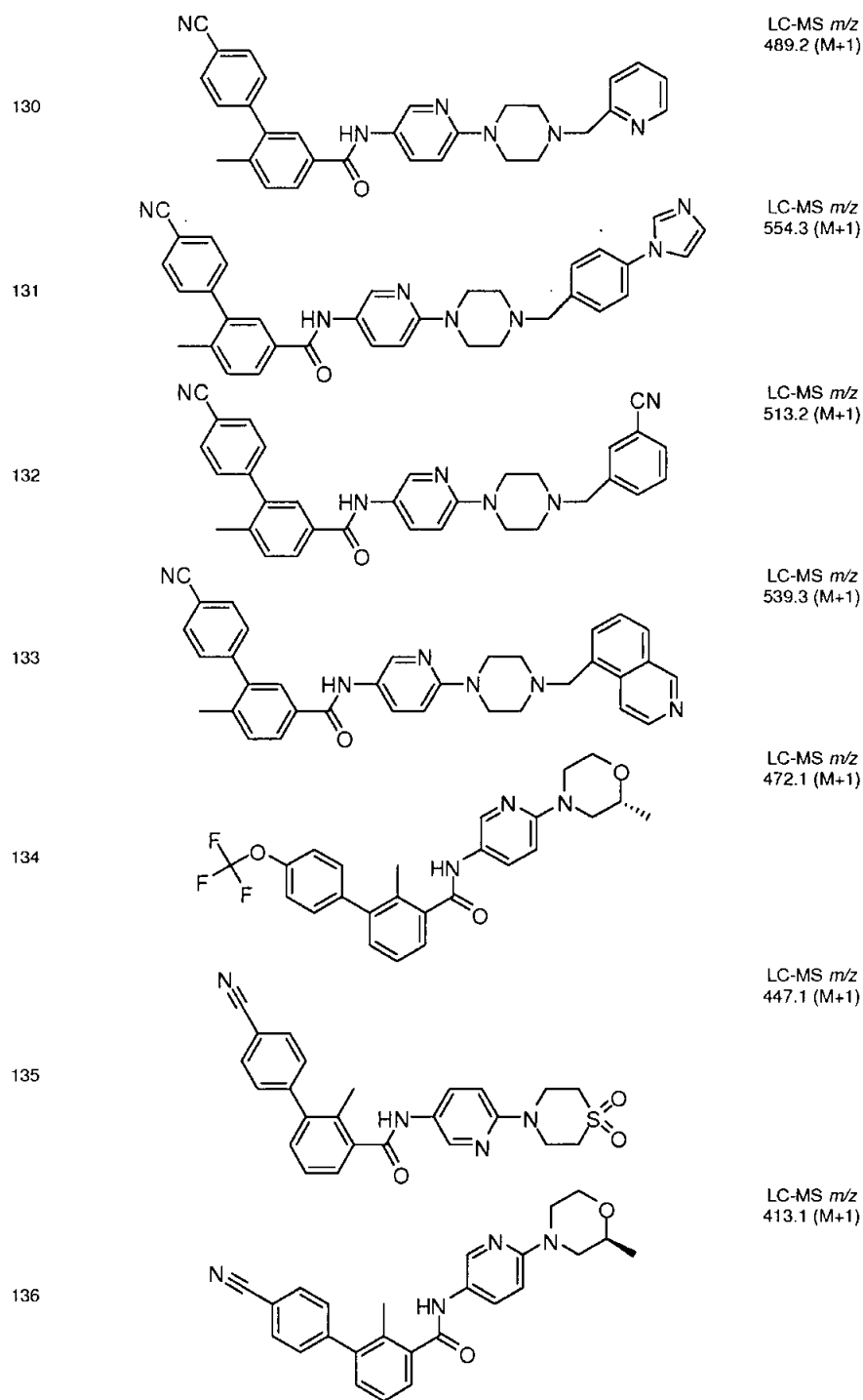
121

LC-MS m/z
544.3 (M+1)

51

122		LC-MS m/z 544.3 (M+1)
123		LC-MS m/z 562.2 (M+1)
124		LC-MS m/z 488.2 (M+1)
125		LC-MS m/z 489.2 (M+1)
126		LC-MS m/z 554.2 (M+1)
127		LC-MS m/z 513.2 (M+1)
128		LC-MS m/z 539.3 (M+1)
129		LC-MS m/z 489.2 (M+1)

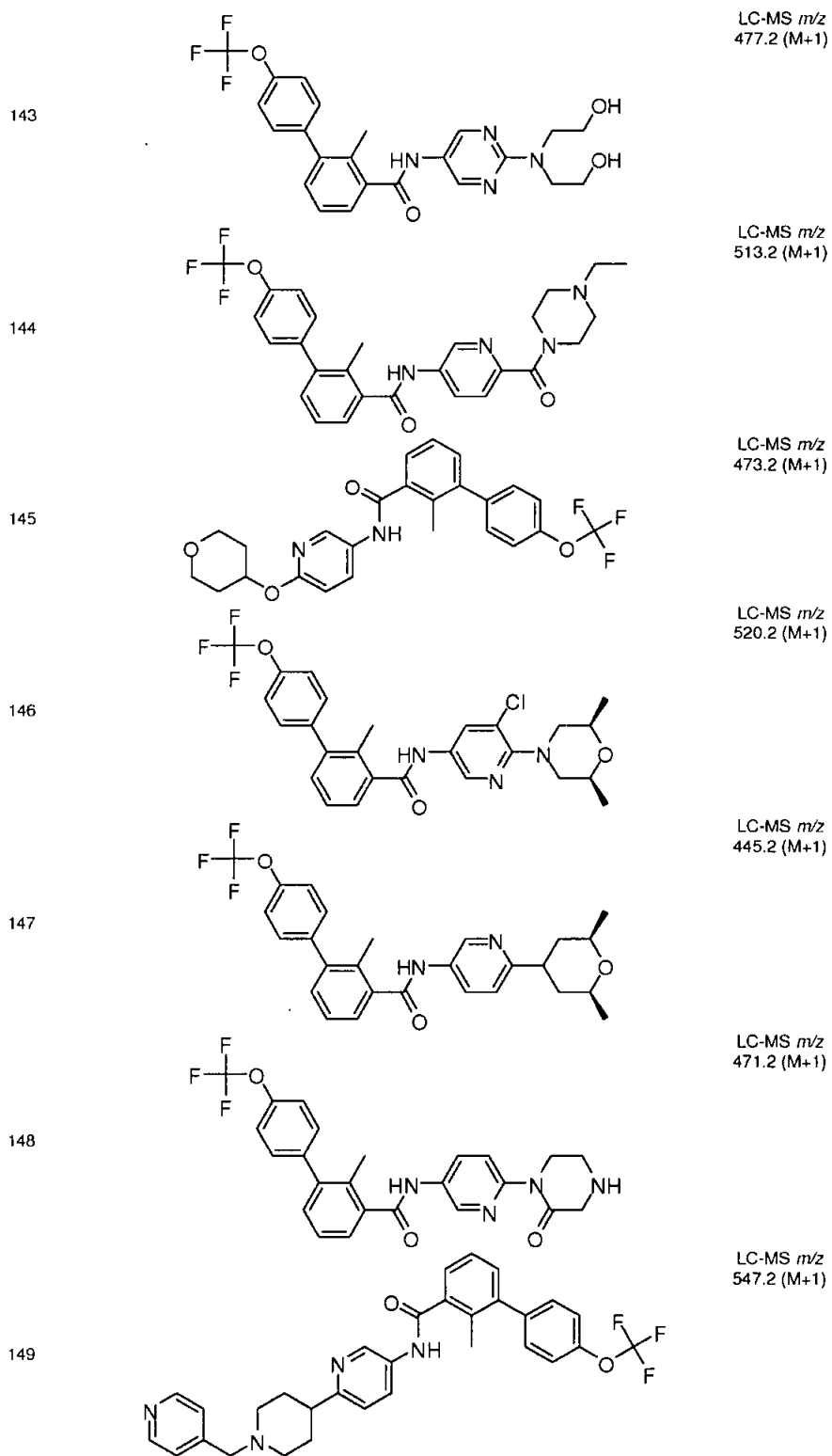
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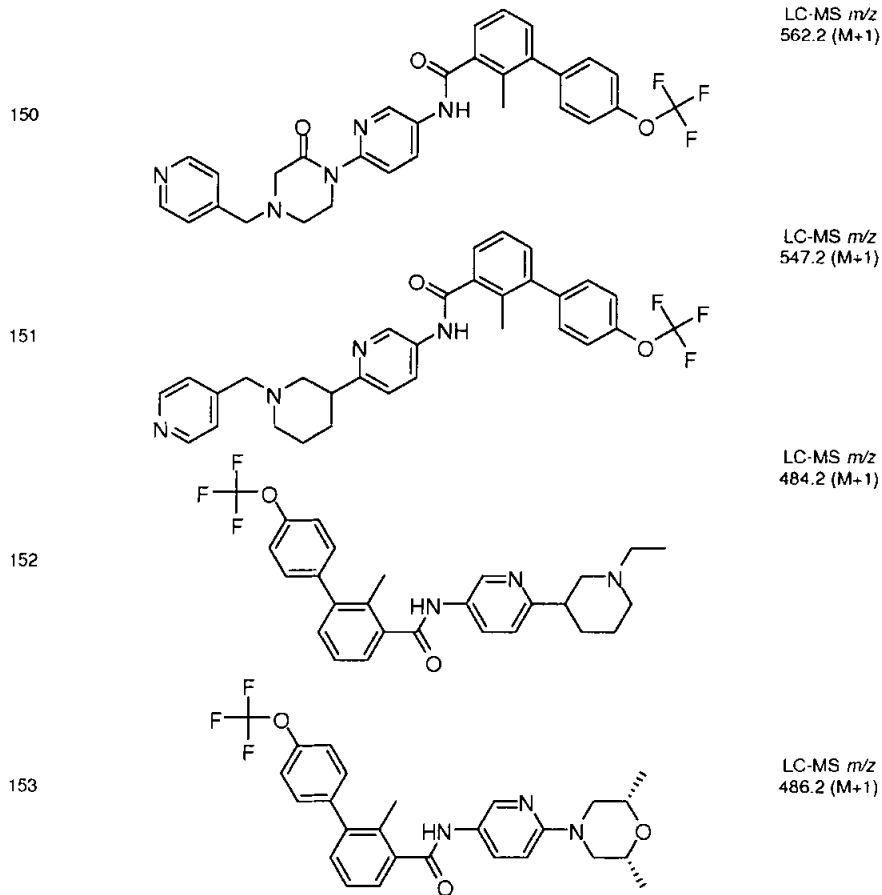




137		LC-MS <i>m/z</i> 492.1 (M+1)
138		LC-MS <i>m/z</i> 431.1 (M+1)
139		LC-MS <i>m/z</i> 441.1 (M+1)
140		LC-MS <i>m/z</i> 428.2 (M+1)
141		LC-MS <i>m/z</i> 471.2 (M+1)
142		LC-MS <i>m/z</i> 487.2 (M+1)

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[0067] Compounds of the present invention are assayed to evaluate their capacity to inhibit the hedgehog signaling pathway.

Gli-Luc Reporter Assay for Hh Pathway Inhibition

[0068] Mouse TM3 cells (obtained from American Type Culture Collection, ATCC, Manassas, VA) are cultured in DMEM/F12 medium (Gibco/Invitrogen, Carlsbad, CA) supplemented with 5% heat inactivated horse serum and 2.5% FBS (Gibco/Invitrogen, Carlsbad, CA), 50 unit/mL penicillin and 50 μ g/mL of streptomycin (Gibco/Invitrogen, Carlsbad, CA) at 37°C with 5% CO₂ in air atmosphere. TM3 cells were transfected with pTA-8xGli-Luc reporter plasmid. A stably transfected clone termed TMHh-12 was selected. TMHh-12 clone showed good response to Shh-N stimulation. To evaluate the IC₅₀s of the antagonists, 8000 TMHh-12 cells were plated

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into each wells in 384-well plates with 50% DMEM/F12 medium supplemented with 2% FBS. After 12 hours, Hh pathway is activated by adding recombinant mouse Shh protein (expressed in E.coli, 8 $\mu\text{g/mL}$) or by adding Smo agonists. The testing compounds are added into plates with different concentrations. After 48 hours, the firefly luciferase luciferase activities are assayed with the Bright-Glo™ Luciferase Assay System (Promega, Madison, WI). The IC_{50} is measured when the effect of the compound reduces the luminescence signal by 50%. Toxicity of these compounds are evaluated in TM3 cells using CellTiter Glo assays or by TM3-Luc cell line (a TM3 cell stably transfected with a constitutive luciferase expression vector).

[0069] Compounds of Formula I preferably have an EC_{50} of less than 500nM, more preferable less than 200nM.

Cyto-toxicity Assay

[0070] A cytotoxicity assay is performed to compare the effects of a compound of the invention on medulloblastoma cells (Daoy cells), basal cell carcinoma cells (TE354.T cells) and control cells (human normal fibroblast) according to the following procedure:

[0071] Daoy cells (medulloblastoma cell line) are purchased from ATCC, and cultured in Minimum essential medium (Eagle) with 2 mM L-glutamine and Earle's BSS adjusted to contain 1.5 g/L sodium bicarbonate, 0.1 mM non-essential amino acids, and 1.0 mM sodium pyruvate and 10% FBS at 37°C with 5% CO_2 in an air atmosphere.

[0072] TE354.T cells (from ATCC) are cultured in Dulbecco's modified Eagle's medium with 4 mM L-glutamine fetal bovine serum and 10% of FBS.

[0073] Normal human dermal fibroblast cells (Clonetics) are cultured in Fibroblast Growth Medium (Clonetics).

[0074] Each of the above cell lines are independently seeded into 96-well plates and cultured to a density of 5,000-10,000 cells/well. A compound of the invention, at different concentrations, is added into the cell cultures. After 2 days, the cell viability is evaluated with Cell Titer-Glo Luminescent Cell Viability Assay Kit (Promega) following the manufacturer's protocol. The cell viability is directly measured by luminescent signaling and EC_{50} s are measured when the signal is inhibited 50%.

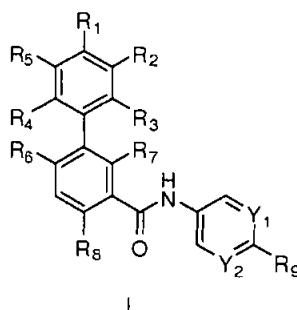
SX

[0075] Compounds of Formula I preferably have an EC_{50} of less than 500nM, more preferable less than 200nM.

[0076] 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:



in which:

Y_1 and Y_2 are independently selected from N and CR_{10} ; wherein R_{10} is selected from hydrogen, halo, C_{1-6} alkyl, halosubstituted- C_{1-6} alkyl, C_{1-6} alkoxy, halosubstituted- C_{1-6} alkoxy and $-OXNR_{10a}R_{10b}$; wherein R_{10a} and R_{10b} are independently selected from hydrogen and C_{1-6} alkyl;

R_1 is selected from cyano, halo, C_{1-6} alkyl, halosubstituted- C_{1-6} alkyl, C_{1-6} alkoxy, halosubstituted- C_{1-6} alkoxy, C_{6-10} aryl, dimethyl-amino, C_{1-6} alkyl-sulfanyl and C_{3-8} heterocycloalkyl optionally substituted with up to 2 C_{1-6} alkyl radicals;

R_2 and R_5 are independently selected from hydrogen, cyano, halo, C_{1-6} alkyl, halosubstituted- C_{1-6} alkyl, C_{1-6} alkoxy, halosubstituted- C_{1-6} alkoxy and dimethylamino;

R_3 and R_4 are independently selected from hydrogen, halo, cyano, C_{1-6} alkyl, halosubstituted- C_{1-6} alkyl, C_{1-6} alkoxy and halosubstituted- C_{1-6} alkoxy; or either R_1 and R_2 or R_1 and R_5 together with the phenyl to which they are both attached form C_{5-10} heteroaryl;

R_6 and R_7 are independently selected from hydrogen, C_{1-6} alkyl, halosubstituted- C_{1-6} alkyl, C_{1-6} alkoxy and halosubstituted- C_{1-6} alkoxy; with the proviso that R_6 and R_7 are not both hydrogen;

R_8 is selected from halo, C_{1-6} alkyl, halosubstituted- C_{1-6} alkyl, C_{1-6} alkoxy and halosubstituted- C_{1-6} alkoxy;

R_9 is selected from $-S(O)_2R_{11}$, $-C(O)R_{11}$, $-NR_{12a}R_{12b}$ and $-R_{11}$;
wherein R_{11} is selected from aryl, heteroaryl, cycloalkyl and heterocycloalkyl; R_{12a}
and R_{12b} are independently selected from C_{1-6} alkyl and hydroxy-substituted- C_{1-6} alkyl;

wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_9 can be
optionally substituted with 1 to 3 radicals independently selected from C_{1-6} alkyl,
halosubstituted- C_{1-6} alkyl, C_{1-6} alkoxy, halosubstituted- C_{1-6} alkoxy, C_{6-10} aryl- C_{0-4} alkyl,
 C_{5-10} heteroaryl- C_{0-4} alkyl, C_{3-12} cycloalkyl and C_{3-8} heterocycloalkyl;

wherein said aryl-alkyl substituent of R_9 is optionally substituted with 1 to 3
radicals independently selected from halo, C_{1-6} alkyl, halosubstituted- C_{1-6} alkyl, C_{1-6}
alkoxy, halosubstituted- C_{1-6} alkoxy and methyl-piperazinyl;

and the pharmaceutically acceptable salts, hydrates, solvates and isomers
thereof.

2. The compound of claim 1 in which:

Y_1 and Y_2 are selected from N and CR_{10} ; wherein R_{10} is selected from
hydrogen, methyl, fluoro, chloro, bromo, dimethylamino-ethoxy and trifluoromethyl;

R_6 and R_7 are independently selected from hydrogen methyl, chloro,
fluoro, bromo, trifluoromethyl and methoxy; with the proviso that R_6 and R_7 are not
both hydrogen; and

R_8 is selected from fluoro, chloro, methyl and trifluoromethyl.

3. The compound of claim 2 in which: R_1 is selected from cyano,
chloro, fluoro, methyl, ethyl, t-butyl, propyl, isobutyl, isopropyl, isopropoxy,
butoxy, methoxy, dimethyl-amino, ethoxy, methyl-sulfanyl, phenyl, trifluoromethyl,
trifluoromethoxy and piperazinyl optionally substituted with up to 2 methyl radicals;

R_2 and R_5 are independently selected from hydrogen, chloro, fluoro,
cyano, methyl, trifluoromethyl, isopropoxy, methoxy, ethoxy, trifluoromethoxy and
dimethylamino; and

R_3 and R_4 are independently selected from hydrogen, chloro, methyl,
methoxy and cyano; or either R_1 and R_2 or R_1 and R_5 together with the phenyl to
which they are both attached form quinoxaliny.

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4. The compound of claim 3 in which R_9 is selected from $-S(O)_2R_{11}$, $-OR_{11}$, $-C(O)R_{11}$, $-NR_{12a}R_{12b}$ and $-R_{11}$; wherein R_{11} is selected from thiomorpholino, sulfonomorpholino, sulfanomorpholino, morpholino, cyclohexyl, phenyl, azepan-1-yl, 2-oxopiperazin-1-yl, 1,4-oxazepan-4-yl, piperidin-1-yl, tetrahydro-2H-pyran-4-yl, piperidin-3-yl, piperazinyl, pyrrolidinyl and 1,4-diazepan-1-yl; R_{12a} and R_{12b} are independently selected from isobutyl, hydroxy-ethyl,

wherein said thiomorpholino, sulfonomorpholino, sulfanomorpholino, morpholino, cyclohexyl, phenyl, azepan-1-yl, 2-oxopiperazin-1-yl, 1,4-oxazepan-4-yl, piperidin-1-yl, tetrahydro-2H-pyran-4-yl, piperidin-3-yl, piperazinyl, pyrrolidinyl or 1,4-diazepan-1-yl of R_9 can be optionally substituted with 1 to 3 radicals independently selected from methyl, ethyl, methoxy, benzyl, thienyl-methyl, pyridinyl-methyl, benzo[d][1,3]dioxol-6-yl and 2,3-dihydrobenzo[b][1,4]dioxin-7-yl;

wherein said phenyl or benzyl substituent of R_9 is optionally substituted with 1 to 3 radicals independently selected from methoxy, ethoxy, methyl-piperazinyl, methyl, trifluoromethoxy, chloro, fluoro and trifluoromethyl.

5. The compound of claim 4 selected from N-(6-((2R,6S)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 4'-cyano-6-methyl-biphenyl-3-carboxylic acid [4-(morpholine-4-sulfonyl)-phenyl]-amide, 4'-cyano-6-methyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Methoxy-2-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Methoxy-2-methyl-biphenyl-3-carboxylic acid (4-cyclohexyl-phenyl)-amide, 4'-Methoxy-2-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Dimethylamino-2-methyl-biphenyl-3-carboxylic acid (4-cyclohexyl-phenyl)-amide, 4'-Dimethylamino-2-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 6-Chloro-4'-dimethylamino-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 6-Chloro-4'-dimethylamino-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 6-Chloro-4'-dimethylamino-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Chloro-4'-methoxy-biphenyl-3-

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carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 6-Chloro-4'-methoxy-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 6-Chloro-4'-methoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Chloro-4'-methoxy-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Dimethylamino-6-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Dimethylamino-6-methyl-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 4'-Dimethylamino-6-methyl-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Ethoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-4'-methylsulfanyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Dimethylamino-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-[1,1';4',1'']terphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Chloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 2',4'-Dichloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 2'-Chloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Chloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3',4'-Dichloro-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Chloro-6-methyl-4'-trifluoromethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6,4'-Dimethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Ethyl-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-tert-Butyl-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-4'-propyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Isobutyl-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Isopropyl-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6,2',6'-Trimethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6,2',3'-Trimethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-



Methyl-4'-trifluoromethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-3'-trifluoromethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-3', 5'-bistrifluoromethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Isopropoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Ethoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 2',6'-Dimethoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-3'-trifluoromethoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 6-Methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 3'-Methoxy-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-(2-Dimethylamino-ethoxy)-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 3'-Dimethylamino-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-Fluoro-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 3'-Fluoro-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 2'-Fluoro-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4-Methyl-N-(4-morpholin-4-yl-phenyl)-3-quinoxalin-6-yl-benzamide, 6-Methyl-4'-(4-methyl-piperazin-1-yl)-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 2'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 3'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (6-[1,4]oxazepan-4-yl-pyridin-3-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-



amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3-bromo-4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (3-methyl-4-morpholin-4-yl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-morpholin-4-yl-3-trifluoromethyl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4-cyclohexyl-phenyl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid biphenyl-4-ylanide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid (4'-methoxy-biphenyl-4-yl)-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [4-(4-benzyl-piperazin-1-yl)-phenyl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [4-(pyrrolidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-methoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Cyano-2-methoxy-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Fluoro-4'-methoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Isopropoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Butoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 3'-Chloro-4'-methoxy-6-methyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Methoxy-6,3'-dimethyl-biphenyl-3-carboxylic acid (6-azepan-1-yl-pyridin-3-yl)-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-fluoro-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 6-Bromo-4'-cyano-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-benzyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-thiophen-3-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Methoxy-2-methyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 2-Methyl-4'-trifluoromethyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-2-methyl-biphenyl-3-carboxylic acid [6-(2-methyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-2-fluoro-

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biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-trifluoromethyl-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-4-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-3-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2,6-dimethoxy-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-ethoxy-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-[2-(4-methyl-piperazin-1-yl)-benzyl]-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-methoxy-2,3-dimethyl-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-2-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-benzo[1,3]dioxol-4-ylmethyl-[1,4]diazepan-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-trifluoromethoxy-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-dimethylamino-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-chloro-5-trifluoromethyl-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2,3-difluoro-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2-chloro-4-fluoro-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(2,6-difluoro-benzyl)-[1,4]diazepan-1-yl]-pyridin-3-yl}-amide, 2-Chloro-4'-cyano-biphenyl-3-carboxylic acid [4-(piperidine-1-sulfonyl)-phenyl]-amide, 4'-Cyano-6-trifluoromethyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 2-Chloro-4'-cyano-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-ethyl-biphenyl-3-carboxylic acid [6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(3-fluoro-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid



{6-[4-(2-trifluoromethoxy-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(3-chloro-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-isobutyl-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-tert-butyl-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(7-methoxy-benzo[1,3]dioxol-5-ylmethyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-benzyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-3-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-difluoromethoxy-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-cyano-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-quinolin-5-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-4-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-pyridin-2-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(4-imidazol-1-yl-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid {6-[4-(3-cyano-benzyl)-piperazin-1-yl]-pyridin-3-yl}-amide, 4'-Cyano-6-methyl-biphenyl-3-carboxylic acid [6-(4-isoquinolin-5-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-amide, (R)-2-methyl-N-(6-(2-methylmorpholino)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 4'-cyano-2-methyl-N-(6-sulfonylmorpholinopyridin-3-yl)biphenyl-3-carboxamide, (S)-4'-cyano-2-methyl-N-(6-(2-methylmorpholino)pyridin-3-yl)biphenyl-3-carboxamide, (R)-6-chloro-N-(6-(2-methylmorpholino)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 4'-cyano-2-methyl-N-(6-sulfinylmorpholinopyridin-3-yl)biphenyl-3-carboxamide, 4'-cyano-N-(6-(diisobutylamino)pyridin-3-yl)-2-methylbiphenyl-3-carboxamide, 4'-cyano-N-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-2-methylbiphenyl-3-carboxamide, N-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-2-methyl-4'-(trifluoromethyl)biphenyl-3-carboxamide, N-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, N-(2-(bis(2-hydroxyethyl)amino)pyrimidin-5-yl)-2-methyl-4'-

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(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(tetrahydro-2H-pyran-4-yloxy)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, N-(5-chloro-6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, N-(6-((2R,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, N-(6-(4-ethylpiperazine-1-carbonyl)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(2-oxopiperazin-1-yl)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(2-oxo-4-(pyridin-4-ylmethyl)piperazin-1-yl)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide, 2-methyl-N-(6-(1-(pyridin-4-ylmethyl)piperidin-3-yl)pyridin-3-yl)-4'-(trifluoromethoxy)biphenyl-3-carboxamide and N-(6-(1-ethylpiperidin-3-yl)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide.

6. A method of inhibiting the hedgehog pathway in a cell, comprising contacting the cell with a compound of claim 1.

7. The method of claim 6 wherein the cell has a phenotype of Ptc loss-of-function, hedgehog gain-of-function, smoothened gain-of-function or Gli gain-of-function.

8. The method of claim 7 wherein the cell is contacted with the hedgehog antagonist in vivo or in vitro.

9. The method of claim 8 wherein the compound is administered to an animal as part of a therapeutic application.

10. The method of claim 9 wherein the therapeutic application is selected from pancreatic cancer, prostate cancer, medulloblastoma, basal cell carcinoma and small-cell lung cancer.

**(12) SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACIÓN
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(81) Estados (Países) Designados (a menos que se indique de otra manera, para cada clase de protección nacional disponible): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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-- con respecto al derecho de la solicitante de reivindicar la prioridad de la solicitud anterior (Regla 4.17(iii))

(71) Solicitante (para todos los estados designados, excepto US):
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(54) Título: **COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA SENDA DE HEDGEHOG**

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COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA SENDA DE HEDGEHOG



Campo de la Invención

5 La invención proporciona un método para modular la actividad de la senda de señalización de Hedgehog. En particular, la invención proporciona un método para inhibir los estados de crecimiento aberrantes resultantes de los fenotipos tales como la pérdida de función de Ptc, la ganancia de función de Hedgehog, la ganancia de
10 función de Smoothened, o la ganancia de función de Gli, el cual comprende poner en contacto una célula con una cantidad suficiente de un compuesto de la Fórmula I.

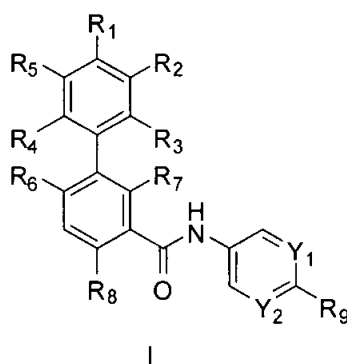
Antecedentes de la Invención

 Durante el desarrollo embrionario, la senda de señalización de
15 Hedgehog es esencial para numerosos procesos, tales como el control de la proliferación celular, la diferenciación, y la formación de patrones de tejido. Sin embargo, la actividad aberrante de la senda de señalización de Hedgehog, por ejemplo como un resultado de la mejor activación, puede tener consecuencias patológicas. En este
20 aspecto, la activación de la senda de Hedgehog en los tejidos adultos puede dar como resultado tipos específicos de cáncer que incluyen, pero no se limitan a, cánceres del cerebro, músculo y piel, de próstata, meduloblastoma, adenocarcinomas pancreáticos, y carcinomas pulmonares de células pequeñas. La mejor activación de
25 la senda de señalización de Hedgehog contribuye a la patología y/o

sintomatología de un número de enfermedades. De conformidad con lo anterior, las moléculas que modulen la actividad de la senda de señalización de Hedgehog son útiles como agentes terapéuticos en el tratamiento de estas enfermedades.

5 **Breve Descripción de la Invención**

En un aspecto, la presente invención proporciona compuestos de la Fórmula I:



en donde:

15 Y₁ e Y₂ se seleccionan independientemente a partir de N y CR₁₀; en donde R₁₀ se selecciona a partir de hidrógeno, halógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, y -OXNR_{10a}R_{10b}; en donde R_{10a} y R_{10b} se seleccionan
20 independientemente a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono;

R₁ se selecciona a partir de ciano, halógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido
25 por halógeno, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6

átomos de carbono sustituido por halógeno, arilo de 6 a 10 átomos
de carbono, dimetil-amino, alquilo de 1 a 6 átomos de carbono-
sulfanilo, y hetero-cicloalquilo de 3 a 8 átomos de carbono
opcionalmente sustituido con hasta 2 radicales de alquilo de 1 a 6
5 átomos de carbono;

R_2 y R_5 se seleccionan independientemente a partir de
hidrógeno, ciano, halógeno, alquilo de 1 a 6 átomos de carbono,
alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcóxido
de 1 a 6 átomos de carbono, alcóxido de 1 a 6 átomos de carbono
10 sustituido por halógeno, y dimetil-amino;

R_3 y R_4 se seleccionan independientemente a partir de
hidrógeno, halógeno, ciano, alquilo de 1 a 6 átomos de carbono,
alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcóxido
de 1 a 6 átomos de carbono, y alcóxido de 1 a 6 átomos de carbono
15 sustituido por halógeno; o R_1 y R_2 , ó R_1 y R_5 , junto con el fenilo con
el que están ambos unidos, forman heteroarilo de 5 a 10 átomos de
carbono;

R_6 y R_7 se seleccionan independientemente a partir de
hidrógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6
20 átomos de carbono sustituido por halógeno, alcóxido de 1 a 6 átomos
de carbono, y alcóxido de 1 a 6 átomos de carbono sustituido por
halógeno; con la condición de que R_6 y R_7 no son ambos hidrógeno;

R_8 se selecciona a partir de hidrógeno, halógeno, alquilo de 1 a
6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido
25 por halógeno, alcóxido de 1 a 6 átomos de carbono, y alcóxido de 1 a

6 átomos de carbono sustituido por halógeno;

R_9 se selecciona a partir de $-S(O)_2R_{11}$, $-C(O)R_{11}$, $-OR_{11}$, $-NR_{12a}R_{12b}$ y $-R_{11}$; en donde R_{11} se selecciona a partir de arilo, heteroarilo, cicloalquilo, y hetero-cicloalquilo; R_{12a} y R_{12b} se
5 seleccionan independientemente a partir de alquilo de 1 a 6 átomos de carbono y alquilo de 1 a 6 átomos de carbono sustituido por hidroxilo;

en donde el arilo, heteroarilo, cicloalquilo, y hetero-cicloalquilo de R_9 pueden estar opcionalmente sustituido con 1 a 3 radicales
10 independientemente seleccionados a partir de alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, arilo de 6 a 10 átomos de carbono-alquilo de 0 a 4 átomos de carbono, hetero-arilo de 5 a 10
15 átomos de carbono-alquilo de 0 a 4 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, y hetero-cicloalquilo de 3 a 8 átomos de carbono;

en donde el sustituyente de aril-alquilo de R_9 está opcionalmente sustituido con 1 a 3 radicales independientemente
20 seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, y metil-piperazinilo; y los derivados de N-óxido, los derivados de pro-fármaco, los derivados protegidos,
25 los isómeros individuales y mezclas de isómeros de los mismos; y las

sales farmacéuticamente aceptables y solvatos (por ejemplo, hidratos) de estos compuestos.

En un segundo aspecto, la presente invención proporciona una composición farmacéutica, la cual contiene un compuesto de la
5 Fórmula I ó un derivado de N-óxido, isómeros individuales y mezclas de isómeros del mismo; o una sal farmacéuticamente aceptable del mismo, mezclado con uno o más excipientes adecuados.

En un tercer aspecto, la presente invención proporciona un método para el tratamiento de una enfermedad en un animal en
10 donde la modulación de la actividad de la senda de Hedgehog pueda prevenir, inhibir, o aliviar la patología y/o sintomatología de las enfermedades, cuyo método comprende administrar al animal una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I, o un derivado de N-óxido, isómeros individuales y mezclas de
15 isómeros del mismo, o una sal farmacéuticamente aceptable del mismo.

En un cuarto aspecto, la presente invención proporciona el uso de un compuesto de la Fórmula I en la fabricación de un medicamento para el tratamiento de una enfermedad en un animal en
20 donde la actividad de la senda de Hedgehog contribuya a la patología y/o sintomatología de la enfermedad.

En un quinto aspecto, la presente invención proporciona un proceso para la preparación de compuestos de la Fórmula I, y los derivados de N-óxido, derivados de pro-fármaco, derivados
25 protegidos, isómeros individuales y mezclas de isómeros de los

mismos, y las sales farmacéuticamente aceptables de los mismos.

Definiciones

“Alquilo”, como un grupo y como un elemento estructural de otros grupos, por ejemplo alquilo y alcoxilo sustituidos por halógeno y alcoxilo, puede ser de cadena recta o ramificada. Alcoxilo de 1 a 4 átomos de carbono incluye metoxilo, etoxilo, y similares. Alquilo sustituido por halógeno incluye trifluoro-metilo, pentafluoro-etilo, y similares.

“Arilo” significa un ensamble de anillo aromático monocíclico o bicíclico fusionado que contiene de 6 a 10 átomos de carbono del anillo. Por ejemplo, arilo puede ser fenilo o naftilo, de preferencia fenilo.

“Arileno” significa un radical divalente derivado a partir de un grupo arilo.

“Heteroarilo” es como se define para arilo anteriormente, en donde uno o más de los miembros del anillo es un heteroátomo. Por ejemplo, heteroarilo de 5 a 10 átomos de carbono es un mínimo de cinco miembros, como se indique por los átomos de carbono, pero estos átomos de carbono pueden ser reemplazados por un heteroátomo. En consecuencia, heteroarilo de 5 a 10 átomos de carbono incluye piridilo, indolilo, indazolilo, quinoxalinilo, quinolinilo, benzo-furanilo, benzo-piranilo, benzo-tiopiranilo, benzo-[1,3]-dioxol, imidazolilo, benzo-imidazolilo, pirimidinilo, furanilo, oxazolilo, isoxazolilo, triazolilo, tetrazolilo, pirazolilo, tienilo, etc.

“Cicloalquilo” significa un ensamble de anillo monocíclico,



bicíclico fusionado, o policíclico puenteado, saturado o parcialmente insaturado, que contiene el número de átomos del anillo indicado. Por ejemplo, cicloalquilo de 3 a 10 átomos de carbono incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etc.

5 “Hetero-cicloalquilo” significa cicloalquilo, como se define en esta solicitud, en el entendido de que uno o más de los átomos de carbono del anillo indicados sean reemplazados por una fracción seleccionada a partir de -O-, -N=, -NR-, -C(O)-, -S-, -S(O)- ó -S(O)₂-, en donde R es hidrógeno, alquilo de 1 a 4 átomos de carbono, o un
10 grupo protector de nitrógeno. Por ejemplo, hetero-cicloalquilo de 3 a 8 átomos de carbono, como se utiliza en esta solicitud para describir los compuestos de la invención, incluye morfolino, pirrolidinilo, pirrolidinil-2-ona, piperazinilo, piperidinilo, piperidinilona, 1,4-dioxa-8-aza-espiro-[4.5]-dec-8-ilo, tiomorfolino, sulfano-morfolino, sulfono-
15 morfolino, etc.

“Halógeno” (ó halo), represente de preferencia cloro o flúor, pero también puede ser bromo o yodo.

“Ganancia de función de Hedgehog” se refiere a una modificación o mutación aberrante de un gen Ptc, gen Hedgehog, o
20 gen Smoothened, o una disminución (o pérdida) en el nivel de expresión de este gen, que da como resultado un fenotipo que parece hacer contacto con una célula con una proteína Hedgehog, por ejemplo una activación aberrante de una senda de Hedgehog. La ganancia de función puede incluir una pérdida de la capacidad del
25 producto genético Ptc para regular el nivel de expresión de los genes



Gli, por ejemplo Gli1, Gli2, y Gli3. El término “ganancia de función de Hedgehog”, también se utiliza en la presente para referirse a cualquier fenotipo celular similar (por ejemplo, que exhiba un exceso de proliferación), que se presente debido a una alteración en cualquier parte de la senda de transducción de señal de Hedgehog, incluyendo, pero no limitándose a, una modificación o mutación del Hedgehog mismo. Por ejemplo, una célula tumoral con un índice de proliferación anormalmente alto debido a la activación de la senda de señalización de Hedgehog, tendría un fenotipo de “ganancia de función de Hedgehog”, inclusive cuando el Hedgehog no esté mutado en esa célula.

“Pérdida de función de Patched” se refiere a una modificación o mutación aberrante de un gen *Ptc*, o a un nivel reducido de expresión del gen, que da como resultado un fenotipo que parece hacer contacto con una célula con una proteína Hedgehog, por ejemplo la activación aberrante de una senda de Hedgehog. La pérdida de función puede incluir una pérdida de la capacidad del producto genético *Ptc* para regular la expresión de los genes Gli, por ejemplo Gli1, Gli2, y Gli3.

“Ganancia de función de Gli” se refiere a una modificación o mutación aberrante de un gen Gli, o a un mayor nivel de expresión del gen, que da como resultado un fenotipo que parece hacer contacto con una célula con una proteína Hedgehog, por ejemplo la activación aberrante de una senda de Hedgehog.

“Ganancia de función de Smoothened” se refiere a una

modificación o mutación aberrante de un gen Smo, o a un mayor nivel de expresión del gen, que da como resultado un fenotipo que parece hacer contacto con una célula con una proteína Hedgehog, por ejemplo la activación aberrante de una senda de Hedgehog.

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

La presente invención se refiere al descubrimiento de que las sendas de transducción de señales reguladas por Hedgehog, (Ptc) Patched, Gli, y/o Smoothened, se pueden modular mediante los
10 compuestos de la Fórmula I.

Descripción de las Modalidades Preferidas

En una modalidad, con respecto a los compuestos de la Fórmula I, Y_1 y Y_2 se seleccionan a partir de N y CR_{10} ; en donde R_{10} se selecciona a partir de hidrógeno, metilo, flúor, cloro, bromo, dimetil-amino-etoxilo, y trifluoro-metilo; R_6 y R_7 se seleccionan
15 independientemente a partir de hidrógeno, metilo, cloro, flúor, bromo, trifluoro-metilo, y metoxilo; con la condición de R_6 y R_7 no son ambos hidrógeno; y R_8 se selecciona a partir de hidrógeno, flúor, cloro, metilo, y trifluoro-metilo.

20 En otra modalidad, R_1 se selecciona a partir de ciano, cloro, flúor, metilo, etilo, butilo terciario, propilo, isobutilo, isopropilo, isopropiloxilo, butoxilo, metoxilo, dimetil-amino, etoxilo, metil-sulfanilo, fenilo, trifluoro-metilo, trifluoro-metoxilo, y piperazinilo, opcionalmente sustituidos con hasta 2 radicales de metilo; R_2 y R_5 se
25 seleccionan independientemente a partir de hidrógeno, cloro, flúor,



ciano, metilo, trifluoro-metilo, isopropiloxilo, metoxilo, etoxilo, trifluoro-metoxilo, y dimetil-amino; y R_3 y R_4 se seleccionan independientemente a partir de hidrógeno, cloro, metilo, metoxilo, y ciano; ó R_1 y R_2 , ó R_1 y R_5 , junto con el fenilo con el que están
5 ambos unidos, forman quinoxalinilo.

En otra modalidad, R_9 se selecciona a partir de $-S(O)_2R_{11}$, $-OR_{11}$, $-C(O)R_{11}$, $-NR_{12a}R_{12b}$ y $-R_{11}$; en donde R_{11} se selecciona a partir de tiomorfolino, sulfono-morfolino, sulfano-morfolino, morfolino, ciclohexilo, fenilo, azepan-1-ilo, 2-oxopiperazin-1-ilo, 1,4-oxazepan-
10 4-ilo, piperidin-1-ilo, tetrahydro-2H-piran-4-ilo, piperidin-3-ilo, piperazinilo, pirrolidinilo, y 1,4-diazepan-1-ilo; R_{12a} y R_{12b} se seleccionan independientemente a partir de isobutilo e hidroxietilo; en donde este tiomorfolino, sulfono-morfolino, sulfano-morfolino, morfolino, ciclohexilo, fenilo, azepan-1-ilo, 2-oxopiperazin-1-ilo, 1,4-
15 oxazepan-4-ilo, piperidin-1-ilo, tetrahydro-2H-piran-4-ilo, piperidin-3-ilo, piperazinilo, pirrolidinilo, ó 1,4-diazepan-1-ilo de R_9 pueden estar opcionalmente sustituidos con 1 a 3 radicales independientemente seleccionados a partir de metilo, etilo, metoxilo, bencilo, tienil-metilo, piridinil-metilo, benzo-[d]-[1,3]-dioxol-6-ilo, y 2,3-dihidro-benzo-[b]-
20 [1,4]-dioxin-7-ilo; en donde el sustituyente de fenilo o bencilo de R_9 está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de metoxilo, etoxilo, metil-piperazinilo, metilo, trifluoro-metoxilo, cloro, flúor, y trifluoro-metilo.

25 Los compuestos preferidos de la Fórmula I se seleccionan a



partir de:

[4-(morfolin-4-sulfonil)-fenil]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-ciano-2-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-metoxi-2-metil-bifenil-3-carboxílico, (4-ciclohexil-fenil)-amida del ácido 4'-metoxi-2-metil-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-metoxi-2-metil-bifenil-3-carboxílico, (4-ciclohexil-fenil)-amida del ácido 4'-dimetil-amino-2-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 4'-dimetil-amino-2-metil-bifenil-3-carboxílico, (6-[1,4]-oxazepan-4-il-piridin-3-il)-amida del ácido 6-cloro-4'-dimetil-amino-bifenil-3-carboxílico, (6-morfolin-4-il-piridin-3-il)-amida del ácido 6-cloro-4'-dimetil-amino-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-cloro-4'-dimetil-amino-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 6-cloro-4'-metoxi-bifenil-3-carboxílico, (6-[1,4]-oxazepan-4-il-piridin-3-il)-amida del ácido 6-cloro-4'-metoxi-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-cloro-4'-metoxi-bifenil-3-carboxílico, (6-morfolin-4-il-piridin-3-il)-amida del ácido 6-cloro-4'-metoxi-bifenil-3-carboxílico, (6-morfolin-4-il-piridin-3-il)-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, (6-[1,4]-oxazepan-4-il-piridin-3-il)-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del

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ácido 4'-dimetil-amino-6-metil-bifenil-3-carboxílico, (6-[1,4]-
oxazepan-4-il-piridin-3-il)-amida del ácido 4'-dimetil-amino-6-metil-
bifenil-3-carboxílico, (6-morfolin-4-il-piridin-3-il)-amida del ácido 4'-
dimetil-amino-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-
5 amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-
il-piridin-3-il)-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico,
(6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-4'-metil-sulfanil-
bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-
dimetil-amino-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-
10 amida del ácido 6-metil-[1,1';4',1'']-terfenil-3-carboxílico, (6-azepan-
1-il-piridin-3-il)-amida del ácido 3'-cloro-6-metil-bifenil-3-carboxílico,
(6-azepan-1-il-piridin-3-il)-amida del ácido 2',4'-dicloro-6-metil-
bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 2'-
cloro-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida
15 del ácido 3'-cloro-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-
3-il)-amida del ácido 3',4'-dicloro-6-metil-bifenil-3-carboxílico, (6-
azepan-1-il-piridin-3-il)-amida del ácido 3'-cloro-6-metil-4'-trifluoro-
metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido
6,4'-dimetil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del
20 ácido 4'-etil-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-
amida del ácido 4'-terbutil-6-metil-bifenil-3-carboxílico, (6-azepan-1-
il-piridin-3-il)-amida del ácido 6-metil-4'-propil-bifenil-3-carboxílico,
(6-azepan-1-il-piridin-3-il)-amida del ácido 4'-isobutil-6-metil-bifenil-
3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-isopropil-
25 6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del



ácido 6,2',6'-trimetil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-
amida del ácido 6,2',3'-trimetil-bifenil-3-carboxílico, (6-azepan-1-il-
piridin-3-il)-amida del ácido 6-metil-4'-trifluoro-metil-bifenil-3-
carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-3'-
5 trifluoro-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida
del ácido 6-metil-3',5'-bis-trifluoro-metil-bifenil-3-carboxílico, (6-
azepan-1-il-piridin-3-il)-amida del ácido 3'-isopropoxi-6-metil-bifenil-
3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-etoxi-6-
metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido
10 2',6'-dimetoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-
amida del ácido 6-metil-4'-trifluoro-metoxi-bifenil-3-carboxílico, (6-
azepan-1-il-piridin-3-il)-amida del ácido 6-metil-3'-trifluoro-metoxi-
bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 6-metil-
bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 4'-metoxi-
15 6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 3'-
metoxi-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del
ácido 4'-(2-dimetil-amino-etoxi)-6-metil-bifenil-3-carboxílico, (4-
morfolin-4-il-fenil)-amida del ácido 3'-dimetil-amino-6-metil-bifenil-3-
carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 4'-fluoro-6-metil-
20 bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 3'-fluoro-
6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 2'-
fluoro-6-metil-bifenil-3-carboxílico, 4-metil-N-(4-morfolin-4-il-fenil)-3-
quinoxalin-6-il-benzamida, (4-morfolin-4-il-fenil)-amida del ácido 6-
metil-4'-(4-metil-piperazin-1-il)-bifenil-3-carboxílico, (4-morfolin-4-il-
25 fenil)-amida del ácido 2'-ciano-6-metil-bifenil-3-carboxílico, (4-



morfolin-4-il-fenil)-amida del ácido 3'-ciano-6-metil-bifenil-3-carboxílico, (6-[1,4]-oxazepan-4-il-piridin-3-il)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (3,4,5,6-tetrahidro-2H-[1,2']-bipiridinil-5'-il)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (6-morfolin-4-il-piridin-3-il)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (3-fluoro-4-morfolin-4-il-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (3-cloro-4-morfolin-4-il-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (3-bromo-4-morfolin-4-il-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (3-metil-4-morfolin-4-il-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-3-trifluoro-metil-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (4-ciclohexil-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, bifenil-4-il-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (4'-metoxi-bifenil-4-il)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [4-(4-bencil-piperazin-1-il)-fenil]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [4-(pirrolidin-1-sulfonil)-fenil]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-ciano-6-metoxi-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-

amida del ácido 4'-ciano-2-metoxi-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-ciano-2-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-fluoro-4'-metoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-isopropoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-butoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-cloro-4'-metoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-metoxi-6,3'-dimetil-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-amida del ácido 4'-ciano-2-metil-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-amida del ácido 4'-ciano-6-fluoro-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-amida del ácido 6-bromo-4'-ciano-bifenil-3-carboxílico, [6-(4-bencil-[1,4]-diazepan-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-tiofen-3-il-metil-[1,4]-diazepan-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(2,4-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-2-metil-bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-metoxi-2-metil-bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 2-metil-4'-trifluoro-metil-bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 2-metil-4'-trifluoro-metoxi-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-2-metil-bifenil-3-carboxílico, [4-(piperidin-1-il-sulfonil)-fenil]-amida del ácido 4'-ciano-2-fluoro-bifenil-3-carboxílico, [4-(piperidin-1-il-sulfonil)-fenil]-amida del ácido 4'-ciano-6-trifluoro-metil-bifenil-3-

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carboxílico, [6-(4-piridin-4-il-metil-[1,4]-diazepan-1-il)-piridin-3-il]-
amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-piridin-3-
il-metil-[1,4]-diazepan-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-
metil-bifenil-3-carboxílico, {6-[4-(2,6-dimetoxi-bencil)-[1,4]-diazepan-
5 1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-
carboxílico, {6-[4-(2-etoxi-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-
amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (6-{4-[2-(4-
metil-piperazin-1-il)-bencil]-[1,4]-diazepan-1-il}-piridin-3-il)-amida del
ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-metoxi-2,3-
10 dimetil-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-
ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2,3-dihidro-benzo-[1,4]-
dioxin-6-il-metil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-
ciano-6-metil-bifenil-3-carboxílico, [6-(4-piridin-2-il-metil-[1,4]-
diazepan-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-
15 carboxílico, [6-(4-benzo-[1,3]-dioxol-4-il-metil-[1,4]-diazepan-1-il)-
piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-
[4-(2-trifluoro-metoxi-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida
del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2-dimetil-
amino-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-
20 ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2-cloro-5-trifluoro-metil-
bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-
metil-bifenil-3-carboxílico, {6-[4-(2,3-difluoro-bencil)-[1,4]-diazepan-
1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-
carboxílico, {6-[4-(2-cloro-4-fluoro-bencil)-[1,4]-diazepan-1-il]-piridin-
25 3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2,6-

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difluoro-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-amida del ácido 2-cloro-4'-ciano-bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-trifluoro-metil-bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 2-cloro-4'-ciano-bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-etil-bifenil-3-carboxílico, {6-[4-(3-fluoro-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2-trifluorometoxi-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(3-cloro-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-isobutil-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-terbutil-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(7-metoxi-benzo-[1,3]-dioxol-5-il-metil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-bencil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-piridin-3-il-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-difluoro-metoxi-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-ciano-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-quinolin-5-il-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-piridin-4-il-metil-

piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-
 carboxílico, [6-(4-piridin-2-il-metil-piperazin-1-il)-piridin-3-il]-amida
 del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-imidazol-1-il-
 bencil)-piperazin-1-il]-piridin-3-il]-amida del ácido 4'-ciano-6-metil-
 5 bifenil-3-carboxílico, {6-[4-(3-ciano-bencil)-piperazin-1-il]-piridin-3-il]-
 amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-
 isoquinolin-5-il-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-
 ciano-6-metil-bifenil-3-carboxílico, (R)-2-metil-N-(6-(2-metil-
 morfolino)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 4'-
 10 ciano-2-metil-N-(6-sulfonil-morfolino-piridin-3-il)-bifenil-3-
 carboxamida, (S)-4'-ciano-2-metil-N-(6-(2-metil-morfolino)-piridin-3-
 il)-bifenil-3-carboxamida, (R)-6-cloro-N-(6-(2-metil-morfolino)-piridin-
 3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 4'-ciano-2-metil-N-(6-
 sulfinil-morfolino-piridin-3-il)-bifenil-3-carboxamida, 4'-ciano-N-(6-(di-
 15 isobutil-amino)-piridin-3-il)-2-metil-bifenil-3-carboxamida, 4'-ciano-N-
 (2-((2S,6R)-2,6-dimetil-morfolino)-pirimidin-5-il)-2-metil-bifenil-3-
 carboxamida, N-(2-((2S,6R)-2,6-dimetil-morfolino)-pirimidin-5-il)-2-
 metil-4'-(trifluoro-metil)-bifenil-3-carboxamida, N-(2-((2S,6R)-2,6-
 dimetil-morfolino)-pirimidin-5-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-
 20 carboxamida, N-(2-(bis(2-hidroxi-etil)-amino)-pirimidin-5-il)-2-metil-
 4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 2-metil-N-(6-(tetrahydro-
 2H-piran-4-iloxi)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-
 carboxamida, N-(5-cloro-6-((2S,6R)-2,6-dimetil-morfolino)-piridin-3-
 il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, N-(6-((2R,6S)-
 25 2,6-dimetil-tetrahydro-2H-piran-4-il)-piridin-3-il)-2-metil-4'-(trifluoro-

metoxi)-bifenil-3-carboxamida, N-(6-(4-etil-piperazin-1-carbonil)-
piridin-3-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 2-
metil-N-(6-(2-oxopiperazin-1-il)-piridin-3-il)-4'-(trifluoro-metoxi)-
bifenil-3-carboxamida, 2-metil-N-(6-(1-(piridin-4-ilmetil)-piperidin-4-
5 il)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 2-metil-N-
(6-(2-oxo-4-(piridin-4-ilmetil)-piperazin-1-il)-piridin-3-il)-4'-(trifluoro-
metoxi)-bifenil-3-carboxamida, 2-metil-N-(6-(1-(piridin-4-ilmetil)-
piperidin-3-il)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida,
N-(6-(1-etil-piperidin-3-il)-piridin-3-il)-2-metil-4'-(trifluoro-metoxi)-
10 bifenil-3-carboxamida, y N-(6-((2R,6S)-2,6-dimetil-morfolino)-piridin-
3-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida.

Por consiguiente, se contempla específicamente que los
compuestos de la Fórmula I que interfieran con aspectos de
Hedgehog, Ptc, o la actividad de transducción de señal de
15 Smoothened, de la misma manera serán capaces de inhibir la
proliferación (u otras consecuencias biológicas) en las células
normales, y/o en las células que tengan un fenotipo de pérdida de
función de Patched, un fenotipo de ganancia de función de
Hedgehog, un fenotipo de ganancia de función de Smoothened, o un
20 fenotipo de ganancia de función de Gli. Por consiguiente, se
contempla que, en ciertas modalidades, estos compuestos pueden
ser útiles para inhibir la actividad de Hedgehog en las células
normales, por ejemplo que no tengan una mutación genética que
active la senda de Hedgehog. En las modalidades preferidas, los
25 compuestos son capaces de inhibir cuando menos algunas de las



actividades biológicas de las proteínas Hedgehog, de preferencia de una manera específica en las células objetivo.

Por lo tanto, los métodos de la presente invención incluyen el uso de compuestos de la Fórmula I que agonicen la inhibición de Ptc de la señalización de Hedgehog, tal como mediante la inhibición de la activación de los componentes de Smoothened o corriente abajo de la senda de señal, en la regulación de la reparación y/o el desempeño funcional de un amplio número de células, tejidos, y órganos, incluyendo células, tejidos, y órganos normales, así como los que tengan el fenotipo de pérdida de función de Ptc, ganancia de función de Hedgehog, ganancia de función de Smoothened, o ganancia de función de Gli. Por ejemplo, el presente método tiene aplicaciones terapéuticas y cosméticas desde la regulación de los tejidos neurales, la formación y reparación de hueso y cartílago, la regulación de la espermatogénesis, la regulación de músculo liso, la regulación del pulmón, del hígado y otros órganos que se presenten desde el intestino primitivo, la regulación de la función hematopoiética, la regulación de la piel y del crecimiento de pelo, etc. Más aún, los presentes métodos se pueden llevar a cabo en células que se proporcionen en cultivo (*in vitro*), o en células en un animal entero (*in vivo*).

En otra modalidad, el presente método puede ser para tratar las células epiteliales que tengan un fenotipo de pérdida de función de Ptc, ganancia de función de Hedgehog, ganancia de función de Smoothened, o ganancia de función de Gli. Por ejemplo, el presente



método se puede emplear para el tratamiento o la prevención de carcinoma de células basales u otros trastornos relacionados con la senda de Hedgehog.

5 En ciertas modalidades, un compuesto de la Fórmula I puede inhibir la activación de una senda de Hedgehog mediante el enlace con proteínas Smoothened o corriente abajo. En ciertas modalidades, un antagonista objeto puede inhibir la activación de una senda de Hedgehog mediante el enlace con un Patched.

10 En otra modalidad preferida, el presente método se puede emplear como parte de un régimen de tratamiento para meduloblastomas malignos y otros tumores neuroectodérmicos malignos primarios del sistema nervioso central.

15 En otro aspecto, la presente invención proporciona preparaciones farmacéuticas que comprenden, como un ingrediente activo, un modulador de la señalización de Hedgehog, tal como un compuesto de la Fórmula I, un agonista de Ptc, un antagonista de Smoothened, o un antagonista de la proteína de la senda de Hedgehog corriente abajo, tal como se describe en la presente, formulado en una cantidad suficiente para inhibir, *in vivo*, la
20 proliferación u otras consecuencias biológicas de la pérdida de función de Ptc, la ganancia de función de Hedgehog, la ganancia de función de Smoothened, o la ganancia de función de Gli.

Los presentes tratamientos que utilizan un compuesto de la Fórmula I, los agonistas de Patched, los antagonistas de
25 Smoothened, o los antagonistas de proteína de la senda de

Hedgehog corriente abajo, pueden ser efectivos tanto para sujetos humanos como animales. Los sujetos animales a los que es aplicable la presente invención se extienden tanto a animales domésticos como al ganado, o al que se cría como mascota o para propósitos comerciales. Los ejemplos son perros, gatos, reses, caballos, ovejas, cerdos, y cabras.

Farmacología y Utilidad

La presente invención pone a disposición métodos y compuestos para inhibir la activación de la senda de señalización de Hedgehog, por ejemplo para inhibir los estados de crecimiento aberrantes resultantes de fenotipos tales como pérdida de función de Ptc, ganancia de función de Hedgehog, ganancia de función de Smoothened, o ganancia de función de Gli, los cuales comprenden poner en contacto la célula con un compuesto de la Fórmula I, en una cantidad suficiente para agonizar una actividad de Ptc normal, antagonizar una actividad de Hedgehog normal, antagonizar una actividad de Smoothened, o antagonizar una actividad de Gli, por ejemplo para revertir o controlar el estado de crecimiento aberrante.

Los miembros de señalización de Hedgehog median muchos procesos de formación de patrones de rango corto y largo durante el desarrollo de los vertebrados. La formación de patrones es la actividad mediante la cual las células embrionarias forman arreglos espaciales ordenados de tejidos diferenciados. La complejidad física de los organismos superiores se presenta durante la embriogénesis a través del interjuego del linaje intrínseco de la célula y la



señalización extrínseca de la célula. Son esenciales las interacciones inductivas para la formación de los patrones embrionarios en el desarrollo de los vertebrados desde el establecimiento más temprano del plan corporal, hasta la formación de patrones de los sistemas de órganos, y ante la generación de diversos tipos de células durante la diferenciación de los tejidos. Los efectos de las interacciones celulares de desarrollo son variados: las células que responden se desvían desde una ruta de diferenciación celular hasta otra mediante la inducción de las células que difieran tanto del estado no inducido como inducido de las células que responden (inducciones). Algunas veces, las células inducen a sus vecinas a diferenciarse como ellas mismas (inducción homeogenética); en otros casos, una célula inhibe a sus vecinas de la diferenciación como ella misma. Las interacciones celulares en el desarrollo temprano pueden ser en secuencia, de tal manera que una inducción inicial entre dos tipos de células conduce a una amplificación progresiva de diversidad. Más aún, se presentan interacciones inductivas no solamente en los embriones, sino también en las células adultas, y pueden actuar para establecer y mantener los patrones morfogenéticos, así como para inducir la diferenciación.

La familia de genes Hedgehog de los vertebrados incluye a tres miembros que existen en los mamíferos, conocidos como los Hedgehogs Desert (Dhh), Sonic (Shh), e Indian (Ihh), todos los cuales codifican las proteínas secretadas. Estas diferentes proteínas



Hedgehog consisten en un péptido de señal, una región N-terminal altamente conservada, y un dominio C-terminal más divergente. Los estudios bioquímicos han demostrado que la disociación auto-proteolítica de la proteína precursora de Hh procede a través de un
5 intermediario de tioéster interno que subsecuentemente se disocia en una sustitución nucleofílica. Es probable que el nucleófilo sea una molécula lipofílica pequeña que llegue a enlazarse covalentemente con el extremo C-terminal del péptido-N, atándolo a la superficie celular. Las implicaciones biológicas son profundas. Como un
10 resultado de esta atadura, se genera una alta concentración local del péptido Hedgehog N-terminal sobre la superficie de las células productoras de Hedgehog. Es este péptido N-terminal el que es tanto necesario como suficiente para las actividades de señalización de Hedgehog de rango corto y largo.

15 Una senda de señalización de Hedgehog inactiva es en donde el receptor de proteína transmembrana Patched (Ptc) inhibe la actividad de Smoothened (Smo), una proteína de siete transmembranas. Se impide que el factor de transcripción Gli, un componente corriente abajo de la señalización de Hh, entre al núcleo
20 a través de las interacciones con las proteínas citoplásmicas, incluyendo Fused y Supresor de Fused (Sufu). Como una consecuencia, se reprime la activación de la transcripción de los genes objetivos Hedgehog. La activación de la senda se inicia a través del enlace de cualquiera de los tres ligandos de mamífero
25 (Dhh, Shh, ó Ihh) con Ptc. El enlace del ligando da como resultado la

reversión de la represión de Smo, activando de esta manera una cascada que conduce a la translocalización de la forma activa del factor de transcripción Gli hasta el núcleo. El Gli nuclear activa la expresión del gen objetivo, incluyendo Ptc y Gli mismos.

- 5 Los mayores niveles de señalización de Hedgehog son suficientes para iniciar la formación de cáncer, y se requieren para la sobrevivencia del tumor. Estos cánceres incluyen, pero no se limitan a, cáncer de próstata ("Hedgehog signaling in prostate regeneration, neoplasia and metastasis", Karhadkar S. S., Bova G. S., Abdallah N, Dhara S, Gardner D, Maitra A, Isaacs J. T., Berman D. M., Beachy P. A., *Nature*. 7 de octubre de 2004; 431(7009):707-12; "Inhibition of prostate cancer proliferation by interference with SONIC HEDGEHOG-GLI1 signaling", Sanchez P, Hernandez A. M., Stecca B, Kahler A. J., DeGueme A. M., Barrett A, Beyna M, Datta M. W., Datta S., Ruiz i Altaba A., *Proc. Natl. Acad. Sci. EUA*. 24 de agosto de 2004; 101(34):12561-6), cáncer de mama ("Hedgehog signaling pathway is a new therapeutic target for patients with breast cancer", Kubo M, Nakamura M, Tasaki A, Yamanaka N, Nakashima H, Nomura M, Kuroki S, Katano M., *Cancer Res*. 1 de septiembre de 2004; 64(17):6071-4), medulloblastoma ("Medulloblastoma growth inhibition by hedgehog pathway blockade", Berman D. M., Karhadkar S. S., Hallahan A. R., Pritchard J. I., Eberhart C. G., Watkins D. N., Chen J. K., Cooper M. K., Taipale J, Olson J. M., Beachy P. A., *Science*. 30 de agosto de 2002; 297(5586):1559-61), carcinoma de células
- 10
- 15
- 20
- 25 basales ("Identification of a small molecule inhibitor of the hedgehog

- signaling pathway: effects on basal cell carcinoma-like lesions", Williams J. A., Guicherit O. M., Zaharian B. I., Xu Y, Chai L, Wichterle H, Kon C, Gatchalian C, Porter J. A., Rubin L. L., Wang F. Y., *Proc. Natl. Acad. Sci. EUA*. 15 de abril de 2003; 100(8):4616-21;
- 5 "Activating Smoothed mutations in sporadic basal-cell carcinoma", Xie J, Murone M, Luoh S. M., Ryan A, Gu Q, Zhang C, Bonifas J. M., Lam C. W, Hynes M, Goddard A, Rosenthal A, Epstein E. H. Jr., de Sauvage F. J., *Nature*. 1 de enero de 1998; 391(6662):90-2), cáncer pancreático ("Hedgehog is an early and late mediator of pancreatic
- 10 cancer tumorigenesis", Thayer S. P., di Magliano M. P., Heiser P. W., Nielsen C. M., Roberts D. J., Lauwers G. Y., Qi Y. P., Gysin S, Fernandez-del Castillo C, Yajnik V, Antoniu B, McMahon M, Warshaw A. L., Hebrok M., *Nature*. 23 de octubre de 2003; 425(6960):851-6;
- 15 "Widespread requirement for Hedgehog ligand stimulation in growth of digestive tract tumours", Berman D. M., Karhadkar S. S., Maitra A, Montes De Oca R, Gerstenblith M. R., Briggs K, Parker A. R., Shimada Y, Eshleman J. R., Watkins D. N., Beachy P. A., *Nature*. 23 de octubre de 2003; 425(6960):846-51), y cáncer pulmonar de células pequeñas ("Hedgehog signalling within airway epithelial
- 20 progenitors and in small-cell lung cancer", Watkins D. N, Berman D. M., Burkholder S. G., Wang B, Beachy P. A., Baylin S. B., *Nature*. 20 de marzo de 2003; 422(6929):313-7).

De conformidad con lo anterior, la presente invención proporciona además un método para prevenir o tratar cualquiera de

25 las enfermedades o trastornos descritos anteriormente, en un sujeto

que necesite dicho tratamiento, cuyo método comprende administrar a este sujeto una cantidad terapéuticamente efectiva ("Administration and Pharmaceutical Compositions", *infra*) de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo. Para
5 cualquiera de los usos anteriores, la dosificación requerida variará dependiendo del modo de administración, de la condición particular que se vaya a tratar, y del efecto deseado.

Administración y Composiciones Farmacéuticas:

En general, los compuestos de la invención se administrarán en
10 cantidades terapéuticamente efectivas mediante cualquiera de los modos usuales y aceptables conocidos en la técnica, ya sea solos o en combinación con uno o más agentes terapéuticos. Una cantidad terapéuticamente efectiva puede variar ampliamente, dependiendo de la severidad de la enfermedad, de la edad y salud relativa del sujeto,
15 de la potencia del compuesto utilizado, y de otros factores. En general, se indica que se obtienen resultados satisfactorios sistémicamente con dosificaciones diarias de aproximadamente 0.03 a 2.5 miligramos/kilogramo de peso corporal. Una dosificación diaria indicada en el mamífero superior, por ejemplo en los seres humanos,
20 está en el intervalo de aproximadamente 0.5 miligramos a aproximadamente 100 miligramos, convenientemente administrados, por ejemplo, en dosis divididas hasta cuatro veces al día, o en una forma retardada. Las formas de dosificación unitaria adecuadas para administración oral comprenden de aproximadamente 1 a 50
25 miligramos de ingrediente activo.

Los compuestos de la invención se pueden administrar como composiciones farmacéuticas por cualquier vía convencional, en particular enteralmente, por ejemplo oralmente, por ejemplo en la forma de tabletas o cápsulas, o parenteralmente, por ejemplo en la forma de soluciones o suspensiones inyectables, tópicamente, por ejemplo en la forma de lociones, geles, ungüentos o cremas, o en una forma nasal o de supositorio. Las composiciones farmacéuticas que comprenden un compuesto de la presente invención en forma libre o en forma de sal farmacéuticamente aceptable, en asociación con cuando menos un vehículo o diluyente farmacéuticamente aceptable, se pueden fabricar de una manera convencional mediante métodos de mezcla, granulación, o recubrimiento. Por ejemplo, las composiciones orales pueden ser tabletas o cápsulas de gelatina que comprendan al ingrediente activo junto con: a) diluyentes, por ejemplo lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa, y/o glicina; b) lubricantes, por ejemplo sílice, talco, ácido esteárico, su sal de magnesio o de calcio, y/o polietilenglicol; para tabletas también c) aglutinantes, por ejemplo silicato de magnesio y aluminio, pasta de almidón, gelatina, tragacanto, metil-celulosa, carboxi-metil-celulosa de sodio, y/o polivinil-pirrolidona; si se desea d) desintegrantes, por ejemplo almidones, ágar, ácido algínico o su sal sódica, o mezclas efervescentes; y/o e) adsorbentes, colorantes, saborizantes, y edulcorantes. Las composiciones inyectables pueden ser soluciones o suspensiones isotónicas acuosas, y los supositorios se pueden preparar a partir de emulsiones o suspensiones grasas.

Las composiciones se pueden esterilizar y/o pueden contener adyuvantes, tales como agentes conservadores, estabilizantes, humectantes, o emulsionantes, promotores de solución, sales para regular la presión osmótica, y/o reguladores del pH. En adición, también pueden contener otras sustancias terapéuticamente valiosas. Las formulaciones adecuadas para aplicaciones transdérmicas incluyen una cantidad efectiva de un compuesto de la presente invención con un vehículo. Un vehículo puede incluir solventes farmacológicamente aceptables absorbibles para ayudar al paso a través de la piel del huésped. Por ejemplo, los dispositivos transdérmicos están en la forma de un parche comprendiendo un miembro de respaldo, un depósito conteniendo al compuesto opcionalmente con vehículos, opcionalmente una barrera de control de velocidad para suministrar el compuesto en la piel del huésped a una velocidad controlada y previamente determinada durante un período de tiempo prolongado, y elementos para asegurar el dispositivo a la piel. También se pueden utilizar formulaciones transdérmicas de matriz. Las formulaciones adecuadas para administración tópica, por ejemplo a la piel y a los ojos, de preferencia son soluciones acuosas, ungüentos, cremas, o geles, bien conocidos en este campo. Éstos pueden contener solubilizantes, estabilizantes, agentes mejoradores de tonicidad, reguladores del pH, y conservadores.

Los compuestos de la invención se pueden administrar en cantidades terapéuticamente efectivas en combinación con uno o

más agentes terapéuticos (combinaciones farmacéuticas). Por ejemplo, se pueden presentar efectos sinérgicos con las sustancias inmunomoduladoras o anti-inflamatorias u otros agentes terapéuticos anti-tumorales. Cuando los compuestos de la invención se administran en conjunto con otras terapias, las dosificaciones de los compuestos co-administrados, por supuesto, variarán dependiendo del tipo de co-fármaco empleado, del fármaco específico empleado, de la condición que se esté tratando, etc.

La invención también proporciona combinaciones farmacéuticas, por ejemplo un kit, el cual comprende: a) un primer agente que es un compuesto de la invención como se da a conocer en la presente, en forma libre o en forma de sal farmacéuticamente aceptable, y b) cuando menos un co-agente. El kit puede comprender instrucciones para su administración.

Los términos "co-administración" o "administración combinada", o similares, como se utilizan en la presente, pretenden abarcar la administración de los agentes terapéuticos seleccionados a un solo paciente, y pretenden incluir regímenes de tratamiento en donde los agentes no necesariamente se administren por la misma vía de administración o al mismo tiempo.

El término "combinación farmacéutica", como se utiliza en la presente, significa un producto que resulta de la mezcla o combinación de más de un ingrediente activo, e incluye las combinaciones tanto fijas como no fijas de los ingredientes activos. El término "combinación fija" significa que los ingredientes activos,

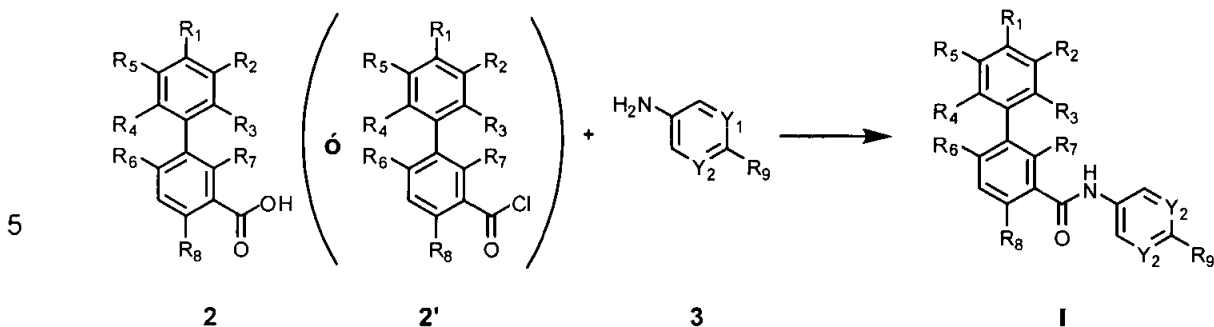
por ejemplo un compuesto de la Fórmula I y un co-agente, se administran ambos a un paciente de una manera simultánea en la forma de una sola entidad o dosificación. El término "combinación no fija" significa que los ingredientes activos, por ejemplo un compuesto de la Fórmula I y un co-agente, se administran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

Procesos para Elaborar los Compuestos de la Invención

La presente invención también incluye procesos para la preparación de los compuestos de la invención. En las reacciones descritas, puede ser necesario proteger a los grupos funcionales reactivos, por ejemplo los grupos hidroxilo, amino, imino, tio, o carboxilo, en donde se deseen éstos en el producto final, con el fin de evitar su participación indeseada en las reacciones. Se pueden utilizar los grupos protectores convencionales de acuerdo con la práctica estándar, por ejemplo, ver T. W. Greene y P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

Los compuestos de la Fórmula I se pueden preparar procediendo como en el siguiente Esquema de Reacción I:

Esquema de Reacción I



en donde Y_1 , Y_2 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , y R_9 son como se definen para la Fórmula I en la Breve Descripción de la Invención. Un compuesto de la Fórmula I se puede preparar mediante la reacción de un compuesto de la Fórmula 2 (ó 2') con un compuesto de la Fórmula 3 en la presencia de un solvente adecuado (por ejemplo, dicloro-metano, N,N-dimetil-formamida, o similar), en un intervalo de temperatura de aproximadamente -20°C a aproximadamente 100°C . La reacción puede tomar hasta aproximadamente 20 horas para terminarse.

Los ejemplos detallados de la síntesis de los compuestos de la Fórmula I se pueden encontrar en los Ejemplos que se encuentran más adelante.

Procesos Adicionales para la Elaboración de los Compuestos de la Invención

Un compuesto de la invención se puede preparar como una sal de adición de ácido farmacéuticamente aceptable, mediante la reacción de la forma de base libre del compuesto con un ácido inorgánico u orgánico farmacéuticamente aceptable. De una manera alternativa, se puede preparar una sal de adición de base

farmacéuticamente aceptable de un compuesto de la invención mediante la reacción de la forma de ácido libre del compuesto con una base inorgánica u orgánica farmacéuticamente aceptable.

Alternativamente, las formas de sal de los compuestos de la invención se pueden preparar utilizando las sales de los materiales de partida o de los intermediarios.

Las formas de ácido libre o de base libre de los compuestos de la invención se pueden preparar a partir de la forma de sal de adición de base o de sal de adición de ácido correspondiente, respectivamente. Por ejemplo, un compuesto de la invención en forma de sal de adición de ácido se puede convertir hasta la base libre correspondiente mediante su tratamiento con una base adecuada (por ejemplo, una solución de hidróxido de amonio, hidróxido de sodio, y similares). Un compuesto de la invención en forma de sal de adición de base se puede convertir hasta el ácido libre correspondiente mediante su tratamiento con un ácido adecuado (por ejemplo, ácido clorhídrico, etc.).

Los compuestos de la invención en una forma no oxidada se pueden preparar a partir de los N-óxidos de los compuestos de la invención, mediante su tratamiento con un agente de reducción (por ejemplo, azufre, dióxido de azufre, trifenil-fosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fósforo, tribromuro, o similares) en un solvente orgánico inerte adecuado (por ejemplo, acetonitrilo, etanol, dioxano acuoso, o similar), de 0°C a 80°C.

Los derivados de pro-fármaco de los compuestos de la

NO3

invención se pueden preparar mediante métodos conocidos por los expertos ordinarios en la materia (por ejemplo, para los detalles adicionales, ver Saulnier y colaboradores (1994), Bioorganic and Medicinal Chemistry Letters, Volumen 4, página 1985). Por ejemplo, se pueden preparar los pro-fármacos apropiados mediante la reacción de un compuesto no derivado de la invención con un agente carbamilo adecuado (por ejemplo, carbano-clorhidato de 1,1-aciloxi-alquilo, carbonato de *para*-nitro-fenilo, o similares).

Se pueden hacer derivados protegidos de los compuestos de la invención por medios conocidos por los expertos ordinarios en este campo. Se puede encontrar una descripción detallada de las técnicas aplicables a la creación de los grupos protectores y su remoción en T. W. Greene, "Protecting Groups in Organic Chemistry", 3ª Edición, John Wiley and Sons, Inc., 1999.

Los compuestos de la presente invención convenientemente se pueden preparar o formar durante el proceso de la invención, como solvatos (por ejemplo, hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar convenientemente mediante recristalización a partir de una mezcla de solventes acuosos/orgánicos, utilizando solventes orgánicos tales como dioxina, tetrahidrofurano, o metanol.

Los compuestos de la invención se pueden preparar como sus estereoisómeros individuales mediante la reacción de una mezcla racémica del compuesto con un agente de resolución ópticamente activo, para formar un par de compuestos diaestereoisoméricos,

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separar los diaestereómeros, y recuperar los enantiómeros ópticamente puros. Aunque la resolución de los enantiómeros se puede llevar a cabo utilizando derivados diaestereoméricos divalentes de los compuestos de la invención, se prefieren los complejos disociables (por ejemplo, las sales diaestereoméricas cristalinas). Los diaestereómeros tienen propiedades físicas distintas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.), y se pueden separar fácilmente aprovechando estas diferencias. Los diaestereómeros se pueden separar mediante cromatografía, o de preferencia mediante técnicas de separación/resolución basadas en las diferencias en la solubilidad. Entonces se recupera el enantiómero ópticamente puro, junto con el agente de resolución, mediante cualquier medio práctico que no dé como resultado la racemización. Se puede encontrar una descripción más detallada de las técnicas aplicables a la resolución de estereoisómeros de los compuestos a partir de sus mezclas racémicas en Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

En resumen, los compuestos de la Fórmula I se pueden hacer mediante un proceso que involucra:

- (a) aquéllos del Esquema de Reacción I; y
- (b) opcionalmente convertir un compuesto de la invención en una sal farmacéuticamente aceptable;
- (c) opcionalmente convertir una forma de sal de un

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compuesto de la invención hasta una forma que no sea de sal;

(d) opcionalmente convertir una forma no oxidada de un compuesto de la invención en un N-óxido farmacéuticamente aceptable;

5 (e) opcionalmente convertir una forma de N-óxido de un compuesto de la invención hasta su forma no oxidada;

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

(g) opcionalmente convertir un compuesto no derivado de la
10 invención en un derivado de pro-fármaco farmacéuticamente aceptable; y

(h) opcionalmente convertir un derivado de pro-fármaco de un compuesto de la invención hasta su forma no derivada.

Hasta donde no se describa particularmente la producción de
15 los materiales de partida, los compuestos son conocidos o se pueden preparar de una manera análoga a los métodos conocidos en la técnica, o como se da a conocer en los Ejemplos que se encuentran posteriormente en la presente.

Un experto en la materia apreciará que las transformaciones
20 anteriores solamente son representativas de los métodos para la preparación de los compuestos de la presente invención, y que se pueden emplear similarmente otros métodos bien conocidos.

Ejemplos

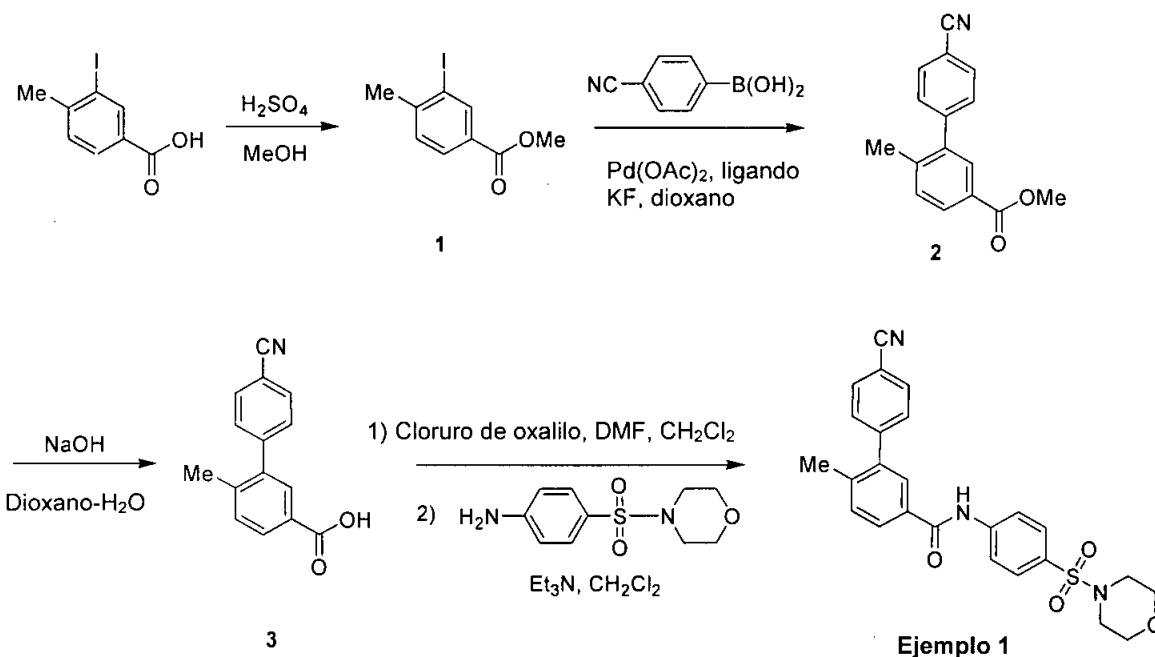
La presente invención se ejemplifica adicionalmente, pero no
25 se limita, mediante el siguiente Ejemplo que ilustra la preparación de

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los compuestos de la Fórmula I de acuerdo con la invención.

Ejemplo 1

[4-(morfolin-4-sulfonyl)-fenil]-amida del ácido 4'-ciano-4-metil-bifenil-3-carboxílico



Paso 1: A una solución del ácido 3-yodo-4-metil-benzoico (10.0 gramos, 38.2 milimoles) en metanol (70 mililitros), se le agrega ácido sulfúrico concentrado (0.5 mililitros). La mezcla de reacción se calienta a 70°C durante 48 horas, se enfría a temperatura ambiente, y luego se concentra. Después de eso, se agregan acetato de etilo (100 mililitros), y una solución acuosa de NaHCO₃ (saturada, 100 mililitros) al residuo. La capa orgánica se separa y se lava nuevamente con una solución acuosa de NaHCO₃ (saturada, 100 mililitros). La capa orgánica se separa, se seca sobre Na₂SO₄ anhidro, y se concentra, para proporcionar el metil-éster del ácido 3-

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yodo-4-metil-benzoico 1. Éste se utiliza sin mayor purificación en el siguiente paso. ^1H RMN (400 MHz, DMSO- d_6) δ 8.31 (s, 1 H), 7.87 (d, 1 H, $J = 8.4$ Hz), 7.48 (d, 1 H, $J = 8.4$ Hz), 3.85 (s, 3 H), 3.35 (s, 3H); LC-MS m/z : 277.0 ($M+1$).

5 **Paso 2:** A un matraz de fondo redondo que contiene el metil-éster del ácido 3-yodo-4-metil-benzoico (1.38 gramos, 5.00 milimoles), ácido 4-ciano-fenil-borónico (1.10 gramos, 7.48 milimoles), acetato de paladio (168 miligramos, 0.748 milimoles), 2-(diciclo-hexil-fosfino)-bifenilo (0.526 gramos, 1.50 milimoles), y
10 fluoruro de potasio (0.870 gramos, 15.0 milimoles), se le agrega 1,4-dioxano anhidro (15 mililitros). El matraz se purga con argón y se sella. La mezcla se agita a 130°C durante 18 horas, se enfría a temperatura ambiente, y luego se agregan agua (20 mililitros) y acetato de etilo (20 mililitros). El sólido se remueve mediante
15 filtración al vacío. El filtrado se extrae con EtOAc (20 mililitros, dos veces). Las capas orgánicas se combinan, se lavan con HCl acuoso (al 5 por ciento, 20 mililitros), y NaHCO_3 saturado (20 mililitros). Se secan sobre MgSO_4 , y se concentran. El residuo se purifica mediante
20 cromatografía en columna de gel de sílice (EtOAc/hexano, gradiente), para dar el metil-éster del ácido 4'-ciano-6-metil-bifenil-3-carboxílico 2: LC-MS m/z : 252.1 ($M+1$).

Paso 3: A una solución del metil-éster del ácido 4'-ciano-6-metil-bifenil-3-carboxílico 2 (2.56 gramos, 10.3 milimoles) en 1,4-dioxano- H_2O (mezcla de 1:1, 20 mililitros), se le agrega NaOH (1.22
25 gramos, 30.2 milimoles). La reacción se agita a temperatura

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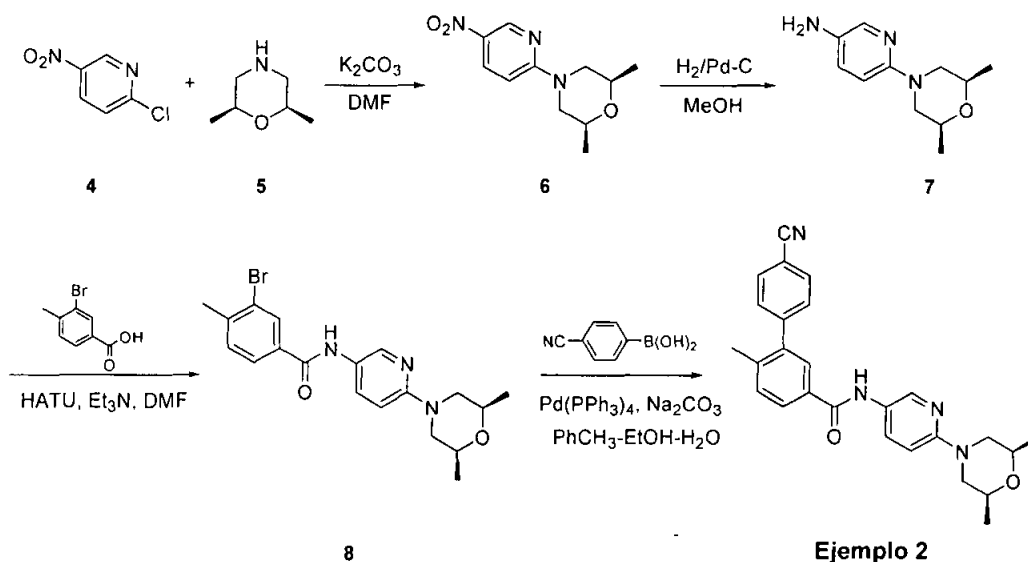
ambiente durante 24 horas. A esta mezcla se le agrega HCl acuoso (1N, 36 mililitros), y luego se extrae con acetato de etilo (140 mililitros, tres veces). Las capas orgánicas se combinan, y se secan sobre Na₂SO₄ anhidro. Se remueve el solvente. El sólido obtenido se lava con una pequeña cantidad de acetonitrilo, y se seca al aire, para dar el ácido 4'-ciano-6-metil-bifenil-3-carboxílico 3: ¹H RMN (DMSO-d₆) δ 7.94 (d, 2 H, J = 8.0 Hz), 7.84 (dd, 1 H, J₁ = 8.4 Hz, J₂ = 1.2 Hz), 7.75 (d, 1 H, J = 1.2 Hz), 7.61 (d, 2 H, J = 8.0 Hz), 7.48 (d, 1 H, J = 8.4 Hz), 2.29 (s, 3 H); LC-MS m/z 238.1 (M+1).

Paso 4: A una suspensión del ácido 4'-ciano-6-metil-bifenil-3-carboxílico 3 (40 miligramos, 0.17 milimoles) en cloruro de metileno anhidro (5 mililitros), se le agregan 2 gotas de dimetil-formamida. Luego se agrega cloruro de oxalilo (32 miligramos, 22 microlitros, 0.25 milimoles). La mezcla se agita a temperatura ambiente hasta que se hace transparente. Después de eso, se concentra, se vuelve a disolver en cloruro de metileno anhidro (3 mililitros), y se agrega a una solución de 4-(morfolin-4-sulfonil)-fenil-amina (61 miligramos, 0.25 milimoles) y trietil-amina (34 miligramos, 47 microlitros, 0.33 milimoles) en cloruro de metileno (2 mililitros). La mezcla se agita durante 2 horas, se concentra, y el residuo se purifica mediante HPLC de preparación dirigida a la masa (columna C18, eluida con CH₃CN-H₂O conteniendo ácido trifluoro-acético al 0.05 por ciento), para dar la [4-(morfolin-4-sulfonil)-fenil]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico: ¹H RMN (DMSO-d₆) δ 10.64 (s, 1 H), 8.07(d, 2 H, J = 8.8 Hz), 7.97 (d, 2 H, J = 8.4 Hz),

7.95 (d, 1 H, $J = 8.8$ Hz), 7.89 (s, 1 H), 7.43 (d, 2 H, $J = 8.4$ Hz), 7.67 (d, 2 H, $J = 8.8$ Hz), 7.53 (d, 2 H, $J = 8.8$ Hz), 3.63 (m, 4 H), 2.84 (m, 4 H) 2.32 (s, 3 H); LC-MS m/z : 462.1 ($M+1$).

Ejemplo 2

5 [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico



Paso 1: A una solución de la 2-cloro-5-nitro-piridina 4 (2.38 gramos, 15 milimoles), y *cis*-2,6-dimetil-morfolina (1.73 gramos, 15 milimoles), se le agrega K_2CO_3 (4.14 gramos, 30 milimoles). La mezcla se calienta a $50^\circ C$ durante la noche. Después de la concentración, el residuo se divide entre EtOAc y agua. La capa de EtOAc se seca sobre Na_2SO_4 anhidro, y se concentra, para dar el producto crudo 6 como un sólido amarillo. El producto crudo se utiliza directamente en el siguiente paso sin mayor purificación. LC-MS m/z : 238.1 ($M+1$).

Paso 2: El material crudo 6 anterior se hidrogena en la

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presencia de Pd-C (0.2 gramos) en MeOH (100 mililitros) bajo hidrógeno durante 10 horas. La suspensión se filtra a través de Celite, y el filtrado se concentra, para dar el producto crudo 7 como un aceite color café oscuro, el cual se utiliza directamente en el siguiente paso sin mayor purificación. LC-MS m/z: 208.1 (M+1).

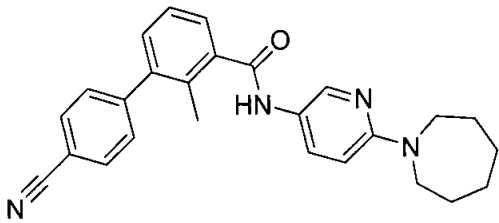
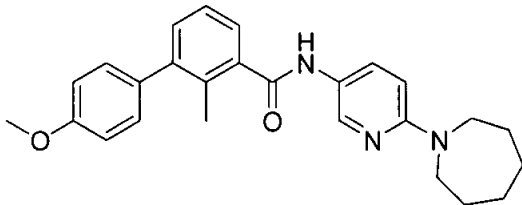
Paso 3: A una solución del ácido 3-bromo-4-metil-benzoico (108 miligramos, 0.5 milimoles), 6-(2,6-dimetil-morfolin-4-il)-piridin-3-il-amina 7 (104 miligramos, 0.5 milimoles), y HATU (190 miligramos, 0.5 milimoles) en dimetil-formamida seca (5 mililitros), se le agrega trietil-amina (139 microlitros, 1.0 milimoles) por goteo. La mezcla resultante se agita a temperatura ambiente durante 2 horas. Después de la concentración, el residuo se divide entre EtOAc y agua. La capa orgánica se seca y se concentra para dar el producto crudo. El compuesto final se purifica mediante cromatografía en columna por evaporación instantánea, utilizando EtOAc al 50 por ciento en hexano como eluyente, para dar el 8 como un sólido blanco. LC-MS m/z: 404.1 (M+1).

Paso 4: Una mezcla del ácido 4-ciano-fenil-borónico (18 miligramos, 0.12 milimoles), 3-bromo-N-[6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-4-metil-benzamida 8 (40 miligramos, 0.1 milimoles), Pd(PPh₃)₄ (11 miligramos, 0.01 milimoles), y Na₂CO₃ (42 miligramos, 0.4 milimoles) en un sistema de solventes combinados de tolueno (0.2 mililitros) y agua (0.2 mililitros) y etanol (0.05 mililitros), se calienta a 140°C bajo irradiación por microondas durante 30 minutos. La mezcla de reacción se diluye con EtOAc y agua. La capa acuosa

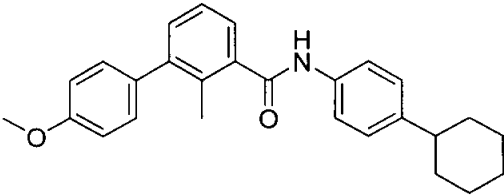
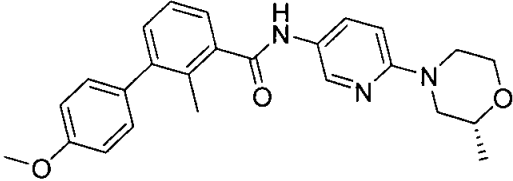
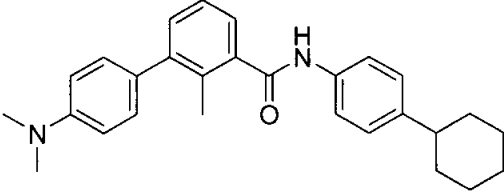
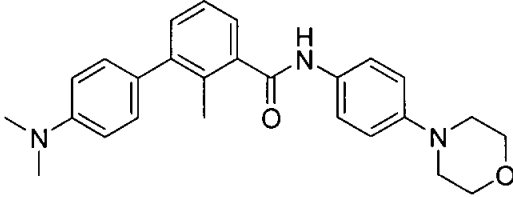
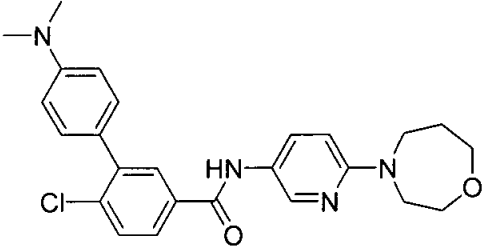
se extrae con EtOAc. La capa orgánica combinada se lava con salmuera y se concentra, para dar el producto crudo, el cual se purifica mediante HPLC de preparación dirigida a la masa (columna C18, eluida con CH₃CN-H₂O conteniendo ácido trifluoro-acético al 0.05 por ciento), para dar la [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico. LC-MS m/z: 427.2 (M+1).

Mediante la repetición de los procedimientos descritos en los Ejemplos anteriores, utilizando los materiales de partida apropiados, se obtienen los siguientes compuestos de la Fórmula I, como se identifican en la Tabla 1.

Tabla 1

Compuesto Número	Estructura	Datos Físicos MS (m/z)
3		LC-MS m/z 411.2 (M+1).
4		LC-MS m/z 416.2 (M+1).

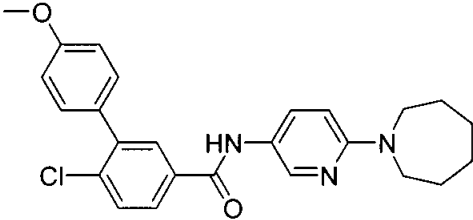
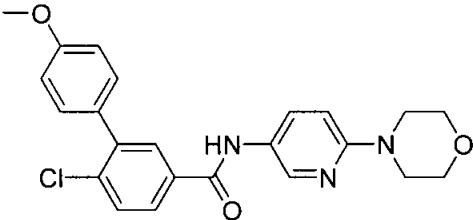
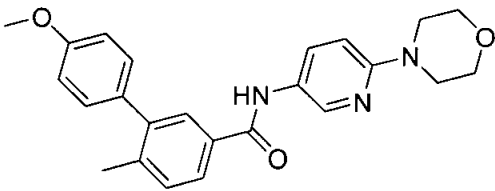
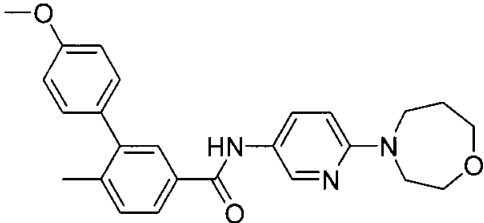
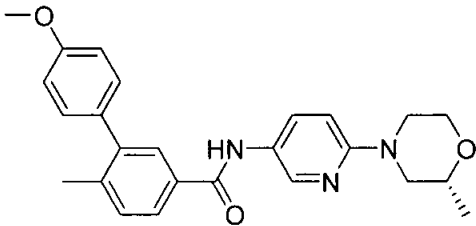
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Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	5		LC-MS <i>m/z</i> 400.2 (M+1).
10	6		LC-MS <i>m/z</i> 418.2 (M+1).
15	7		LC-MS <i>m/z</i> 413.2 (M+1).
20	8		LC-MS <i>m/z</i> 416.2 (M+1).
25	9		LC-MS <i>m/z</i> 451.2 (M+1).

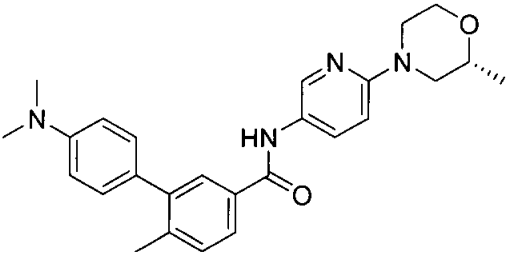
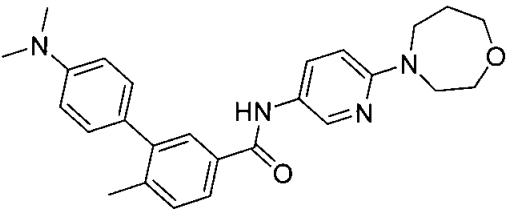
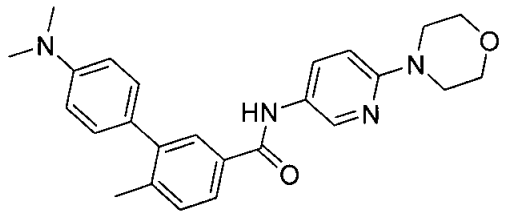
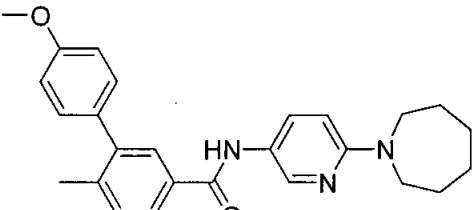
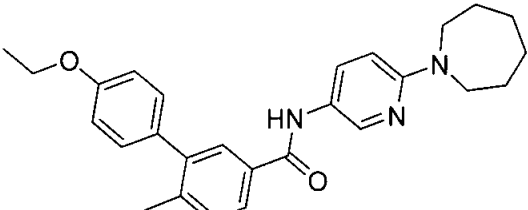


Compuesto Número	Estructura	Datos Físicos MS (m/z)
5		LC-MS <i>m/z</i> 437.2 (M+1).
10		
10		LC-MS <i>m/z</i> 449.2 (M+1).
15		
15		LC-MS <i>m/z</i> 438.2 (M+1).
20		
20		LC-MS <i>m/z</i> 438.2 (M+1).
25		

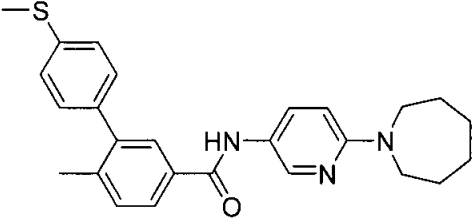
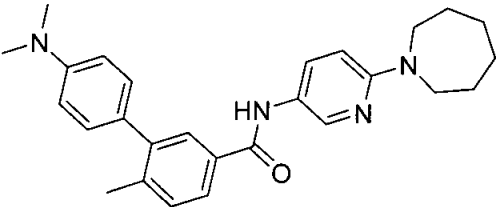
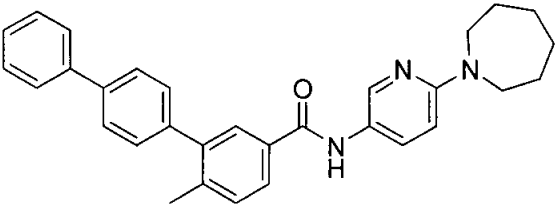
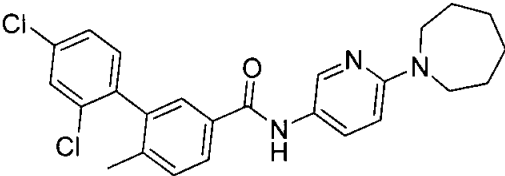
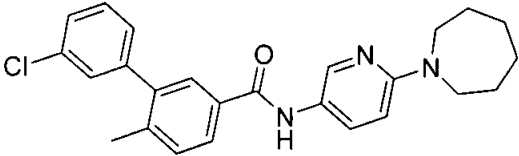
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Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	14		LC-MS <i>m/z</i> 436.2 (M+1).
10	15		LC-MS <i>m/z</i> 424.1 (M+1).
15	16		LC-MS <i>m/z</i> 404.2 (M+1).
20	17		LC-MS <i>m/z</i> 418.2 (M+1).
25	18		LC-MS <i>m/z</i> 418.2 (M+1).

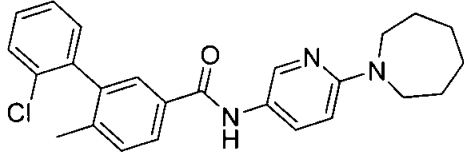
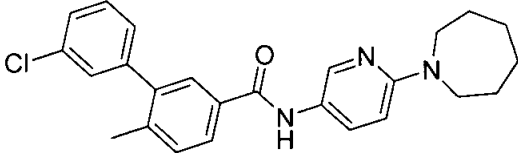
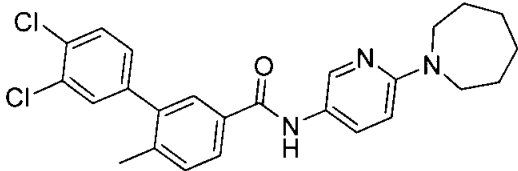
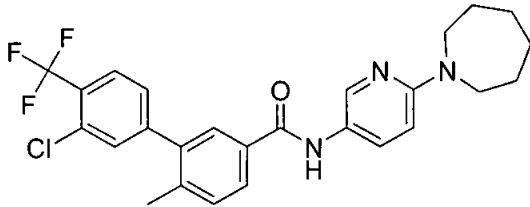
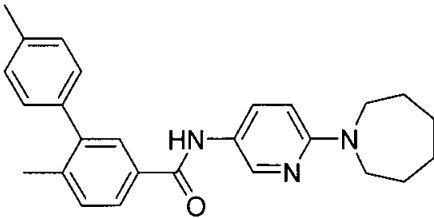
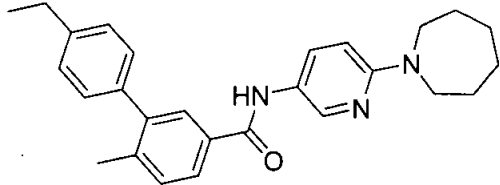
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Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	19		LC-MS <i>m/z</i> 431.2 (M+1).
10	20		LC-MS <i>m/z</i> 431.2 (M+1).
15	21		LC-MS <i>m/z</i> 417.2 (M+1).
20	22		LC-MS <i>m/z</i> 416.2 (M+1).
25	23		LC-MS <i>m/z</i> 430.2 (M+1).

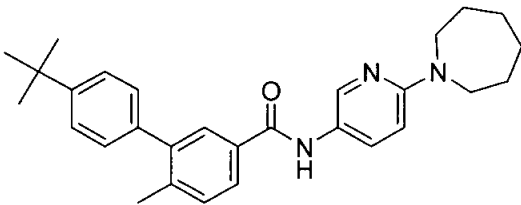
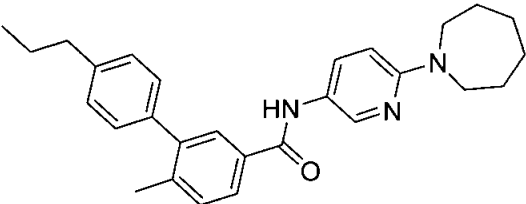
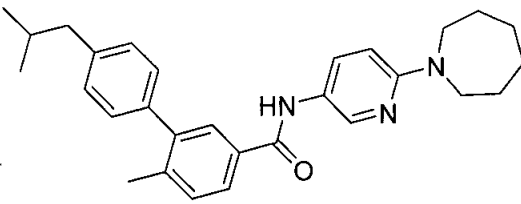
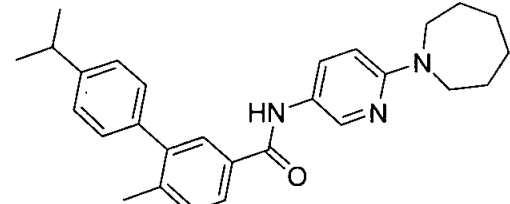
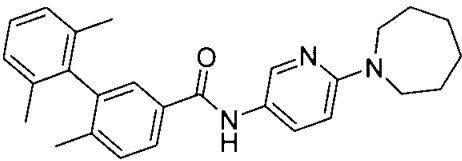
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Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	24		LC-MS <i>m/z</i> 432.2 (M+1).
10	25		LC-MS <i>m/z</i> 429.2 (M+1).
15	26		LC-MS <i>m/z</i> 462.2 (M+1).
20	27		LC-MS <i>m/z</i> 454.1 (M+1).
25	28		LC-MS <i>m/z</i> 420.2 (M+1).

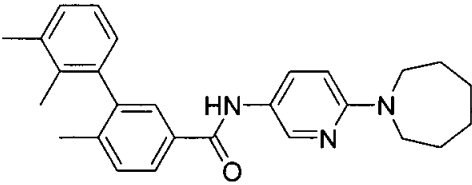
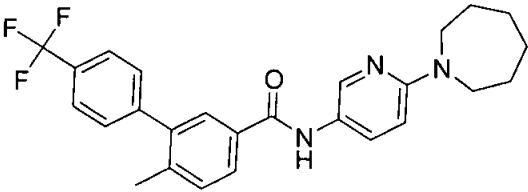
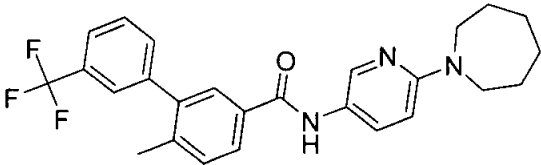
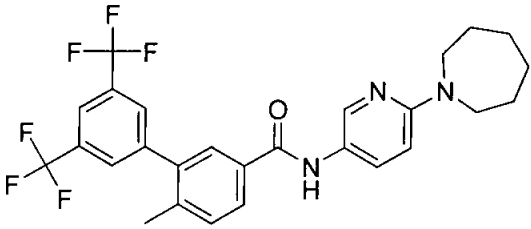
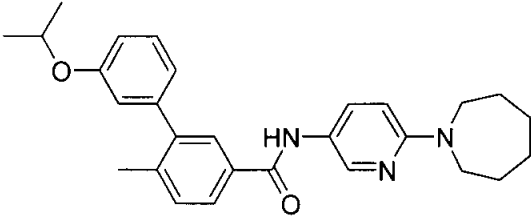
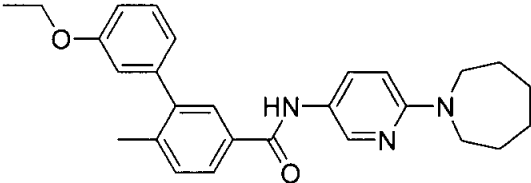
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Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	29		LC-MS m/z 420.2 (M+1).
	30		LC-MS m/z 420.2 (M+1).
10	31		LC-MS m/z 454.2 (M+1).
	32		LC-MS m/z 488.1 (M+1).
15	33		LC-MS m/z 400.2 (M+1).
	34		LC-MS m/z 414.2 (M+1).
20			
25			

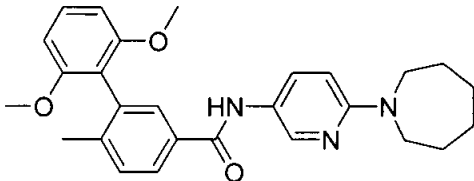
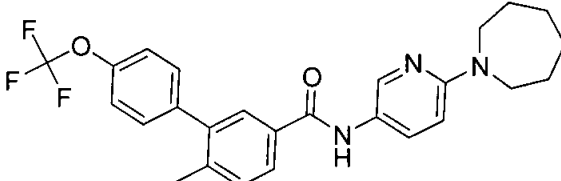
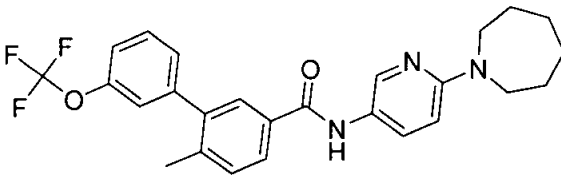
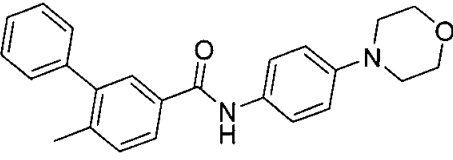
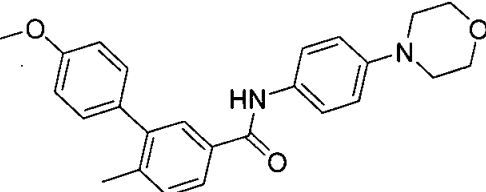
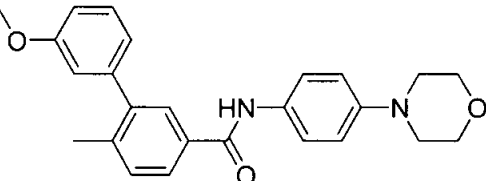
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Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	35		LC-MS <i>m/z</i> 442.2 (M+1).
10	36		LC-MS <i>m/z</i> 428.2 (M+1).
15	37		LC-MS <i>m/z</i> 442.2 (M+1).
20	38		LC-MS <i>m/z</i> 428.2 (M+1).
25	39		LC-MS <i>m/z</i> 414.2 (M+1).

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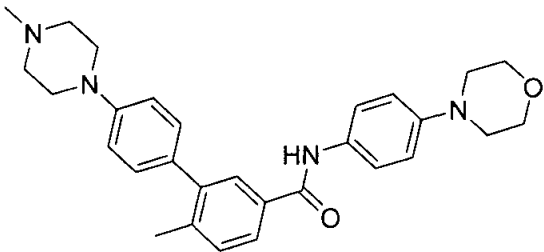
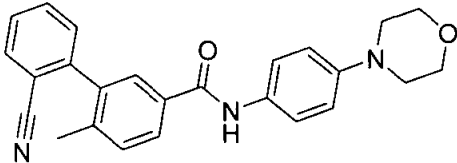
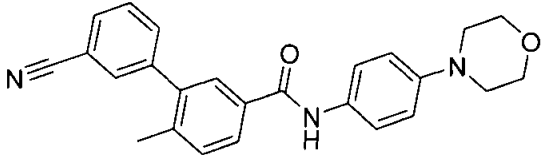
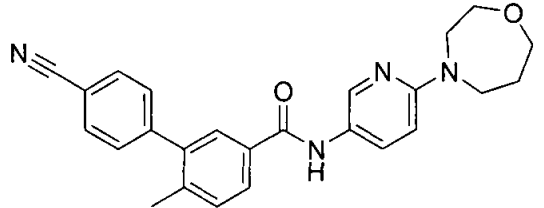
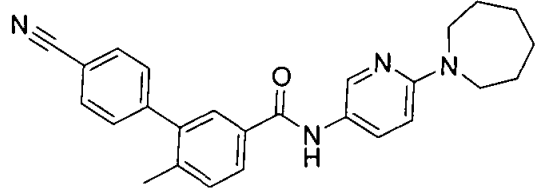
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5	40		LC-MS <i>m/z</i> 414.2 (M+1).
	41		LC-MS <i>m/z</i> 454.2 (M+1).
	42		LC-MS <i>m/z</i> 454.2 (M+1).
	43		LC-MS <i>m/z</i> 522.2 (M+1).
	44		LC-MS <i>m/z</i> 444.2 (M+1).
25	45		LC-MS <i>m/z</i> 430.2 (M+1).

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Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	46		LC-MS <i>m/z</i> 446.2 (M+1).
10	47		LC-MS <i>m/z</i> 470.2 (M+1).
15	48		LC-MS <i>m/z</i> 470.2 (M+1).
20	49		LC-MS <i>m/z</i> 373.2 (M+1).
25	50		LC-MS <i>m/z</i> 403.2 (M+1).
25	51		LC-MS <i>m/z</i> 403.2 (M+1).

Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	52		LC-MS <i>m/z</i> 460.2 (M+1).
	53		LC-MS <i>m/z</i> 416.2 (M+1).
	54		LC-MS <i>m/z</i> 391.2 (M+1).
	55		LC-MS <i>m/z</i> 391.2 (M+1).
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25	57		LC-MS <i>m/z</i> 425.2 (M+1).

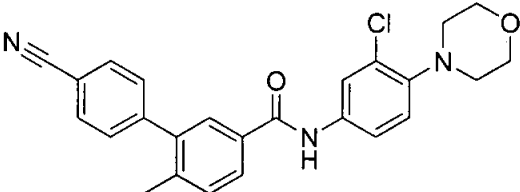
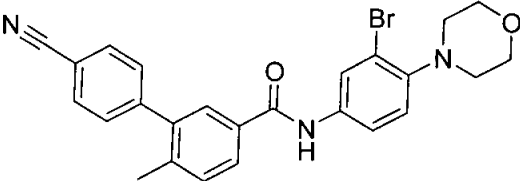
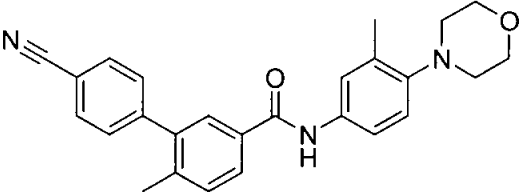
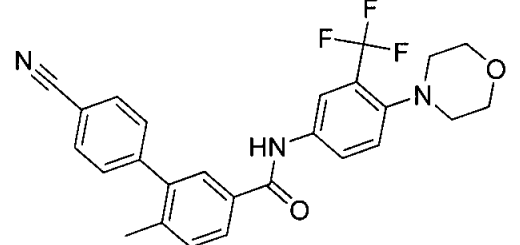
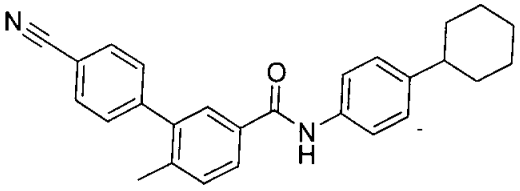
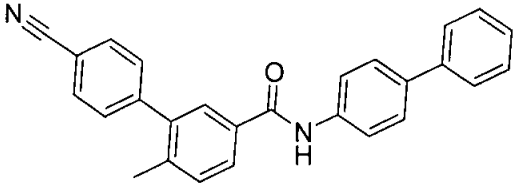
122

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 58		LC-MS <i>m/z</i> 471.2 (M+1).
10 59		LC-MS <i>m/z</i> 398.2 (M+1).
15 60		LC-MS <i>m/z</i> 398.2 (M+1).
20 61		LC-MS <i>m/z</i> 413.2 (M+1).
25 62		LC-MS <i>m/z</i> 411.2 (M+1).



Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	63		LC-MS m/z
			413.2 (M+1).
10	64		LC-MS m/z
			397.2 (M+1).
15	65		LC-MS m/z
			399.2 (M+1).
20	66		LC-MS m/z
			412.2 (M+1).
25	67		LC-MS m/z
			398.2 (M+1).
	68		LC-MS m/z 416.2 (M+1).

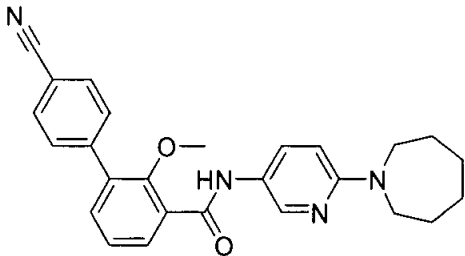
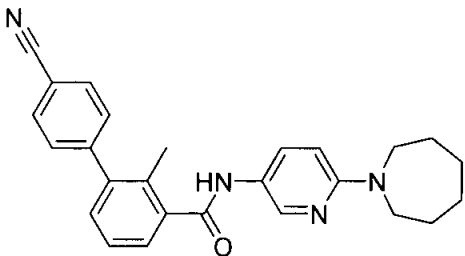
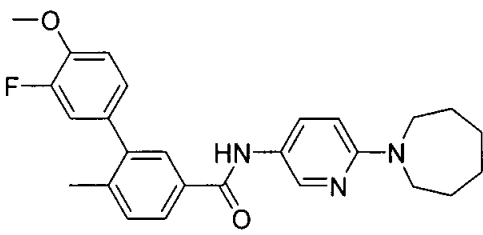
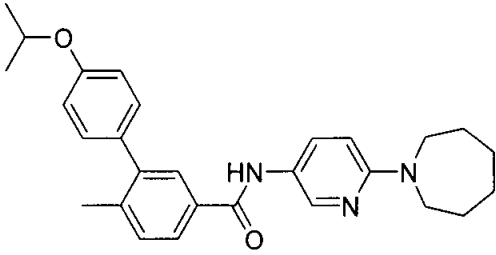
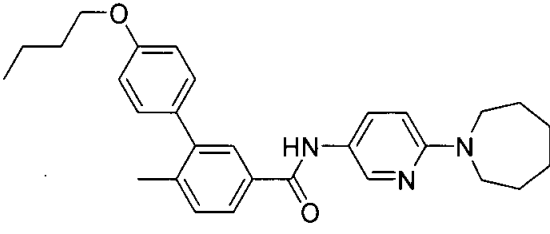
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Compuesto Número		Estructura	Datos Físicos MS (m/z)
5	69		LC-MS m/z 432.1 (M+1).
	70		LC-MS m/z 476.1 (M+1).
	71		LC-MS m/z 412.2 (M+1).
	72		LC-MS m/z 466.2 (M+1).
	73		LC-MS m/z 385.2 (M+1).
25	74		LC-MS m/z 389.1 (M+1).

125

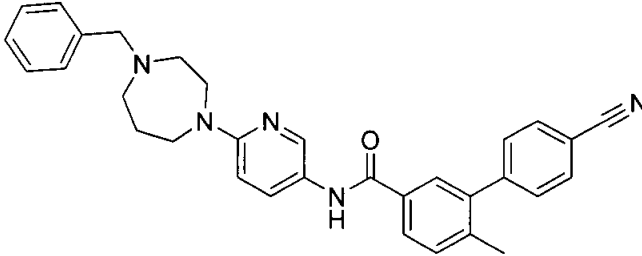
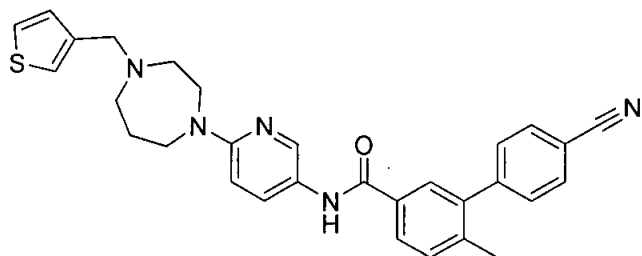
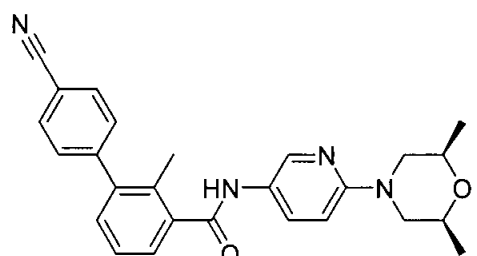
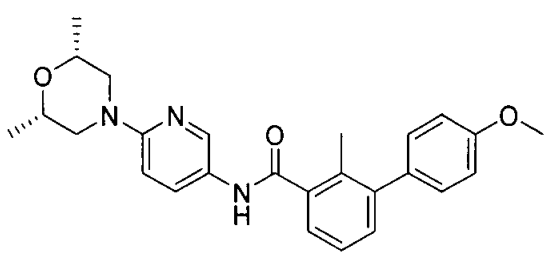
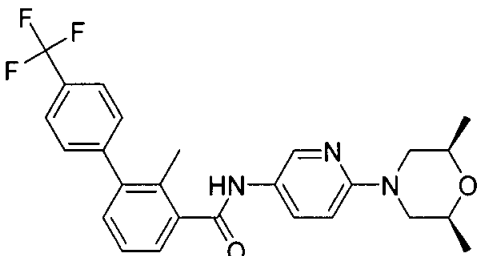
Compuesto Número	Estructura	Datos Físicos MS (m/z)
5	75	LC-MS m/z 419.2 (M+1).
10	76	LC-MS m/z 487.2 (M+1).
15	77	LC-MS m/z 460.2 (M+1).
20	78	LC-MS m/z 446.1 (M+1).
25	79	LC-MS m/z 427.2 (M+1).

Pb

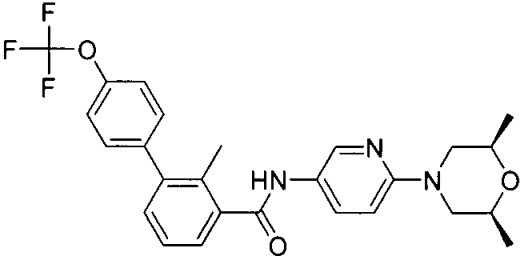
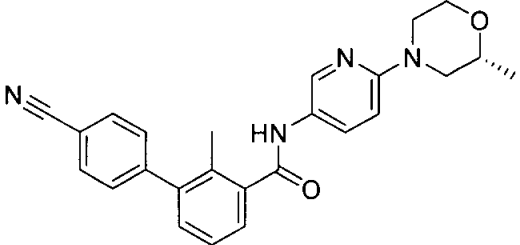
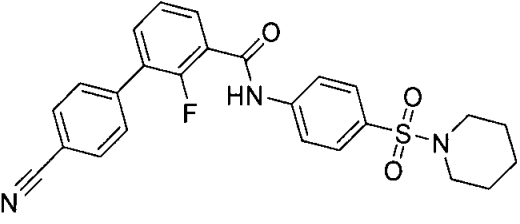
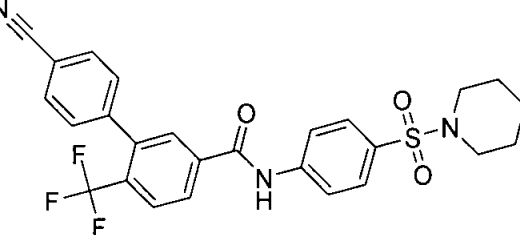
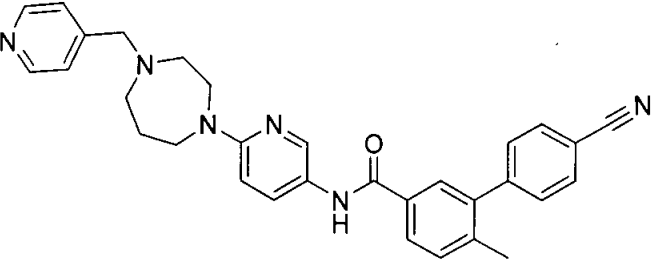
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5 80		LC-MS <i>m/z</i> 427.2 (M+1)
10 81		LC-MS <i>m/z</i> 411.2 (M+1)
15 82		LC-MS <i>m/z</i> 434.2 (M+1)
20 83		LC-MS <i>m/z</i> 444.3 (M+1)
25 84		LC-MS <i>m/z</i> 458.3 (M+1)

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 85		LC-MS <i>m/z</i> 450.2 (M+1)
10 86		LC-MS <i>m/z</i> 430.2 (M+1)
15 87		LC-MS <i>m/z</i> 460.2 (M+1)
20 88		LC-MS <i>m/z</i> 464.1(M+1)
25 89		LC-MS <i>m/z</i> 524.1 (M+1)

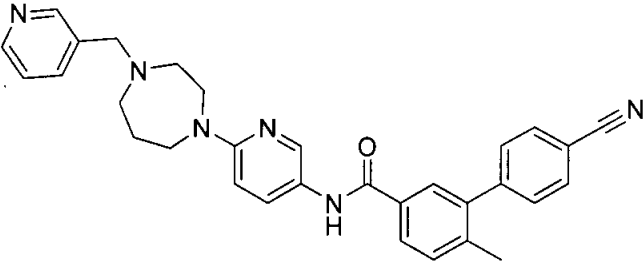
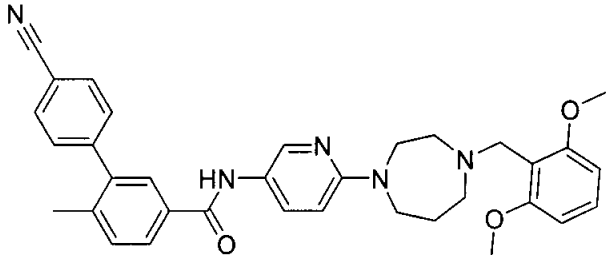
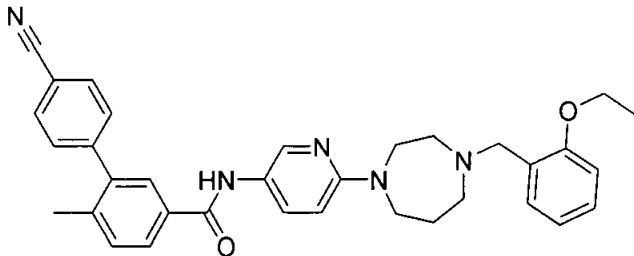
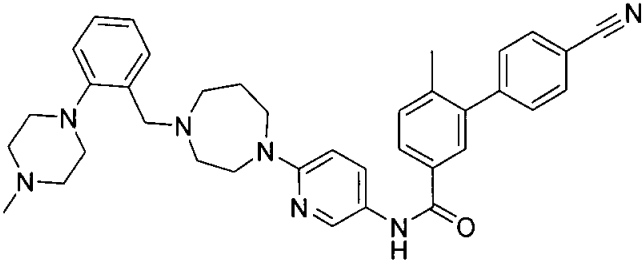
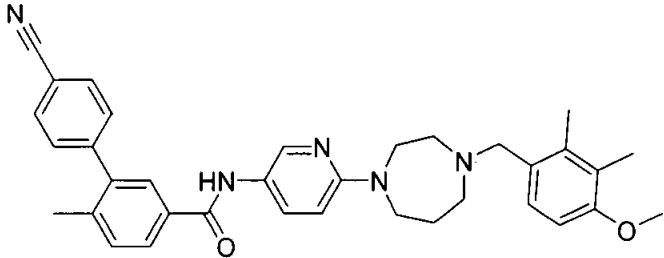
128

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 90		LC-MS <i>m/z</i> 502.3 (M+1)
10 91		LC-MS <i>m/z</i> 508.2 (M+1)
15 92		LC-MS <i>m/z</i> 427.2 (M+1)
20 93		LC-MS <i>m/z</i> 432.2 (M+1)
25 94		LC-MS <i>m/z</i> 470.2 (M+1)

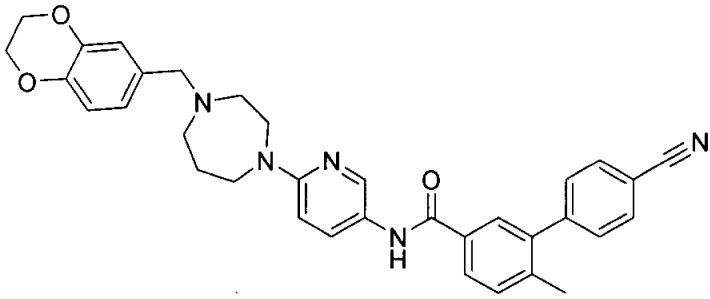
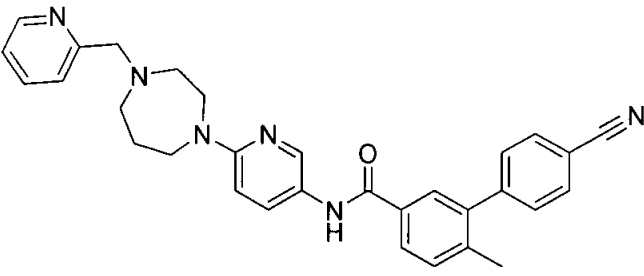
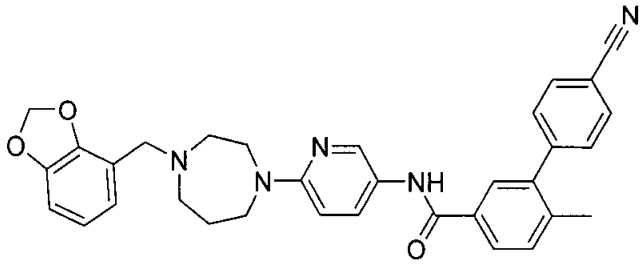
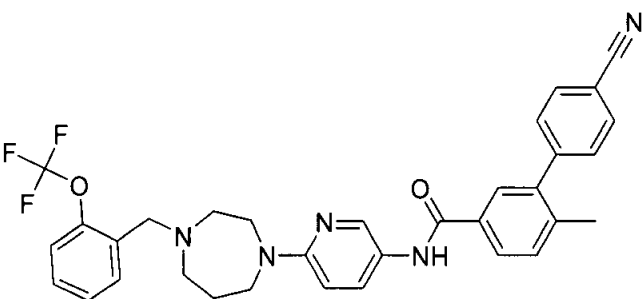
129

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 95		LC-MS <i>m/z</i> 486.2 (M+1)
10 96		LC-MS <i>m/z</i> 413.2 (M+1)
15 97		LC-MS <i>m/z</i> 464.1 (M+1)
20 98		LC-MS <i>m/z</i> 514.1 (M+1)
25 99		LC-MS <i>m/z</i> 503.3 (M+1)

190

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 100		LC-MS <i>m/z</i> 503.3 (M+1)
10 101		LC-MS <i>m/z</i> 562.3 (M+1)
15 102		LC-MS <i>m/z</i> 546.3 (M+1)
20 103		LC-MS <i>m/z</i> 600.3 (M+1)
25 104		LC-MS <i>m/z</i> 560.3 (M+1)

B1

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 105		LC-MS <i>m/z</i> 560.3 (M+1)
10 106		LC-MS <i>m/z</i> 503.3 (M+1)
15 107		LC-MS <i>m/z</i> 546.2 (M+1)
20 108		LC-MS <i>m/z</i> 586.2 (M+1)

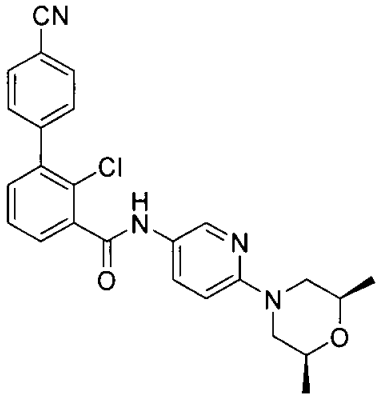
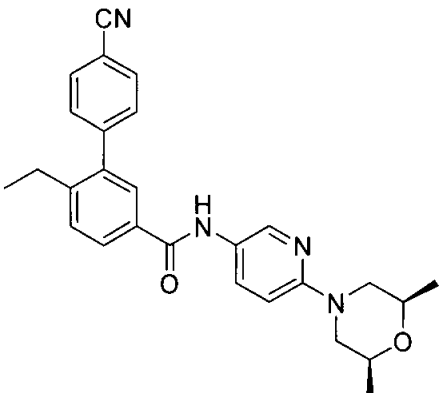
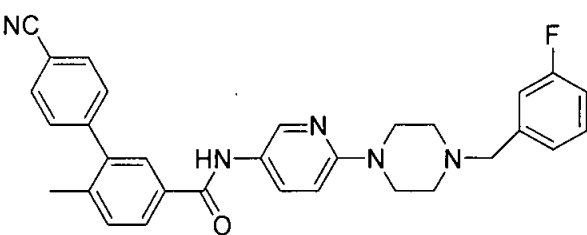
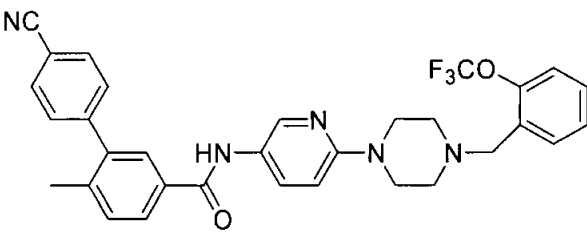


Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 109		LC-MS <i>m/z</i> 545.3 (M+1)
10 110		LC-MS <i>m/z</i> 604.2 (M+1)
15 111		LC-MS <i>m/z</i> 538.2 (M+1)
20 112		LC-MS <i>m/z</i> 554.2 (M+1)
25		



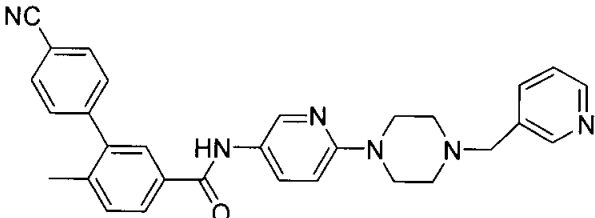
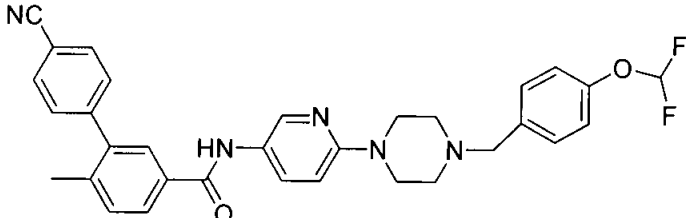
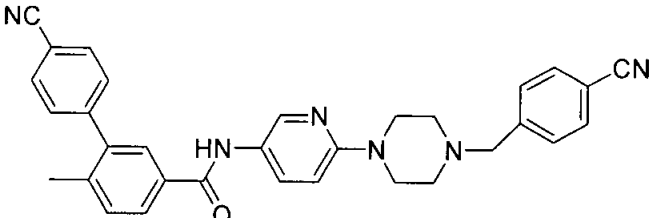
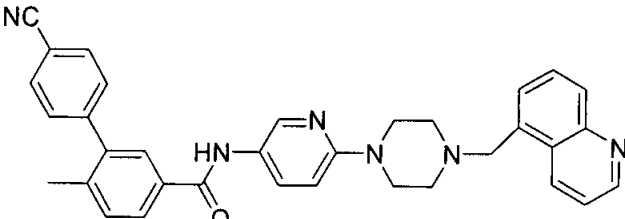
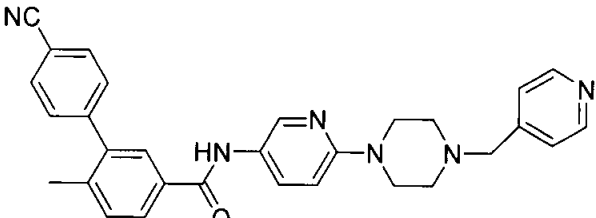
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5 113		LC-MS <i>m/z</i> 538.2 (M+1)
10 114		LC-MS <i>m/z</i> 480.1 (M+1)
20 115		LC-MS <i>m/z</i> 481.2 (M+1)
25		

34

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 116		LC-MS <i>m/z</i> 447.2 (M+1)
10 117		LC-MS <i>m/z</i> 441.2 (M+1)
15 118		LC-MS <i>m/z</i> 506.2 (M+1)
20 119		LC-MS <i>m/z</i> 572.2 (M+1)
25		



Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 120		LC-MS <i>m/z</i> 522.2 (M+1)
10 121		LC-MS <i>m/z</i> 544.3 (M+1)
15 122		LC-MS <i>m/z</i> 544.3 (M+1)
20 123		LC-MS <i>m/z</i> 562.2 (M+1)
25 124		LC-MS <i>m/z</i> 488.2 (M+1)

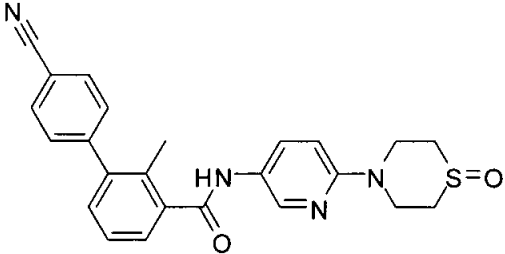
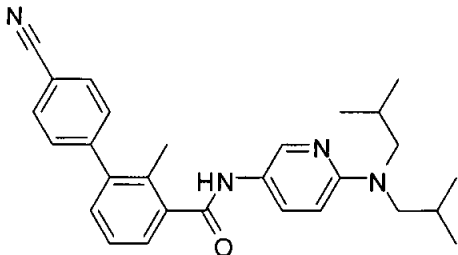
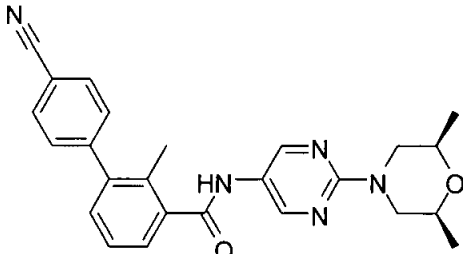
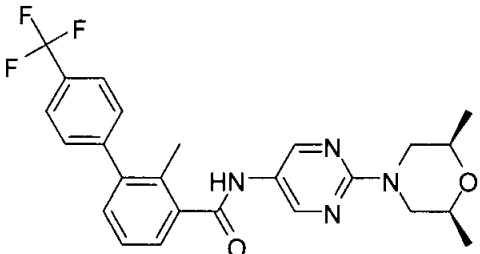
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5 125		LC-MS <i>m/z</i> 489.2 (M+1)
10 126		LC-MS <i>m/z</i> 554.2 (M+1)
15 127		LC-MS <i>m/z</i> 513.2 (M+1)
20 128		LC-MS <i>m/z</i> 539.3 (M+1)
25 129		LC-MS <i>m/z</i> 489.2 (M+1)

136

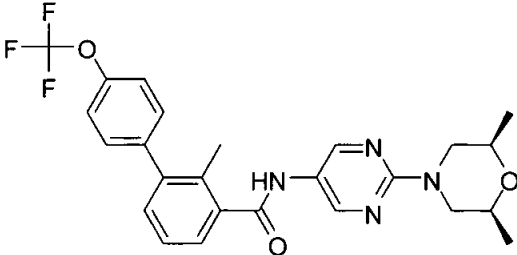
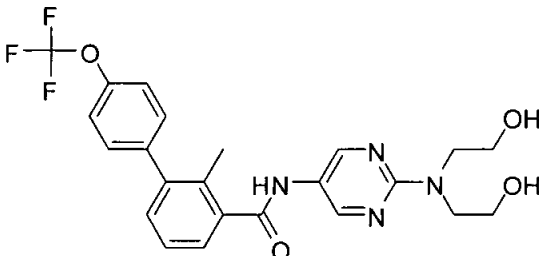
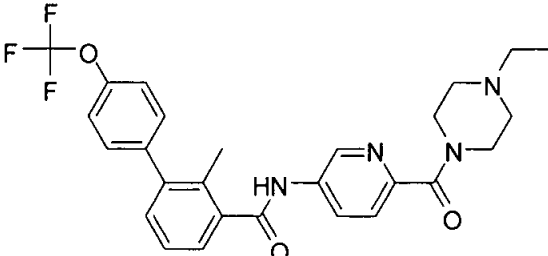
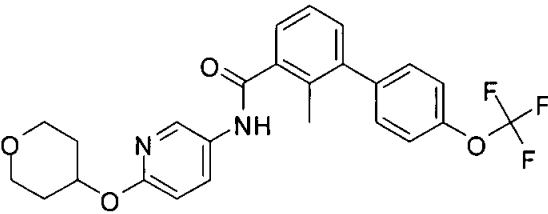


Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 130		LC-MS <i>m/z</i> 489.2 (M+1)
10 131		LC-MS <i>m/z</i> 554.3 (M+1)
15 132		LC-MS <i>m/z</i> 513.2 (M+1)
20 133		LC-MS <i>m/z</i> 539.3 (M+1)
25		

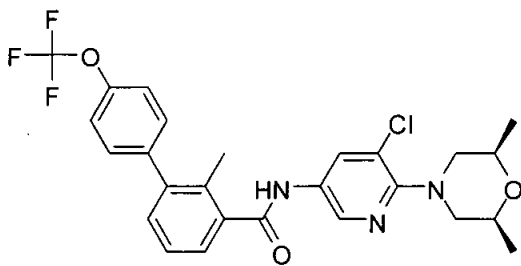
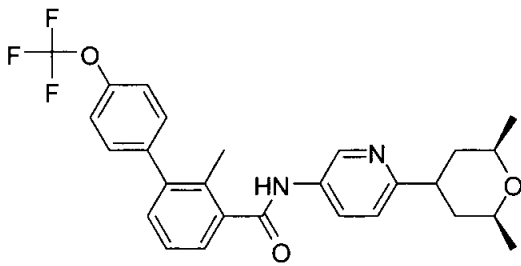
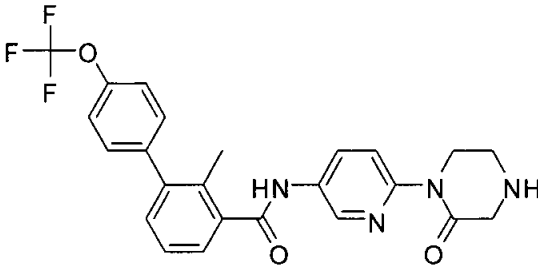
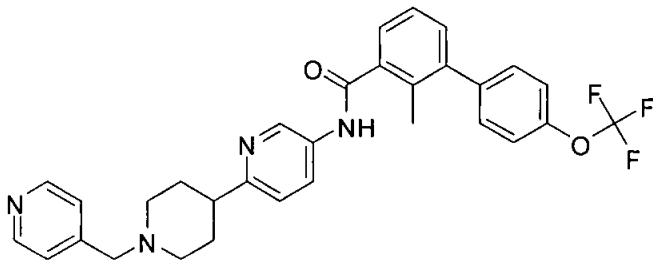
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5 134		LC-MS <i>m/z</i> 472.1 (M+1)
10 135		LC-MS <i>m/z</i> 447.1 (M+1)
15 136		LC-MS <i>m/z</i> 413.1 (M+1)
20 137		LC-MS <i>m/z</i> 492.1 (M+1)
25		

	Compuesto Número	Estructura	Datos Físicos MS (m/z)
5	138		LC-MS <i>m/z</i> 431.1 (M+1)
10	139		LC-MS <i>m/z</i> 441.1 (M+1)
15	140		LC-MS <i>m/z</i> 428.2 (M+1)
20	141		LC-MS <i>m/z</i> 471.2 (M+1)
25			

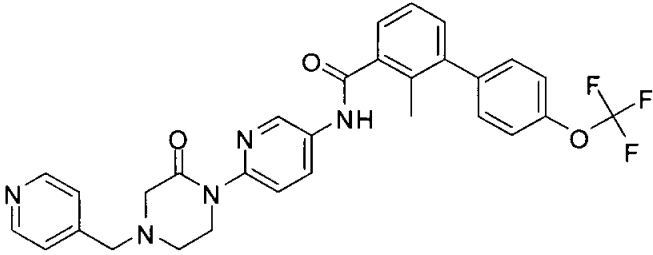
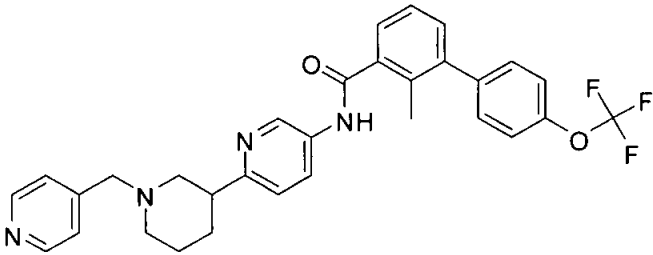
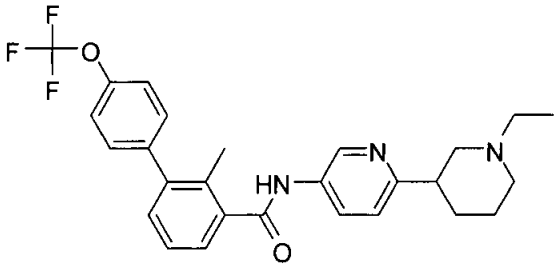
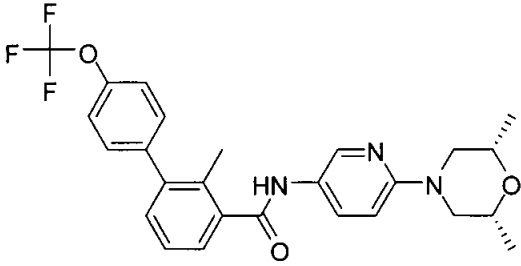
140

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 142		LC-MS <i>m/z</i> 487.2 (M+1)
10 143		LC-MS <i>m/z</i> 477.2 (M+1)
15 144		LC-MS <i>m/z</i> 513.2 (M+1)
20 145		LC-MS <i>m/z</i> 473.2 (M+1)

141

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 146		LC-MS <i>m/z</i> 520.2 (M+1)
10 147		LC-MS <i>m/z</i> 445.2 (M+1)
15 148		LC-MS <i>m/z</i> 471.2 (M+1)
20 149		LC-MS <i>m/z</i> 547.2 (M+1)
25		

142

Compuesto Número	Estructura	Datos Físicos MS (m/z)
5 150		LC-MS <i>m/z</i> 562.2 (M+1)
10 151		LC-MS <i>m/z</i> 547.2 (M+1)
15 152		LC-MS <i>m/z</i> 484.2 (M+1)
20 153		LC-MS <i>m/z</i> 486.2 (M+1)
25		

Los compuestos de la presente invención se ensayan para evaluar su capacidad para inhibir la senda de señalización de Hedgehog.

Ensayo de Reportero Gli-Luc para la Inhibición de la Senda de Hh

5 Las células de ratón TM3 (obtenidas en la American Type Culture Collection, ATCC, Manassas, VA) se cultivan en un medio de DMEM/F12 (Gibco/Invitrogen, Carlsbad, CA) complementado con suero de caballo inactivado por calor al 5 por ciento y suero bovino fetal al 2.5 por ciento (Gibco/Invitrogen, Carlsbad, CA), 50
10 unidades/mililitro de penicilina, y 50 microgramos/mililitro de estreptomicina (Gibco/Invitrogen, Carlsbad, CA) a 37°C, con CO₂ al 5 por ciento en una atmósfera de aire. Las células TM3 se transfectan con el plásmido reportero pTA-8xGli-Luc. Se seleccionó un clon establemente transfectado denominado como TMHh-12. El clon
15 TMHh-12 mostró una buena respuesta al estímulo de Shh-N. Con el fin de evaluar las IC₅₀s de los antagonistas, se aplicaron 8,000 células TMHh-12 en cada pozo de placas de 384 pozos con medio de DMEM/F12 al 50 por ciento complementado con suero bovino fetal al 2 por ciento. Después de 12 horas, se activa la senda de Hh
20 mediante la adición de la proteína Shh de ratón recombinante (expresada en *E. coli*, 8 microgramos/mililitro), o mediante la adición de agonistas de Smo. Se agregan los compuestos de prueba a las placas en diferentes concentraciones. Después de 48 horas, se ensayan las actividades de luciferasa de luciérnaga con el Sistema
25 de Ensayo de Luciferasa Bright-Glo^{MR} (Promega, Madison, WI). La

IC₅₀ se mide cuando el efecto del compuesto reduce la señal de luminiscencia por el 50 por ciento. Se evalúa la toxicidad de estos compuestos en las células TM3 utilizando los ensayos CellTiter Glo, o mediante la línea celular TM3-Luc (una célula TM3 establemente transfectada con un vector de expresión de luciferasa constitutivo).

Los compuestos de la Fórmula I de preferencia tienen una EC₅₀ menor a 500 nM, más preferiblemente menor a 200 nM.

Ensayo de Citotoxicidad

Se lleva a cabo un ensayo de citotoxicidad para comparar los efectos de un compuesto de la invención sobre las células de meduloblastoma (células Daoy), las células de carcinoma de células basales (células TE354.T), y las células de control (fibroblastos humanos normales), de acuerdo con el siguiente procedimiento:

Las células Daoy (línea celular de meduloblastoma) se adquieren en la ATCC, y se cultivan en un medio esencial mínimo (Eagle) con L-glutamina 2 mM, y BSS de Earle ajustado para contener 1.5 gramos/litro de bicarbonato de sodio, aminoácidos no esenciales 0.1 mM, y piruvato de sodio 1.0 mM, y suero bovino fetal al 10 por ciento, a 37°C, con CO₂ al 5 por ciento en una atmósfera de aire.

Las células TE354.T (de ATCC) se cultivan en un medio de Eagle modificado por Dulbecco, con L-glutamina 4 mM, y suero bovino fetal al 10 por ciento.

Las células de fibroblastos dérmicos humanos normales (Clonetics) se cultivan en un Medio de Crecimiento de Fibroblastos

(Clonetics).

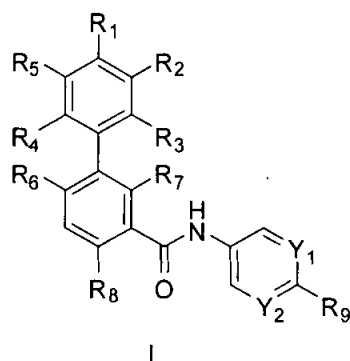
Cada una de las líneas celulares anteriores se siembra independientemente en placas de 96 pozos, y se cultiva hasta una densidad de 5,000 a 10,000 células/pozo. Se agrega un compuesto de la invención, en diferentes concentraciones, a los cultivos celulares. Después de 2 días, se evalúa la viabilidad celular con el Kit de Ensayo de Viabilidad Celular Luminiscente Cell Titer-Glo (Promega), siguiendo el protocolo del fabricante. La viabilidad celular se mide directamente mediante señalización luminescente, y las EC₅₀s se miden cuando se inhibe la señal por el 50 por ciento.

Los compuestos de la Fórmula I de preferencia tienen una EC₅₀ menor a 500 nM, más preferiblemente menor a 200 nM.

Se entiende que los Ejemplos y las modalidades descritas en la presente son solamente para propósitos ilustrativos, y que se sugerirán diferentes modificaciones o cambios a la luz de las mismas para las personas expertas en la técnica, y se van a incluir dentro del espíritu y alcance de esta solicitud, y dentro del alcance de las reivindicaciones adjuntas. Todas las publicaciones, patentes, y solicitudes de patente citadas en la presente se incorporan a la presente como referencia para todos los propósitos.

REIVINDICACIONES

1. Un compuesto de la Fórmula I:



10 en donde:

Y_1 e Y_2 se seleccionan independientemente a partir de N y CR_{10} ; en donde R_{10} se selecciona a partir de hidrógeno, halógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, y $-OXNR_{10a}R_{10b}$; en donde R_{10a} y R_{10b} se seleccionan independientemente a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono;

15

R_1 se selecciona a partir de ciano, halógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, arilo de 6 a 10 átomos de carbono, dimetil-amino, alquilo de 1 a 6 átomos de carbonosulfanilo, y hetero-cicloalquilo de 3 a 8 átomos de carbono

20

25 opcionalmente sustituido con hasta 2 radicales de alquilo de 1 a 6

Mx

átomos de carbono;

R_2 y R_5 se seleccionan independientemente a partir de hidrógeno, ciano, halógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, y dimetil-amino;

R_3 y R_4 se seleccionan independientemente a partir de hidrógeno, halógeno, ciano, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, y alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno; o R_1 y R_2 , ó R_1 y R_5 , junto con el fenilo con el que están ambos unidos, forman heteroarilo de 5 a 10 átomos de carbono;

R_6 y R_7 se seleccionan independientemente a partir de hidrógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, y alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno; con la condición de que R_6 y R_7 no son ambos hidrógeno;

R_8 se selecciona a partir de hidrógeno, halógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, y alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno;

R_9 se selecciona a partir de $-S(O)_2R_{11}$, $-C(O)R_{11}$, $-NR_{12a}R_{12b}$ y $-R_{11}$; en donde R_{11} se selecciona a partir de arilo, heteroarilo, cicloalquilo, y hetero-cicloalquilo; R_{12a} y R_{12b} se seleccionan

independientemente a partir de alquilo de 1 a 6 átomos de carbono y alquilo de 1 a 6 átomos de carbono sustituido por hidroxilo;

en donde el arilo, heteroarilo, cicloalquilo, y hetero-cicloalquilo de R_9 pueden estar opcionalmente sustituidos con 1 a 3 radicales
5 independientemente seleccionados a partir de alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, arilo de 6 a 10 átomos de carbono-alquilo de 0 a 4 átomos de carbono, hetero-arilo de 5 a
10 10 átomos de carbono-alquilo de 0 a 4 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, y hetero-cicloalquilo de 3 a 8 átomos de carbono;

en donde el sustituyente de aril-alquilo de R_9 está opcionalmente sustituido con 1 a 3 radicales independientemente
15 seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido por halógeno, y metil-piperazinilo;

y las sales farmacéuticamente aceptables, hidratos, solvatos, e
20 isómeros del mismo.

2. El compuesto de la reivindicación 1, en donde:

Y_1 e Y_2 se seleccionan a partir de N y CR_{10} ; en donde R_{10} se selecciona a partir de hidrógeno, metilo, flúor, cloro, bromo, dimetil-amino-etoxilo, y trifluoro-metilo;

25 R_6 y R_7 se seleccionan independientemente a partir de

hidrógeno, metilo, cloro, flúor, bromo, trifluoro-metilo, y metoxilo; con la condición de R_6 y R_7 no son ambos hidrógeno; y

R_8 se selecciona a partir de hidrógeno, flúor, cloro, metilo, y trifluoro-metilo.

5 3. El compuesto de la reivindicación 2, en donde: R_1 se selecciona a partir de ciano, cloro, flúor, metilo, etilo, butilo terciario, propilo, isobutilo, isopropilo, isopropiloxilo, butoxilo, metoxilo, dimetil-amino, etoxilo, metil-sulfanilo, fenilo, trifluoro-metilo, trifluoro-metoxilo, y piperazinilo, opcionalmente sustituidos con hasta
10 2 radicales de metilo;

R_2 y R_5 se seleccionan independientemente a partir de hidrógeno, cloro, flúor, ciano, metilo, trifluoro-metilo, isopropiloxilo, metoxilo, etoxilo, trifluoro-metoxilo, y dimetil-amino; y

R_3 y R_4 se seleccionan independientemente a partir de
15 hidrógeno, cloro, metilo, metoxilo, y ciano; ó R_1 y R_2 , ó R_1 y R_5 , junto con el fenilo con el que están ambos unidos, forman quinoxalinilo.

4. El compuesto de la reivindicación 3, en donde R_9 se selecciona a partir de $-S(O)_2R_{11}$, $-OR_{11}$, $-C(O)R_{11}$, $-NR_{12a}R_{12b}$ y $-R_{11}$; en donde R_{11} se selecciona a partir de tiomorfolino, sulfono-
20 morfolino, sulfano-morfolino, morfolino, ciclohexilo, fenilo, azepan-1-ilo, 2-oxopiperazin-1-ilo, 1,4-oxazepan-4-ilo, piperidin-1-ilo, tetrahidro-2H-piran-4-ilo, piperidin-3-ilo, piperazinilo, pirrolidinilo, y 1,4-diazepan-1-ilo; R_{12a} y R_{12b} se seleccionan independientemente a partir de isobutilo e hidroxietilo;

25 en donde este tiomorfolino, sulfono-morfolino, sulfano-

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morfolino, morfolino, ciclohexilo, fenilo, azepan-1-ilo, 2-oxopiperazin-1-ilo, 1,4-oxazepan-4-ilo, piperidin-1-ilo, tetrahidro-2H-piran-4-ilo, piperidin-3-ilo, piperazinilo, pirrolidinilo, ó 1,4-diazepan-1-ilo de R₉ pueden estar opcionalmente sustituidos con 1 a 3 radicales
5 independientemente seleccionados a partir de metilo, etilo, metoxilo, bencilo, tienil-metilo, piridinil-metilo, benzo-[d]-[1,3]-dioxol-6-ilo, y 2,3-dihidro-benzo-[b]-[1,4]-dioxin-7-ilo;

en donde el sustituyente de fenilo o bencilo de R₉ está opcionalmente sustituido con 1 a 3 radicales independientemente
10 seleccionados a partir de metoxilo, etoxilo, metil-piperazinilo, metilo, trifluoro-metoxilo, cloro, flúor, y trifluoro-metilo.

5. El compuesto de la reivindicación 4, seleccionado a partir de N-(6-((2R,6S)-2,6-dimetil-morfolino)-piridin-3-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, [4-(morfolin-4-sulfonil)-fenil]-
15 amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-ciano-2-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-metoxi-2-metil-bifenil-3-carboxílico, (4-ciclohexil-fenil)-amida del
20 ácido 4'-metoxi-2-metil-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-metoxi-2-metil-bifenil-3-carboxílico, (4-ciclohexil-fenil)-amida del ácido 4'-dimetil-amino-2-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 4'-dimetil-amino-2-metil-bifenil-3-carboxílico, (6-[1,4]-oxazepan-4-il-piridin-3-il)-amida
25 del ácido 6-cloro-4'-dimetil-amino-bifenil-3-carboxílico, (6-morfolin-4-

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il-piridin-3-il)-amida del ácido 6-cloro-4'-dimetil-amino-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-cloro-4'-dimetil-amino-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 6-cloro-4'-metoxi-bifenil-3-carboxílico, (6-[1,4]-oxazepan-4-il-piridin-3-il)-amida del ácido 6-cloro-4'-metoxi-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-cloro-4'-metoxi-bifenil-3-carboxílico, (6-morfolin-4-il-piridin-3-il)-amida del ácido 6-cloro-4'-metoxi-bifenil-3-carboxílico, (6-morfolin-4-il-piridin-3-il)-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, (6-[1,4]-oxazepan-4-il-piridin-3-il)-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-dimetil-amino-6-metil-bifenil-3-carboxílico, (6-[1,4]-oxazepan-4-il-piridin-3-il)-amida del ácido 4'-dimetil-amino-6-metil-bifenil-3-carboxílico, (6-morfolin-4-il-piridin-3-il)-amida del ácido 4'-dimetil-amino-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-4'-metil-sulfanil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-dimetil-amino-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-[1,1';4',1'']-terfenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-cloro-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 2',4'-dicloro-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-

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amida del ácido 2'-cloro-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-cloro-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3',4'-dicloro-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-cloro-6-metil-4'-trifluoro-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6,4'-dimetil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-etil-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-terbutil-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-4'-propil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-isobutil-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-isopropil-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6,2',6'-trimetil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6,2',3'-trimetil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-4'-trifluoro-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-3'-trifluoro-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-3',5'-bis-trifluoro-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-isopropoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-etoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 2',6'-dimetoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-4'-trifluoro-metoxi-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 6-metil-3'-trifluoro-metoxi-bifenil-3-



carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 4'-metoxi-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 3'-metoxi-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 4'-

5 (2-dimetil-amino-etoxi)-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 3'-dimetil-amino-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 4'-fluoro-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 3'-fluoro-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 2'-fluoro-

10 6-metil-bifenil-3-carboxílico, 4-metil-N-(4-morfolin-4-il-fenil)-3-quinoxalin-6-il-benzamida, (4-morfolin-4-il-fenil)-amida del ácido 6-metil-4'-(4-metil-piperazin-1-il)-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 2'-ciano-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 3'-ciano-6-metil-bifenil-3-

15 carboxílico, (6-[1,4]-oxazepan-4-il-piridin-3-il)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (3,4,5,6-tetrahidro-2H-[1,2']-bipiridinil-5'-il)-amida del ácido 4'-ciano-

20 6-metil-bifenil-3-carboxílico, (6-morfolin-4-il-piridin-3-il)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-

25 carboxílico, (3-fluoro-4-morfolin-4-il-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (3-cloro-4-morfolin-4-il-fenil)-amida del

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ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (3-bromo-4-morfolin-4-il-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (3-metil-4-morfolin-4-il-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (4-morfolin-4-il-3-trifluoro-metil-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (4-ciclohexil-fenil)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, bifenil-4-il-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (4'-metoxi-bifenil-4-il)-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [4-(4-bencil-piperazin-1-il)-fenil]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [4-(pirrolidin-1-sulfonil)-fenil]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-ciano-6-metoxi-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-ciano-2-metoxi-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-ciano-2-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-fluoro-4'-metoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-isopropoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-butoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 3'-cloro-4'-metoxi-6-metil-bifenil-3-carboxílico, (6-azepan-1-il-piridin-3-il)-amida del ácido 4'-metoxi-6,3'-dimetil-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-amida del ácido 4'-ciano-2-metil-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-amida del ácido 4'-ciano-6-fluoro-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-amida del ácido 6-bromo-4'-ciano-



bifenil-3-carboxílico, [6-(4-bencil-[1,4]-diazepan-1-il)-piridin-3-il]-
 amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-tiofen-3-
 il-metil-[1,4]-diazepan-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-
 metil-bifenil-3-carboxílico, [6-(2,4-dimetil-morfolin-4-il)-piridin-3-il]-
 5 amida del ácido 4'-ciano-2-metil-bifenil-3-carboxílico, [6-(2,6-dimetil-
 morfolin-4-il)-piridin-3-il]-amida del ácido 4'-metoxi-2-metil-bifenil-3-
 carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida del ácido
 2-metil-4'-trifluoro-metil-bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-
 4-il)-piridin-3-il]-amida del ácido 2-metil-4'-trifluoro-metoxi-bifenil-3-
 10 carboxílico, [6-(2-metil-morfolin-4-il)-piridin-3-il]-amida del ácido 4'-
 ciano-2-metil-bifenil-3-carboxílico, [4-(piperidin-1-il-sulfonil)-fenil]-
 amida del ácido 4'-ciano-2-fluoro-bifenil-3-carboxílico, [4-(piperidin-
 1-il-sulfonil)-fenil]-amida del ácido 4'-ciano-6-trifluoro-metil-bifenil-3-
 carboxílico, [6-(4-piridin-4-il-metil-[1,4]-diazepan-1-il)-piridin-3-il]-
 15 amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-piridin-3-
 il-metil-[1,4]-diazepan-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-
 metil-bifenil-3-carboxílico, {6-[4-(2,6-dimetoxi-bencil)-[1,4]-diazepan-
 1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-
 carboxílico, {6-[4-(2-etoxi-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-
 20 amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-[2-(4-
 metil-piperazin-1-il)-bencil]-[1,4]-diazepan-1-il]-piridin-3-il}-amida del
 ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-metoxi-2,3-
 dimetil-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-
 ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2,3-dihidro-benzo-[1,4]-
 25 dioxin-6-il-metil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-

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ciano-6-metil-bifenil-3-carboxílico, [6-(4-piridin-2-il-metil-[1,4]-
diazepan-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-
carboxílico, [6-(4-benzo-[1,3]-dioxol-4-il-metil-[1,4]-diazepan-1-il)-
piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-
5 [4-(2-trifluoro-metoxi-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida
del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2-dimetil-
amino-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-
ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2-cloro-5-trifluoro-metil-
bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-
10 metil-bifenil-3-carboxílico, {6-[4-(2,3-difluoro-bencil)-[1,4]-diazepan-
1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-
carboxílico, {6-[4-(2-cloro-4-fluoro-bencil)-[1,4]-diazepan-1-il]-piridin-
3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2,6-
difluoro-bencil)-[1,4]-diazepan-1-il]-piridin-3-il}-amida del ácido 4'-
15 ciano-6-metil-bifenil-3-carboxílico, [4-(piperidin-1-sulfonil)-fenil]-
amida del ácido 2-cloro-4'-ciano-bifenil-3-carboxílico, [6-(2,6-dimetil-
morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-trifluoro-metil-
bifenil-3-carboxílico, [6-(2,6-dimetil-morfolin-4-il)-piridin-3-il]-amida
del ácido 2-cloro-4'-ciano-bifenil-3-carboxílico, [6-(2,6-dimetil-
20 morfolin-4-il)-piridin-3-il]-amida del ácido 4'-ciano-6-etil-bifenil-3-
carboxílico, {6-[4-(3-fluoro-bencil)-piperazin-1-il]-piridin-3-il}-amida
del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(2-trifluoro-
metoxi-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-
metil-bifenil-3-carboxílico, {6-[4-(3-cloro-bencil)-piperazin-1-il]-
25 piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-



[4-(4-isobutil-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-terbutil-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(7-metoxi-benzo-[1,3]-dioxol-5-il-metil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-bencil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-piridin-3-il-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-difluoro-metoxi-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-ciano-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-quinolin-5-il-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-piridin-4-il-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-piridin-2-il-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(4-imidazol-1-il-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, {6-[4-(3-ciano-bencil)-piperazin-1-il]-piridin-3-il}-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, [6-(4-isoquinolin-5-il-metil-piperazin-1-il)-piridin-3-il]-amida del ácido 4'-ciano-6-metil-bifenil-3-carboxílico, (R)-2-metil-N-(6-(2-metil-morfolino)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 4'-ciano-2-metil-N-(6-sulfonil-morfolino-piridin-3-il)-bifenil-3-carboxamida, (S)-4'-ciano-2-metil-N-(6-(2-metil-morfolino)-piridin-3-il)-bifenil-3-carboxamida, (R)-6-cloro-N-(6-(2-metil-morfolino)-piridin-

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3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 4'-ciano-2-metil-N-(6-sulfinil-morfolino-piridin-3-il)-bifenil-3-carboxamida, 4'-ciano-N-(6-(diisobutil-amino)-piridin-3-il)-2-metil-bifenil-3-carboxamida, 4'-ciano-N-(2-((2S,6R)-2,6-dimetil-morfolino)-pirimidin-5-il)-2-metil-bifenil-3-carboxamida, N-(2-((2S,6R)-2,6-dimetil-morfolino)-pirimidin-5-il)-2-metil-4'-(trifluoro-metil)-bifenil-3-carboxamida, N-(2-((2S,6R)-2,6-dimetil-morfolino)-pirimidin-5-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, N-(2-(bis(2-hidroxi-etil)-amino)-pirimidin-5-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 2-metil-N-(6-(tetrahidro-2H-piran-4-iloxi)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, N-(5-cloro-6-((2S,6R)-2,6-dimetil-morfolino)-piridin-3-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, N-(6-((2R,6S)-2,6-dimetil-tetrahidro-2H-piran-4-il)-piridin-3-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, N-(6-(4-etil-piperazin-1-carbonil)-piridin-3-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 2-metil-N-(6-(2-oxopiperazin-1-il)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 2-metil-N-(6-(1-(piridin-4-ilmetil)-piperidin-4-il)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 2-metil-N-(6-(2-oxo-4-(piridin-4-ilmetil)-piperazin-1-il)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, 2-metil-N-(6-(1-(piridin-4-ilmetil)-piperidin-3-il)-piridin-3-il)-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, N-(6-(1-etil-piperidin-3-il)-piridin-3-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida, y N-(6-((2R,6S)-2,6-dimetil-morfolino)-piridin-3-il)-2-metil-4'-(trifluoro-metoxi)-bifenil-3-carboxamida.

25 6. Un método para inhibir la senda de Hedgehog en una

célula, el cual comprende poner en contacto la célula con un compuesto de la reivindicación 1.

7. El método de la reivindicación 6, en donde la célula tiene un fenotipo de pérdida de función de Ptc, ganancia de función de Hedgehog, ganancia de función de Smoothened, o ganancia de función de Gli.

8. El método de la reivindicación 7, en donde la célula se pone en contacto con el antagonista de Hedgehog *in vivo* ó *in vitro*.

9. El método de la reivindicación 8, en donde el compuesto se administra a un animal como parte de una aplicación terapéutica.

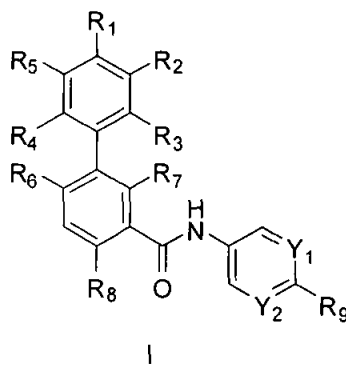
10. El método de la reivindicación 9, en donde la aplicación terapéutica se selecciona a partir de cáncer pancreático, cáncer de próstata, meduloblastoma, carcinoma de células basales, y cáncer pulmonar de células pequeñas.

11. Un método para inhibir la proliferación indeseada de una célula, el cual comprende poner en contacto la célula con un compuesto de la reivindicación 1.

12. El método de la reivindicación 11, en donde la célula se selecciona a partir de cáncer pancreático, cáncer de próstata, meduloblastoma, carcinoma de células basales, y cáncer pulmonar de células pequeñas.

RESUMEN

La invención proporciona un método para modular la actividad de la senda de señalización de Hedgehog. En particular, la invención proporciona un método para inhibir los estados de crecimiento aberrantes resultantes de los fenotipos tales como pérdida de función de Ptc, ganancia de función de Hedgehog, ganancia de función de Smoothened, o ganancia de función de Gli, el cual comprende poner en contacto una célula con una cantidad suficiente de un compuesto de la Fórmula I.



PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

To:

GENOMICS INSTITUTE OF THE NOVARTIS
RESEARCH FOUNDATION
Attn. Reid, Scott W.
10675 John Jay Hopkins Drive
San Diego CA 92121
ETATS-UNIS D'AMERIQUE

(PCT Rule 44.1)

Date of mailing
(day/month/year) 23/01/2008

Applicant's or agent's file reference P1255PC10	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2007/068292	International filing date (day/month/year) 04/05/2007
Applicant IRM LLC	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  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	Authorized officer Chantal Gottar
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P1255PC10	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2007/068292	International filing date (day/month/year) 04/05/2007	(Earliest) Priority Date (day/month/year) 05/05/2006
Applicant IRM LLC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

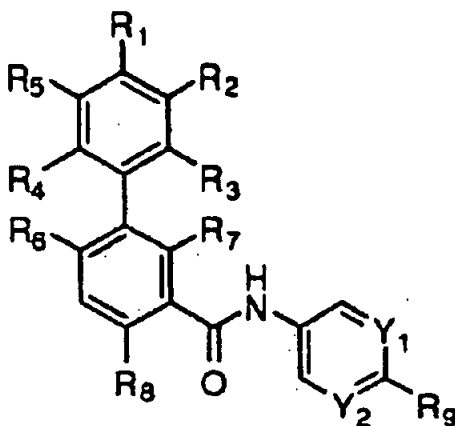
- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/068292

Box No. IV Text of the abstract (Continuation of Item 5 of the first sheet)

The invention provides a method for modulating the activity of the hedgehog signaling pathway. In particular, the invention provides a method for inhibiting aberrant growth states resulting from phenotypes such as Ptc loss-of-function, hedgehog gain-of-function, smoothened gain-of-function or Gli gain-of-function, comprising contacting a cell with a sufficient amount of a compound of Formula I.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/068292

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/75 C07D401/04 C07D401/12 C07D401/14 C07D405/12
C07D409/12 C07D413/04 C07D295/135 C07D295/26 C07D239/49
A61K31/4433 C07C233/65 C07C233/75 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 A61K C07C A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/028958 A (GENENTECH INC [US]; CURIS INC [US]; GUNZNER JANET [US]; SUTHERLIN DANI) 16 March 2006 (2006-03-16) Claims 1-37; Formula (I); examples -----	1-12
X	WO 2006/044975 A (COMPASS PHARMACEUTICALS LLC [US]; KANNE DAVID [US]; WARD JOHN [US]; LO) 27 April 2006 (2006-04-27) Claims 1-62; Formula (I); Fig. 1-A20, CP5018931; Fig. 1-A21, CP5018932 -----	1-12
X	WO 2005/030206 A (IMCLONE SYSTEMS INC [US]; LIU HU [US]; MIAO HUA-QUAN [US]) 7 April 2005 (2005-04-07) Claims 1-11; Formula (I); Table I, compounds 58, 61, 63, 66, 70; p. 27, l. 10-11, 14-15, 19-20, 27-28; p. 30, l. 20-21; example 31 ----- -/-	1-12

☒ 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.

Z document member of the same patent family

Date of the actual completion of the international search

30 November 2007

Date of mailing of the international search report

23/01/2008

Name and mailing address of the ISA/

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

Authorized officer

Kirsch, Cécile

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/068292

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/039718 A (AMGEN INC [US]) 13 April 2006 (2006-04-13) Claims 1-48; Formula (I); examples 409, 413 -----	1-12
X	WO 2004/002948 A (MITSUBISHI PHARMA CORP [JP]; NAITO YOUICHIRO [JP]; USHIO HIROYUKI [JP]) 8 January 2004 (2004-01-08) Claims 1-18; Formula (I); example 4 -----	1-5
A	WO 2005/033288 A (UNIV JOHNS HOPKINS [US]; BEACHY PHILIP A [US]; CHEN JAMES K [US]; TAIP) 14 April 2005 (2005-04-14) Claims 1-59; Formulae (I), (1)-(7); -----	1-12
P,X	WO 2006/078283 A (GENENTECH INC [US]; KOEHLER MICHAEL F T [US]; GOLDSMITH RICHARD [US];) 27 July 2006 (2006-07-27) Claims 1-35; Formula (I); examples -----	1-32
P,X	WO 2007/031791 A (ARROW THERAPEUTICS LTD [GB]; WHEELHOUSE CHRISTOPHER JAMES [GB]; THOMAS) 22 March 2007 (2007-03-22) Claims 1-34; Formula (I); cores 1-4; examples 1-116 -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/068292

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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-12 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 report covers 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/US2007/068292

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2006028958	A	16-03-2006	AU 2005282722 A1 CA 2579002 A1 EP 1789390 A2 KR 20070085243 A US 2006063779 A1	16-03-2006 16-03-2006 30-05-2007 27-08-2007 23-03-2006
WO 2006044975	A	27-04-2006	EP 1802606 A2	04-07-2007
WO 2005030206	A	07-04-2005	NONE	
WO 2006039718	A	13-04-2006	AU 2005292152 A1 CA 2582029 A1 EP 1836174 A2 US 2007054916 A1	13-04-2006 13-04-2006 26-09-2007 08-03-2007
WO 2004002948	A	08-01-2004	JP 2002338537 A	27-11-2002
WO 2005033288	A	14-04-2005	NONE	
WO 2006078283	A	27-07-2006	AU 2005325267 A1 CA 2565237 A1 CN 101018783 A EP 1745041 A2 KR 20070005736 A	27-07-2006 27-07-2006 15-08-2007 24-01-2007 10-01-2007
WO 2007031791	A	22-03-2007	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

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To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2007/068292

International filing date (day/month/year)
04.05.2007

Priority date (day/month/year)
05.05.2006

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

INV. C07D213/75 C07D401/04 C07D401/12 C07D401/14 C07D405/12 C07D409/12 C07D413/04 C07D295/135
C07D295/26 C07D239/49 A61K31/4433 C07C233/65 C07C233/75 A61P35/00

Applicant
IRM LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/068292

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/068292

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 6-12

because:

☒ the said international application, or the said claims Nos. 6-12 relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13~~ter~~.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>5</u>
	No: Claims	<u>1-4,6-12</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-12</u>
Industrial applicability (IA)	Yes: Claims	<u>1-5</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No. 

PCT/US2007/068292

Reference is made to the following documents:

- D1: WO 2006/028958
- D2: WO 2006/044975
- D3: WO 2005/030206
- D4: WO 2006/039718
- D5: WO 2004/002948
- D6: WO 2005/033288
- D7: WO 2006/078283 (P-document)
- D8: WO 2007/031791 (P-document)

The present application deals with N-(Het)arylcarboxamide biphenyl derivatives as hedgehog signalling pathway inhibitors for treating tumors.

Re Item I

Basis of the report

The application does not meet the requirements of Article 6 PCT, because claims 1-5 are not clear (see point VIII below).

The use of contradictory definitions in the claims and the description for substituents R1 and R8 is considered to lead to a lack of clarity because the claims in the light of the description do not clearly identify the products encompassed by it. As a result, the application does not comply with the requirement of clarity under Article 6 PCT.

The lack of clarity is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1-5.

The search was not only restricted to the subject-matter of the claims but also taking into account the teaching disclosed in the examples.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 6-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Document D2 discloses biphenylamide derivatives for treating tumors. Document D3 relates to benzimidazole phenyl derivatives as heparinase inhibitors for treating tumors and angiogenesis. Document D4 deals with aryl N-containing bicyclic derivatives as protein kinase modulators for treating inflammation, cancer, etc. Document D5 describes N-aryl benzamide derivatives as IL-4 inhibitors in Th2 cells for treating allergic diseases.

On the basis of claim 1, it turns out that there is an overlap between the claimed subject-matter and the teaching of D2 (when Y is CR₂, R₆ is H, R₁₀ is aryl or heteroaryl, Z is a biphenyl, a 4-sulfanylphenyl, 4-halophenyl), D3 (when n is 0, R₂ is hydrogen and -CO- arylsubstituted with R₅ and R₅ is aryl), D4 (when A₂ and A₃ are CR₅, B is a direct bon, R₃ is an unsaturated carbocycle substituted by CONR₁₀R₁₀ and R₁₀ is a substituted cycloalkyl or cycloakenyl), and D5 (when Q and R₁ are phenyl, R₂ is H, R₅ is NR₆R₇ where R₆ and R₇ forme together a ring) and the applicant has not defined in which way this overlap could be regarded as novel vis-à-vis D2-D5, that is to say, the applicant has not defined the new technical element common to the compounds of the present application which fall within the overlap and which can be regarded as adding a new element to the state of the art. Since, this new technical feature, which is necessary to established novelty, fails, this overlap is considered identical to what has already been disclosed in D2-D5. In this context the attention of the applicant is drawn to the fact that the content of D2-D5 is neither limited to its examples nor to the preferred embodiments disclosed therein. The content of D2-D5 should be regarded as a whole and all the information contained therein is state of the art in the sense of Article 33(2) PCT.

2. Document D1 describes pyridyl derivatives as hedgehog signalling pathway inhibitors for treating tumors. Document D1 overlaps with formula (I) of claim 1 of the present application when Y is absent or SO₂, X is NR₄C(O) and R is a carbocycle substituted with a carbocycle. However, the specific presence of a biphenyl moiety is not explicitly disclosed in D1 and represents a new teaching which was not disclosed in D1. Thus, the subject-matter of claims 1-12 represents a new selection with regard to document D1 (Art. 33(2) PCT).

Document D6 discloses N-aryl 4-pyridylbenzamide derivatives as hedgehog signalling pathway inhibitors for treating tumors. The compounds of D6 possess a 4-pyridylphenyl moiety instead of the biphenyl moiety characteristic of the compounds of the invention. Novelty of claims 1-12 seems to be established with regard to document D6 (Art. 33(2) PCT).

3. Document D1, which is considered to represent the most relevant state of the art, reveals N-pyridylaryl benzamide derivatives as hedgehog signalling pathway inhibitors for treating tumors. The present application represents a new selection of biphenyl compounds generically described in the prior art.

The problem to be solved by the present invention may therefore be considered as the provision of further N-pyridylaryl benzamide derivatives for use in the treatment of cancer.

Starting from D1, it appears that all the compounds claimed therein are expected to exhibit the claimed activity as long as the characteristic core structure is present. The indiscriminate selection of some defined compounds among many is *prima facie* obvious. The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity. One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating cancer.

Therefore, the mere selection of a specific family of compound within a broader group known for its biological activity cannot be considered inventive in the sense of Art. 56

EPC since there is a clear indication for the skilled to seek in this direction.

In the light of D1, the problem may be reformulated as the provision of further N-pyridylaryl benzamide derivatives exhibiting unexpected effect(s).

Since no precise biological data about the actual physiological properties of the claimed compounds and no comparative tests which could demonstrate the superiority of the claimed compounds with regard to the related compounds of the prior art have been made available so that it is not apparent whether the problem has actually been solved or not (Art. 33(3) PCT). Consequently, the applicant is invited to submit all information available to him to substantiate that all claimed compounds are a solution to the problem underlying the current application or, if necessary to restrict the claims to the compounds which illustrate reasonable patentable effects (to be shown).

4. Claim 6-9 and 11-12, which subject matter is defined as the inhibition of hedgehog pathway, cannot be considered:
- i) as industrial applicable as the inhibition of hedgehog pathway cannot be considered in itself as a therapeutic application. The discovery, that a substance inhibits the hedgehog pathway, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of any pathological condition in order to make a technical contribution to the art, and
 - ii) as clear (Article 6 PCT), since no instructions, in the form of any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise, which conditions fall within the functional definition e.g. any condition susceptible of being improved or prevented by the inhibition of the hedgehog pathway, and accordingly within the scope of the claim.

The reason for the necessity of this clarification is, that a claim referring to a condition to be treated, which is functionally defined, would not be limited to the treatment of said specified condition (here cancer), but by contrast embraces an undefined number of conditions all allegedly capable of being improved or prevented by the inhibition of the hedgehog pathway. Under these circumstances the independent claim can only be regarded as clear if means are available to the skilled person for assessing whether or not an additional condition not expressly filed in the application but nevertheless affected

by the administration of the said compounds is comprised in the scope of the claim.

5. For the assessment of the present claims 6-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2006/078283	27/07/2006	29/04/2005	30/04/2004
WO2007/031791	22/03/2007	18/09/2006	16/09/2005 30/05/2006

Documents D7 and D8 have been published between the priority date and the filing date of the present application. According to Rule 64.3 PCT, these documents may not be taken into account for the assessment of novelty and inventive step during the international phase. The attention of the applicant is however drawn to the fact that this document may prove relevant in the examination process during regional phase.

Re Item VIII

Certain observations on the international application

1. The embodiments of the invention described on pages 23-47 do not fall within the scope of claims 1-4. According to these claims, R8 may not represent hydrogen whereas all the

examples provided in the description are unsubstituted at that position. Furthermore, examples 52, 59 and 60 disclose compounds wherein the substituent in 4'-position of the biphenyl does not fall within the definition of R1. This inconsistency between the claims and the description as well as within the claims (see claim 5) leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

2. Additionally, some terms used in the claims are interpreted in the description in a different way than their usual meaning. According to p. 4, [0012], heterocycloalkyl also encompasses cycloalkyl substituted by an oxo group. In this context, examples 148 and 150 describe compounds wherein the piperazine ring is substituted with a doubly bond oxygen atom, which is not disclosed as substituent according to the claims. The same applies for the term C5-10heteroaryl which, according to p. 20, [0020], does not refer to heteroaryl containing from 5 to 10 carbon atoms but rather to heteroaryl containing from 5 to 10 members. In this context, in example 57, R1 and R5 form together a heteroaryl containing only 4 carbon atoms whereas according to claim 1 such a ring must contain from 5 to 10 carbon atoms. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.
3. In claim 1, R10 is defined a.o. as -OXNR10aR10b, however, no definition for X is provided in the claims, thereby rendering the claims unclear, Article 6 PCT.
4. The use of the disclaimer in claim 1 has not been explained in the description. The Applicant is therefore kindly invited to justify the use of this disclaimer. If this disclaimer has been introduced in order to restore novelty with regard to a prior art document the applicant is aware of, then the document should be identified in the description.
5. The term "isomers" refers to compounds that have the same chemical formula but different arrangements of the atoms within the molecule, i.e. isomers of the claimed compounds may not contain the N-arylcarboxamide biphenyl core structure characteristic of the invention. This term is considered as imprecise and could comprise compounds which would not exhibit the claimed activity.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPEA (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

(19) World Intellectual Property Organization
International Bureau



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15 November 2007 (15.11.2007)

PCT

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(26) Publication Language: English

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

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

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

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

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: **COMPOUNDS AND COMPOSITIONS AS HEDGEHOG PATHWAY MODULATORS**

(57) Abstract: The invention provides a method for modulating the activity of the hedgehog signaling pathway. In particular, the invention provides a method for inhibiting aberrant growth states resulting from phenotypes such as Ptc loss-of-function, hedgehog gain-of-function, smoothened gain-of-function or Gli gain-of-function, comprising contacting a cell with a sufficient amount of a compound of Formula I.

WO 2007/131201 A2

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/068292

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/75 C07D401/04 C07D401/12 C07D401/14 C07D405/12
 C07D409/12 C07D413/04 C07D295/135 C07D295/26 C07D239/49
 A61K31/4433 C07C233/65 C07C233/75 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 A61K C07C A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/028958 A (GENENTECH INC [US]; CURIS INC [US]; GUNZNER JANET [US]; SUTHERLIN DANI) 16 March 2006 (2006-03-16) Claims 1-37; Formula (I); examples	1-12
X	WO 2006/044975 A (COMPASS PHARMACEUTICALS LLC [US]; KANNE DAVID [US]; WARD JOHN [US]; LO) 27 April 2006 (2006-04-27) Claims 1-62; Formula (I); Fig. 1-A20, CP5018931; Fig. 1-A21, CP5018932	1-12
X	WO 2005/030206 A (IMCLONE SYSTEMS INC [US]; LIU HU [US]; MIAO HUA-QUAN [US]) 7 April 2005 (2005-04-07) Claims 1-11; Formula (I); Table I, compounds 58, 61, 63, 66, 70; p. 27, l. 10-11, 14-15, 19-20, 27-28; p. 30, l. 20-21; example 31	1-12
	-/--	

☒ 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.

Z document member of the same patent family

Date of the actual completion of the international search

30 November 2007

Date of mailing of the international search report

23/01/2008

Name and mailing address of the ISA/

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Authorized officer

Kirsch, Cécile

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/068292

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/039718 A (AMGEN INC [US]) 13 April 2006 (2006-04-13) Claims 1-48; Formula (I); examples 409, 413 -----	1-12
X	WO 2004/002948 A (MITSUBISHI PHARMA CORP [JP]; NAITO YUICHIRO [JP]; USHIO HIROYUKI [JP]) 8 January 2004 (2004-01-08) Claims 1-18; Formula (I); example 4 -----	1-5
A	WO 2005/033288 A (UNIV JOHNS HOPKINS [US]; BEACHY PHILIP A [US]; CHEN JAMES K [US]; TAIP) 14 April 2005 (2005-04-14) Claims 1-59; Formulae (I), (1)-(7); -----	1-12
P,X	WO 2006/078283 A (GENENTECH INC [US]; KOEHLER MICHAEL F T [US]; GOLDSMITH RICHARD [US];) 27 July 2006 (2006-07-27) Claims 1-35; Formula (I); examples -----	1-32
P,X	WO 2007/031791 A (ARROW THERAPEUTICS LTD [GB]; WHEELHOUSE CHRISTOPHER JAMES [GB]; THOMAS) 22 March 2007 (2007-03-22) Claims 1-34; Formula (I); cores 1-4; examples 1-116 -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/068292

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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-12 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 all searchable 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 report covers 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/US2007/068292

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2006028958	A	16-03-2006	AU 2005282722 A1	16-03-2006
			CA 2579002 A1	16-03-2006
			EP 1789390 A2	30-05-2007
			KR 20070085243 A	27-08-2007
			US 2006063779 A1	23-03-2006
WO 2006044975	A	27-04-2006	EP 1802606 A2	04-07-2007
WO 2005030206	A	07-04-2005	NONE	
WO 2006039718	A	13-04-2006	AU 2005292152 A1	13-04-2006
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION



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 []

Sandoz

Firma Responsable

Fecha 4-11-08

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