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Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 08-2327

54 **TÍTULO** *INHIBIDORES DE HISTONA DEACETILASA*

51 **CLASIFICACIÓN INTERNACIONAL**

71 **SOLICITANTE** *TAKEDA SAN DIEGO, INC*

DOMICILIO *CALIFORNIA, ESTADOS UNIDOS DE AMERICA*

74 **APODERADO** *DILIA MARIA RODRIGUEZ D'ALEMAN*

22 **BOGOTÁ, D. C.,** *ENERO 11, 2008*

(FORMA P 10)

PETITOR

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Fecha: 2008-01-11 16:08:40 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 628

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 14 Feb. 2008

1) SOLICITUD DE:

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☒ Capitulo I. ☐ Capitulo II.

2) SOLICITANTE (71)	**Nombre: TAKEDA SAN DIEGO, INC.** **Dirección: 10410 Science Center Drive, San Diego, California 92121 Estados Unidos** **Nacionalidad o domicilio: California, Estados Unidos** **Lugar de constitución: California, Estados Unidos**	**IDENTIFICACIÓN** **C.C.** ☐ **NIT:** ☐ **C.E.** ☐ **OTRO** ☐ **Cual** _____ **NÚMERO** _____
	Teléfono: Fax: **E. Mail:**	
3) REPRESENTANTE O APODERADO	Nombre: DILIA MARÍA RODRÍGUEZ D´ALEMAN Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C. Teléfono: 6181088 Fax: 6350824 E. Mail: info@clarkemodet.com.co	**IDENTIFICACIÓN** **C.C.** ☒ **NIT:** ☐ **C.E.** ☐ **OTRO** ☐ **NÚMERO:** 41.654.882 **TP:** 20824 CSJ
4) INVENTOR (ES) (72)	**Nombre: 1. BRESSI, Jerome C.; 2. GANGLOFF, Anthony R.; 3. KWOK, Lily** **Dirección: 1. 3799 Ibis Street, San Diego, California 92103 Estados Unidos; 2. 4969 Dick Street, San Diego, California 92115, Estados Unidos; 3. 10937 Caminito Arcada, San Diego, California 92131 Estados Unidos** **Nacionalidad o Domicilio: Todos los anteriores, Estadounidenses**	

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6)Titulo (54) INHIBIDORES DE HISTONA DEACETILASA

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	Estados Unidos	**Julio 14, 2005**	**60/699,139**

9) Comprobant de pago N°.

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

10) ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Comprobante de pago por reivindicación de prioridad
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- [ ] Poderes, si fuera el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- [ ] Copia del examen preliminar 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 y 6 x 6 cm
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- [x] Otros:
  1. Reporte internacional de búsqueda
  2. IB304

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D´ALEMAN

FIRMA: _____

C.C. 41.654.882 de Bogotá **TP** 20824 CSJ

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16

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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FECHA : DICIEMBRE 26 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	67072355	26/12/2007	26,830,000.00

***** 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	482,000.00
			TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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CLARKE MODET Y CO. COLOMBCONSIGNACION		BANCO DE BOGOTA	062754387	2662954	08/01/2008	40,235,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	116	CERTIFICACION DE SOLICITUD PARA R	15,000.00
			TOTAL : $	15,000.00

SON: QUINCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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

CANT.	RENTISTICO		CONCEPTO		TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	2,000.00
				TOTAL : $	2,000.00

SON: DOS MIL PESOS

RESPONSABLE : _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 1,969
FECHA : ENERO 8 DE 2008

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CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	2662954	08/01/2008	40,235,000.00

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CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	2,000.00
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(75) Inventors/Applicants *(for US only)*: **BRESSI, Jerome C.** [US/US]; 3799 Ibis Street, San Diego, California 92103 (US). **GANGLOFF, Anthony R.** [US/US]; 4969 Dick Street, San Diego, California 92115 (US). **KWOK, Lily** [US/US]; 10937 Caminito Arcada, San Diego, California 92131 (US).

(74) Agents: **WEITZ, David J.** et al.; TAKEDA SAN DIEGO, INC., 10410 Science Center Drive, San Diego, California 92121 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, 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, 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, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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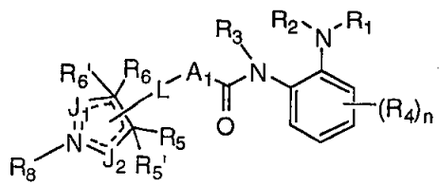
(54) Title: HISTONE DEACETYLASE INHIBITORS



(I)

(57) Abstract: Compounds, pharmaceutical compositions, kits and methods are provided for use with HDAC that comprise a compound selected from the group consisting of: (formula) wherein the substituents are as defined herein.

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HISTONE DEACETYLASE INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention relates to compounds that may be used to inhibit histone deacetylases (HDACs), as well as compositions of matter and kits comprising these compounds. The invention also relates to methods for inhibiting HDACs and treatment methods using compounds according to the present invention. In particular, the present invention relates to compounds, compositions of matter, kits and methods used to inhibit Class I HDACs, such as HDAC1, HDAC2, HDAC6 and HDAC8.

BACKGROUND OF THE INVENTION

[0002] DNA in eukaryotic cells is tightly complexed with proteins (histones) to form chromatin. Histones are small, positively charged proteins that are rich in basic amino acids (positively charged at physiological pH), which contact the phosphate groups (negatively charged at physiological pH) of DNA. There are five main classes of histones H1, H2A, H2B, H3, and H4. The amino acid sequences of H2A, H2B, H3, and H4 show remarkable conservation between species, wherein H1 varies somewhat and in some cases is replaced by another histone, *e.g.*, H5. Four pairs of each of H2A, H2B, H3 and H4 together form a disk-shaped octomeric protein core, around which DNA (about 140 base pairs) is wound to form a nucleosome. Individual nucleosomes are connected by short stretches of linker DNA associated with another histone molecule to form a structure resembling a beaded string, which is itself arranged in a helical stack, known as a solenoid.

[0003] The majority of histones are synthesized during the S phase of the cell cycle, and newly synthesized histones quickly enter the nucleus to become associated with DNA. Within minutes of its synthesis, new DNA becomes associated with histones in nucleosomal structures.

[0004] A small fraction of histones, more specifically, the amino acid side chains thereof, are enzymatically modified by post-translational addition of methyl, acetyl, or phosphate groups, neutralizing the positive charge of the side chain, or converting it to a negative charge. For example, lysine and arginine groups may be methylated, lysine

groups may be acetylated, and serine groups may be phosphorylated. For lysine, the -$(CH_2)_4$-NH_2 sidechain may be acetylated, for example by an acetyltransferase enzyme to give the amide -$(CH_2)_4$-NHC(=O)CH_3. Methylation, acetylation, and phosphorylation of amino termini of histones that extend from the nucleosomal core affects chromatin structure and gene expression. Spencer and Davie 1999. Gene 240:1 1-12.

[0005] Acetylation and deacetylation of histones is associated with transcriptional events leading to cell proliferation and/or differentiation. Regulation of the function of transcriptional factors is also mediated through acetylation. Recent reviews on histone deacetylation include Kouzarides *et al.*, 1999, Curr. Opin. Genet. Dev. 9:1, 40-48 and Pazin *et al.*, 1997, 89:3 325-328.

[0006] The correlation between acetylation status of histones and the transcription of genes has been known for quite some time. Certain enzymes, specifically acetylases (*e.g.*, histone acetyltransferases (HAT) and deacetylases (histone deacetylases or HDACs), which regulate the acetylation state of histones have been identified in many organisms and have been implicated in the regulation of numerous genes, confirming a link between acetylation and transcription. In general, histone acetylation is believed to correlate with transcriptional activation, whereas histone deacetylation is believed to be associated with gene repression.

[0007] A growing number of histone deacetylases (HDACs) have been identified. HDACs function as part of large multiprotein complexes, which are tethered to the promoter and repress transcription. Well characterized transcriptional repressors such as MAD, nuclear receptors and YY1 associate with HDAC complexes to exert their repressor function.

[0008] Studies of HDAC inhibitors have shown that these enzymes play an important role in cell proliferation and differentiation. HDACs are believed to be associated with a variety of different disease states including, but not limited to cell proliferative diseases and conditions (Marks, P.A., Richon, V.M., Breslow, R. and Rifkind, R.A., J. Natl. Cancer Inst. (Bethesda) 92, 1210-1215, 2000) such as leukemia (Lin *et al.*, 1998. Nature 391: 811-814; Grignani *et al.*1998. Nature 391: 815-818; Warrell *et al.*, 1998, J. Natl. Cancer Inst. 90:1621-1625; Gelmetti *et al.*, 1998, Mol. Cell Biol. 18:7185-7191; Wang *et al.*, 1998, PNAS 951 0860-10865), melanomas/squamous cell carcinomas (Gillenwater *et al.*, 1998,

Int. J. Cancer 75217-224; Saunders *et al.*, 1999, Cancer Res. 59:399-404), breast cancer, prostrate cancer, bladder cancer (Gelmetti *et al.*, 1998, Mol. Cell Biol. 18:7185-7191; Wang *et al.*, 1998, PNAS 951 0860-10865), lung cancer, ovarian cancer, colon cancer (Hassig *et al.*, 1997, Chem. Biol. 4:783-789; Archer *et al.*, 1998, PNAS, 956791-6796; Swendeman *et al.*, 1999, Proc. Amer. Assoc. Cancer Res. 40, Abstract #3836), and hyperproliferative skin disease such as cancerous and precancerous skin lesions, as well as inflammatory cutaneous disorders.

[0009] Histone deacetylase inhibitors are potent inducers of growth arrest, differentiation, or apoptotic cell death in a variety of transformed cells in culture and in tumor bearing animals (*Histone deacetylase inhibitors as new cancer drugs*, Marks, P.A., Richon, V.M., Breslow, R. and Rifkind, R.A., Current Opinions in Oncology, 2001, Nov. 13 (6): 477-83; *Histone deacetylases and cancer: causes and therapies,* Marks, P., Rifkind, R.A., Richon, V.M., Breslow, R., Miller, T. and Kelly, W.K., Nat. Rev. Cancer 2001 Dec.1 (3):194-202). In addition, HDAC inhibitors are useful in the treatment or prevention of protozoal diseases (US Patent 5,922,837) and psoriasis (PCT Publication No. WO 02/26696).

[0010] Accordingly, despite the various HDAC inhibitors that have been reported to date, a need continues to exist for new and more effective inhibitors of HDACs.

SUMMARY OF THE INVENTION

[0011] The present invention relates to compounds that have activity for inhibiting histone deacetylases (HDACs). The present invention also provides compositions, articles of manufacture and kits comprising these compounds.

[0012] In one embodiment, a pharmaceutical composition is provided that comprises an HDAC inhibitor according to the present invention as an active ingredient. Pharmaceutical compositions according to the invention may optionally comprise 0.001%-100% of one or more HDAC inhibitors of this invention. These pharmaceutical compositions may be administered or coadministered by a wide variety of routes, including for example, orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery (for example by

catheter or stent), subcutaneously, intraadiposally, intraarticularly, or intrathecally. The compositions may also be administered or co-administered in slow release dosage forms.

[0013] The invention is also directed to kits and other articles of manufacture for treating disease states associated with one or more HDAC.

[0014] In one embodiment, a kit is provided that comprises a composition comprising at least one HDAC inhibitor of the present invention in combination with instructions. The instructions may indicate the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also comprise packaging materials. The packaging material may comprise a container for housing the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0015] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one HDAC inhibitor of the present invention in combination with packaging materials. The packaging material may comprise a container for housing the composition. The container may optionally comprise a label indicating the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0016] Also provided are methods for preparing compounds, compositions and kits according to the present invention. For example, several synthetic schemes are provided herein for synthesizing compounds according to the present invention. In still another embodiment, reactive intermediates are provided for use in conjunction with the synthetic schemes.

[0017] Also provided are methods for using compounds, compositions, kits and articles of manufacture according to the present invention.

[0018] In one embodiment, the compounds, compositions, kits and articles of manufacture are used to inhibit one or more HDAC.

[0019] In another embodiment, the compounds, compositions, kits and articles of manufacture are used to treat a disease state for which one or more HDAC possesses activity that contributes to the pathology and/or symptomology of the disease state.

[0020] In another embodiment, a compound is administered to a subject wherein HDAC activity within the subject is altered, preferably reduced.

[0021] In another embodiment, a prodrug of a compound is administered to a subject that is converted to the compound *in vivo* where it inhibits one or more HDAC.

[0022] In another embodiment, a method of inhibiting one or more HDAC is provided that comprises contacting an HDAC with a compound according to the present invention.

[0023] In another embodiment, a method of inhibiting one or more HDAC is provided that comprises causing a compound according to the present invention to be present in a subject in order to inhibit the HDAC *in vivo*.

[0024] In another embodiment, a method of inhibiting an HDAC is provided that comprises administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits the HDAC *in vivo*. It is noted that the compounds of the present invention may be the first or second compounds.

[0025] In another embodiment, a therapeutic method is provided that comprises administering a compound according to the present invention.

[0026] In another embodiment, a method of treating a condition in a patient which is known to be mediated by one or more HDAC, or which is known to be treated by HDAC inhibitors, comprising administering to the patient a therapeutically effective amount of a compound according to the present invention.

[0027] In another embodiment, a method is provided for treating a disease state for which one or more HDAC possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: causing a compound according to the present invention to be present in a subject in a therapeutically effective amount for the disease state.

[0028] In another embodiment, a method is provided for treating a disease state for which one or more HDAC possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: administering a first compound to a subject that is converted *in vivo* to a second compound such that the second

compound is present in the subject in a therapeutically effective amount for the disease state. It is noted that the compounds of the present invention may be the first or second compounds.

[0029] In another embodiment, a method is provided for treating a disease state for which one or more HDAC possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: administering a compound according to the present invention to a subject such that the compound is present in the subject in a therapeutically effective amount for the disease state.

[0030] In another embodiment, a method is provided for using a compound according to the present invention in order to manufacture a medicament for use in the treatment of a disease state that is known to be mediated by one or more HDAC, or that is known to be treated by HDAC inhibitors.

[0031] It is noted in regard to all of the above embodiments that the present invention is intended to encompass all pharmaceutically acceptable ionized forms (*e.g.*, salts) and solvates (*e.g.*, hydrates) of the compounds, regardless of whether such ionized forms and solvates are specified since it is well know in the art to administer pharmaceutical agents in an ionized or solvated form. It is also noted that unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all possible stereoisomers (*e.g.*, enantiomers or diastereomers depending on the number of chiral centers), independent of whether the compound is present as an individual isomer or a mixture of isomers. Further, unless otherwise specified, recitation of a compound is intended to encompass all possible resonance forms and tautomers. With regard to the claims, the language "compound comprising the formula" is intended to encompass the compound and all pharmaceutically acceptable ionized forms and solvates, all possible stereoisomers, and all possible resonance forms and tautomers unless otherwise specifically specified in the particular claim.

[0032] It is further noted that prodrugs may also be administered which are altered *in vivo* and become a compound according to the present invention. The various methods of using the compounds of the present invention are intended, regardless of whether prodrug delivery is specified, to encompass the administration of a prodrug that is converted *in vivo* to a compound according to the present invention. It is also noted that certain

compounds of the present invention may be altered *in vivo* prior to inhibiting kinases and thus may themselves be prodrugs for another compound. Such prodrugs of another compound may or may not themselves independently have kinase inhibitory activity.

BRIEF DESCRIPTION OF THE FIGURES

[0033] Figure 1 illustrates residues 1-482 of HDAC1 and a Flag tag at both the N- and C- terminus (SEQ ID NO: 1).

[0034] Figure 2 illustrates the DNA sequence (SEQ ID NO: 2) that was used to encode SEQ ID NO: 1.

[0035] Figure 3 illustrates residues 1-488 of HDAC2 and a 6-histidine tag at the C-terminus (SEQ ID NO: 3).

[0036] Figure 4 illustrates the DNA sequence (SEQ ID NO: 4) that was used to encode SEQ ID NO: 3.

[0037] Figure 5 illustrates residues 73-845 of HDAC6 and a 6-histidine tag at the C-terminus (SEQ ID NO: 5).

[0038] Figure 6 illustrates the DNA sequence (SEQ ID NO: 6) that was used to encode SEQ ID NO: 5.

[0039] Figure 7 illustrates residues 1-377 of HDAC8 and a 6-histidine tag at the N-terminus (SEQ ID NO: 7).

[0040] Figure 8 illustrates the DNA sequence (SEQ ID NO: 8) that was used to encode SEQ ID NO: 7.

DEFINITIONS

[0041] Unless otherwise stated, the following terms used in the specification and claims shall have the following meanings for the purposes of this Application.

[0042] "Alicyclic" means a moiety comprising a non-aromatic ring structure. Alicyclic moieties may be saturated or partially unsaturated with one, two or more double or triple bonds. Alicyclic moieties may also optionally comprise heteroatoms such as nitrogen, oxygen and sulfur. The nitrogen atoms can be optionally quaternerized or oxidized and the sulfur atoms can be optionally oxidized. Examples of alicyclic moieties include, but are not limited to moieties with C_{3-8} rings such as cyclopropyl, cyclohexane, cyclopentane,

cyclopentene, cyclopentadiene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, cycloheptene, cycloheptadiene, cyclooctane, cyclooctene, and cyclooctadiene.

[0043] "Aliphatic" means a moiety characterized by a straight or branched chain arrangement of constituent carbon atoms and may be saturated or partially unsaturated with one, two or more double or triple bonds.

[0044] "Alkoxy" means an oxygen moiety having a further alkyl substituent. The alkoxy groups of the present invention can be optionally substituted.

[0045] "Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having a chain of carbon atoms, optionally with oxygen (See "oxaalkyl") or nitrogen atoms (See "aminoalkyl") between the carbon atoms. C_X alkyl and C_{X-Y} alkyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{1-6} alkyl includes alkyls that have a chain of between 1 and 6 carbons (*e.g.*, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (*e.g.*, as in arylalkyl, heteroarylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (*e.g.*, (C_{6-10})aryl(C_{1-3})alkyl includes, benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-thienylmethyl, 2-pyridinylmethyl and the like).

[0046] "Alkenyl" means a straight or branched, carbon chain that contains at least one carbon-carbon double bond. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

[0047] "Alkynyl" means a straight or branched, carbon chain that contains at least one carbon-carbon triple bond. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

[0048] "Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical. C_X alkylene and C_{X-Y} alkylene are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{1-6} alkylene includes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), trimethylene ($-CH_2CH_2CH_2-$), tetramethylene ($-CH_2CH_2CH_2CH_2-$) 2-butenylene ($-CH_2CH{=}CHCH_2-$),

2-methyltetramethylene (-$CH_2CH(CH_3)CH_2CH_2$-), pentamethylene (-$CH_2CH_2CH_2CH_2CH_2$-) and the like.

[0049] "Alkenylene" means a straight or branched, divalent carbon chain having one or more carbon-carbon double bonds. Examples of alkenylene include ethene-1,2-diyl, propene-1,3-diyl, methylene-1,1-diyl, and the like.

[0050] "Alkynylene" means a straight or branched, divalent carbon chain having one or more carbon-carbon triple bonds. Examples of alkynylene include ethyne-1,2-diyl, propyne-1,3-diyl, and the like.

[0051] "Alkylidene" means a straight or branched saturated or unsaturated, aliphatic radical connected to the parent molecule by a double bond. C_X alkylidene and C_{X-Y} alkylidene are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{1-6} alkylidene includes methylene (=CH_2), ethylidene (=$CHCH_3$), isopropylidene (=$C(CH_3)_2$), propylidene (=$CHCH_2CH_3$), allylidene (=CH-CH=CH_2), and the like).

[0052] "Amido" means the radical –$NR_aC(O)R_b$ where the point of attachment to the molecule is at the nitrogen, and R_a and R_b are further substituents attached to the nitrogen and the carbon of the carbonyl, respectively.

[0053] "Amino" means a nitrogen moiety having two further substituents where, for example, a hydrogen or carbon atom is attached to the nitrogen. For example, representative amino groups include -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -NHC_{1-10}-alkyl, -$N(C_{1-10}$-alkyl$)_2$, -NHaryl, -NHheteroaryl, -N(aryl)$_2$, -N(heteroaryl)$_2$, and the like. Optionally, the two substituents together with the nitrogen may also form a ring. Unless indicated otherwise, the compounds of the invention containing amino moieties may include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

[0054] "Aminoalkyl" means an alkyl, as defined above, except where one or more substituted or unsubstituted nitrogen atoms (-N-) are positioned between carbon atoms of the alkyl. For example, an (C_{2-6}) aminoalkyl refers to a chain comprising between 2 and 6 carbons and one or more nitrogen atoms positioned between the carbon atoms.

[0055] "Animal" includes humans, non-human mammals (*e.g.*, dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (*e.g.*, birds, and the like).

[0056] "Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp^2 hybridized and the total number of pi electrons is equal to 4n+2. An aromatic ring may be such that the ring atoms are only carbon atoms or may include carbon and non-carbon atoms (see Heteroaryl).

[0057] "Aryl" means a monocyclic or polycyclic ring assembly wherein each ring is aromatic or when fused with one or more rings forms an aromatic ring assembly. If one or more ring atoms is not carbon (*e.g.*, N, S), the aryl is a heteroaryl. C_X aryl and C_{X-Y} aryl are typically used where X and Y indicate the number of atoms in the ring.

[0058] "Bicycloalkyl" means a saturated or partially unsaturated fused bicyclic or bridged polycyclic ring assembly.

[0059] "Bicycloaryl" means a bicyclic ring assembly wherein the rings are linked by a single bond or fused and at least one of the rings comprising the assembly is aromatic. C_X bicycloaryl and C_{X-Y} bicycloaryl are typically used where X and Y indicate the number of carbon atoms in the bicyclic ring assembly and directly attached to the ring.

[0060] "Bridging ring" as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure where two ring atoms that are common to both rings are not directly bound to each other. Non-exclusive examples of common compounds having a bridging ring include borneol, norbornane, 7-oxabicyclo[2.2.1]heptane, and the like. One or both rings of the bicyclic system may also comprise heteroatoms.

[0061] "Carbamoyl" means the radical $-OC(O)NR_aR_b$ where R_a and R_b are each independently two further substituents where a hydrogen or carbon atom is attached to the nitrogen.

[0062] "Carbocycle" means a ring consisting of carbon atoms.

[0063] "Carbocyclic ketone derivative" means a carbocyclic derivative wherein the ring contains a -CO– moiety.

[0064] "Carbonyl" means the radical -CO-. It is noted that the carbonyl radical may be further substituted with a variety of substituents to form different carbonyl groups including acids, acid halides, aldehydes, amides, esters, and ketones.

[0065] "Carboxamido" means the radical $-C(O)NR_aR_b$ where the point of attachment to the molecule is at the carbon of the carbonyl, and R_a and R_b are each independently two further substituents on the nitrogen.

[0066] "Carboxy" means the radical $-CO_2-$. It is noted that compounds of the invention containing carboxy moieties may include protected derivatives thereof, *i.e.*, where the oxygen is substituted with a protecting group. Suitable protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the like.

[0067] "Cyano" means the radical -CN.

[0068] "Cycloalkyl" means a non-aromatic, saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly. C_X cycloalkyl and C_{X-Y} cycloalkyl are typically used where X and Y indicate the number of carbon atoms in the ring assembly. For example, C_{3-10} cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the like.

[0069] "Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic or polycyclic ring assembly. C_X cycloalkylene and C_{X-Y} cycloalkylene are typically used where X and Y indicate the number of carbon atoms in the ring assembly.

[0070] "Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, *i.e.*, the "side effects" of such therapy.

[0071] "Fused ring" as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure when the ring atoms that are common to both rings are directly bound to each other. Non-exclusive examples of common fused rings include decalin, naphthalene, anthracene, phenanthrene, indole, furan, benzofuran, quinoline, and the like. Compounds having fused ring systems may be saturated, partially saturated, carbocyclics, heterocyclics, aromatics, heteroaromatics, and the like.

[0072] "Halo" means fluoro, chloro, bromo or iodo.

[0073] "Halo-substituted alkyl", as an isolated group or part of a larger group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (*e.g.*, halo-substituted (C_{1-3})alkyl includes chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

[0074] "Heteroatom" refers to an atom that is not a carbon atom. Particular examples of heteroatoms include, but are not limited to nitrogen, oxygen, and sulfur.

[0075] "Heteroatom moiety" includes a moiety where the atom by which the moiety is attached is not a carbon. Examples of heteroatom moieties include -N=, $-NR_c-$, $-N^+(O^-)=$, -O-, -S- or $-S(O)_2-$, wherein R_c is further substituent.

[0076] "Heterobicycloalkyl" means bicycloalkyl, as defined in this Application, provided that one or more of the atoms within the ring is a heteroatom. For example hetero(C_{9-12})bicycloalkyl as used in this application includes, but is not limited to, 3-aza-bicyclo[4.1.0]hept-3-yl, 2-aza-bicyclo[3.1.0]hex-2-yl , 3-aza-bicyclo[3.1.0]hex-3-yl, and the like.

[0077] "Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms is replaced by a heteroatom.

[0078] "Heteroaryl" means a cyclic aromatic group having five or six ring atoms, wherein at least one ring atom is a heteroatom and the remaining ring atoms are carbon. The nitrogen atoms can be optionally quaternerized and the sulfur atoms can be optionally oxidized. Heteroaryl groups of this invention include, but are not limited to, those derived from furan, imidazole, isothiazole, isoxazole, oxadiazole, oxazole, 1,2,3-oxadiazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrroline, thiazole, 1,3,4-thiadiazole, triazole and tetrazole. "Heteroaryl" also includes, but is not limited to, bicyclic or tricyclic rings, wherein the heteroaryl ring is fused to one or two rings independently selected from the group consisting of an aryl ring, a cycloalkyl ring, a cycloalkenyl ring, and another monocyclic heteroaryl or heterocycloalkyl ring. These bicyclic or tricyclic heteroaryls include, but are not limited to, those derived from benzo[b]furan, benzo[b]thiophene, benzimidazole, imidazo[4,5-c]pyridine, quinazoline, thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, thieno[2,3-b]pyridine, indolizine, imidazo[1,2a]pyridine, quinoline,

isoquinoline, phthalazine, quinoxaline, naphthyridine, quinolizine, indole, isoindole, indazole, indoline, benzoxazole, benzopyrazole, benzothiazole, imidazo[1,5-a]pyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrimidine, imidazo[1,2-c]pyrimidine, imidazo[1,5-a]pyrimidine, imidazo[1,5-c]pyrimidine, pyrrolo[2,3-b]pyridine, pyrrolo[2,3-c]pyridine, pyrrolo[3,2-c]pyridine, pyrrolo[3,2-b]pyridine, pyrrolo[2,3-d]pyrimidine, pyrrolo[3,2-d]pyrimidine, pyrrolo[2,3-b]pyrazine, pyrazolo[1,5-a]pyridine, pyrrolo[1,2-b]pyridazine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrimidine, pyrrolo[1,2-a]pyrazine, triazo[1,5-a]pyridine, pteridine, purine, carbazole, acridine, phenazine, phenothiazene, phenoxazine, 1,2-dihydropyrrolo[3,2,1-*hi*]indole, indolizine, pyrido[1,2-a]indole and 2(1H)-pyridinone. The bicyclic or tricyclic heteroaryl rings can be attached to the parent molecule through either the heteroaryl group itself or the aryl, cycloalkyl, cycloalkenyl or heterocycloalkyl group to which it is fused. The heteroaryl groups of this invention can be substituted or unsubstituted.

[0079] "Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the atoms within the ring is a heteroatom. For example, hetero(C_{4-12})bicycloaryl as used in this Application includes, but is not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, tetrahydroisoquinolinyl, and the like.

[0080] "Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the atoms forming the ring is a heteroatom selected, independently from N, O, or S. Non-exclusive examples of heterocycloalkyl include piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolizinyl, 1,4-diazaperhydroepinyl, 1,3-dioxanyl, 1,4-dioxanyl and the like.

[0081] "Hydroxy" means the radical -OH.

[0082] "IC_{50}" means the molar concentration of an inhibitor that produces 50% inhibition of the target enzyme.

[0083] "Iminoketone derivative" means a derivative comprising the moiety -C(NR)-, wherein R comprises a hydrogen or carbon atom attached to the nitrogen.

[0084] "Isomers" mean any compound having an identical molecular formulae but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed

"diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers." A carbon atom bonded to four nonidentical substituents is termed a "chiral center." A compound with one chiral center has two enantiomeric forms of opposite chirality. A mixture of the two enantiomeric forms is termed a "racemic mixture." A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as ether an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture." When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (*e.g.*, see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992).

[0085] "Leaving group" means a moiety that can be displaced by another moiety, such as by nucleophilic attack, during a chemical reaction. Leaving groups are well known in the art and include, for example, halides and OSO_2R' where R' is, for example, alkyl, haloalkyl, or aryl optionally substituted by halo, alkyl, alkoxy, amino, and the like. Non-limiting examples of leaving groups include chloro, bromo, iodo, mesylate, tosylate, and other similar groups.

[0086] "Nitro" means the radical $-NO_2$.

[0087] "Oxo" means the radical =O.

[0088] "Oxaalkyl" means an alkyl, as defined above, except where one or more oxygen atoms (-O-) are positioned between carbon atoms of the alkyl. For example, an (C_{2-6})oxaalkyl refers to a chain comprising between 2 and 6 carbons and one or more oxygen atoms positioned between the carbon atoms.

[0089] "Oxoalkyl" means an alkyl, further substituted with a carbonyl group. The carbonyl group may be an aldehyde, ketone, ester, amide, acid or acid chloride.

[0090] "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

[0091] "Pharmaceutically acceptable salts" means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

[0092] Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

[0093] "Prodrug" means a compound that is convertible *in vivo* metabolically into an inhibitor according to the present invention. The prodrug itself may or may not also have HDAC inhibitory activity. For example, an inhibitor comprising a hydroxy group may be administered as an ester that is converted by hydrolysis *in vivo* to the hydroxy compound. Suitable esters that may be converted *in vivo* into hydroxy compounds include acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates,

fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates, quinates, esters of amino acids, and the like. Similarly, an inhibitor comprising an amine group may be administered as an amide that is converted by hydrolysis *in vivo* to the amine compound.

[0094] "Protected derivatives" means derivatives of inhibitors in which a reactive site or sites are blocked with protecting groups. Protected derivatives are useful in the preparation of inhibitors or in themselves may be active as inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

[0095] "Ring" means a carbocyclic or a heterocyclic system.

[0096] "Substituted or unsubstituted" means that a given moiety may consist of only hydrogen substituents through available valencies (unsubstituted) or may further comprise one or more non-hydrogen substituents through available valencies (substituted) that are not otherwise specified by the name of the given moiety. For example, isopropyl is an example of an ethylene moiety that is substituted by $-CH_3$. In general, a non-hydrogen substituent may be any substituent that may be bound to an atom of the given moiety that is specified to be substituted. Examples of substituents include, but are not limited to, aldehyde, alicyclic, aliphatic, (C_{1-10})alkyl, alkylene, alkylidene, amide, amino, aminoalkyl, aromatic, aryl, bicycloalkyl, bicycloaryl, carbamoyl, carbocyclyl, carboxyl, carbonyl group, cycloalkyl, cycloalkylene, ester, halo, heterobicycloalkyl, heterocycloalkylene, heteroaryl, heterobicycloaryl, heterocycloalkyl, oxo, hydroxy, iminoketone, ketone, nitro, oxaalkyl, and oxoalkyl moieties, each of which may optionally also be substituted or unsubstituted.

[0097] "Sulfinyl" means the radical –SO-. It is noted that the sulfinyl radical may be further substituted with a variety of substituents to form different sulfinyl groups including sulfinic acids, sulfinamides, sulfinyl esters, and sulfoxides.

[0098] "Sulfonyl" means the radical $-SO_2-$. It is noted that the sulfonyl radical may be further substituted with a variety of substituents to form different sulfonyl groups including sulfonic acids, sulfonamides, sulfonate esters, and sulfones.

[0099] "Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

[0100] "Thiocarbonyl" means the radical -CS-. It is noted that the thiocarbonyl radical may be further substituted with a variety of substituents to form different thiocarbonyl groups including thioacids, thioamides, thioesters, and thioketones.

[0101] "Treatment" or "treating" means any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (*i.e.*, arresting further development of the pathology and/or symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (*i.e.*, reversing the pathology and/or symptomatology).

[0102] It is noted in regard to all of the definitions provided herein that the definitions should be interpreted as being open ended in the sense that further substituents beyond those specified may be included. Hence, a C_1 alkyl indicates that there is one carbon atom but does not indicate what are the substituents on the carbon atom. Hence, a C_1 alkyl comprises methyl (*i.e.*, $-CH_3$) as well as $-CR_aR_bR_c$ where R_a, R_b, and R_c may each independently be hydrogen or any other substituent where the atom attached to the carbon is a heteroatom or cyano. Hence, CF_3, CH_2OH and CH_2CN, for example, are all C_1 alkyls.

DETAILED DESCRIPTION OF THE INVENTION

[0103] The present invention relates to compounds, compositions, kits and articles of manufacture that may be used to inhibit histone deacetylases (HDACs) and, in particular, Class I HDACs such as HDAC1, HDAC2, HDAC6 and HDAC8.

[0104] At least seventeen human genes that encode proven or putative HDACs have been identified to date, some of which are described in Johnstone, R. W., "Histone-

Deacetylase Inhibitors: Novel Drugs for the Treatment of Cancer", Nature Reviews, Volume I, pp. 287-299, (2002) and PCT Publication Nos. 00/10583, 01/18045, 01/42437 and 02/08273.

[0105] HDACs have been categorized into three distinct classes based on their relative size and sequence homology. The different HDACs (Homo sapiens), HDAC classes, sequences and references describing the different HDACs are provided in Tables 1 - 3.

TABLE 1: CLASS I HDACs

HDAC	GenBank Accession Number	Reference
1	NP_004955	Histone deacetylase: a regulator of transcription, Wolffe, A.P., Science 272 (5260), 371-372 (1996)
2	NP_001518	Isolation and mapping of a human gene (RPD3L1) that is homologous to RPD3, a transcription factor in Saccharomyces cerevisiae; Furukawa,Y., Kawakami,T., Sudo,K., Inazawa,J., Matsumine,A., Akiyama,T. and Nakamura,Y., Cytogenet. Cell Genet. 73 (1-2), 130-133 (1996)
3	NP_003874	Isolation and characterization of cDNAs corresponding to an additional member of the human histone deacetylase gene family, Yang,W.M., Yao,Y.L., Sun,J.M., Davie,J.R. and Seto,E., J. Biol. Chem. 272 (44), 28001-28007 (1997)
8	NP_060956	Buggy,J.J., Sideris,M.L., Mak,P., Lorimer,D.D., McIntosh,B. and Clark,J.M. Biochem. J. 350 Pt 1, 199-205 (2000)
11	NP_079103	Cloning and Functional Characterization of HDAC11, a Novel Member of the Human Histone Deacetylase Family, Gao,L., Cueto,M.A., Asselbergs,F. and Atadja,P., J. Biol. Chem. 277 (28), 25748-25755 (2002)

TABLE 2: CLASS II HDACs

HDAC	GenBank Accession Number	Reference
4	NP_006028	Transcriptional control. Sinful repression, Wolffe,A.P., Nature 387 (6628), 16-17 (1997)

HDAC	GenBank Accession Number	Reference
5	NP_631944	Prediction of the coding sequences of unidentified human genes. IX. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro, Nagase,T., Ishikawa,K., Miyajima,N., Tanaka,A., Kotani,H., Nomura,N. and Ohara,O., DNA Res. 5 (1), 31-39 (1998)
6	NP_006035	Transcriptional control. Sinful repression, Wolffe,A.P., Nature 387 (6628), 16-17 (1997)
7	NP_057680	Isolation of a novel histone deacetylase reveals that class I and class II deacetylases promote SMRT-mediated repression, Kao,H.Y., Downes,M., Ordentlich,P. and Evans,R.M., Genes Dev. 14 (1), 55-66 (2000)
9	NP_478056	MEF-2 function is modified by a novel co-repressor, MITR, Sparrow,D.B., Miska,E.A., Langley,E., Reynaud-Deonauth,S., Kotecha,S., Towers,N., Spohr,G., Kouzarides,T. and Mohun,T.J., EMBO J. 18 (18), 5085-5098 (1999)
10	NP_114408	Isolation and characterization of mammalian HDAC10, a novel histone deacetylase, Kao,H.Y., Lee,C.H., Komarov,A., Han,C.C. and Evans,R.M., J. Biol. Chem. 277 (1), 187-193 (2002)

TABLE 3: CLASS III HDACs

HDAC	GenBank Accession Number	Reference
Sirtuin 1	NP_036370	Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity; Frye,R.A.; Biochem. Biophys. Res. Commun. 260 (1), 273-279 (1999)
Sirtuin 2	NP_085096 / NP_036369	A 'double adaptor' method for improved shotgun library construction; Andersson,B., Wentland,M.A., Ricafrente,J.Y., Liu,W. and Gibbs,R.A.; Anal. Biochem. 236 (1), 107-113 (1996)
Sirtuin 3	NP_036371	Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity; Frye,R.A.; Biochem. Biophys. Res. Commun. 260 (1), 273-279 (1999)

HDAC	GenBank Accession Number	Reference
Sirtuin 4	NP_036372	Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity; Frye,R.A.; Biochem. Biophys. Res. Commun. 260 (1), 273-279 (1999)
Sirtuin 5	NP_112534 / NP_036373	Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity; Frye,R.A.; Biochem. Biophys. Res. Commun. 260 (1), 273-279 (1999)
Sirtuin 6	NP_057623	Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins; Frye,R.A.; Biochem. Biophys. Res. Commun. 273 (2), 793-798 (2000)
Sirtuin 7	NP_057622	Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins; Frye,R.A.; Biochem. Biophys. Res. Commun. 273 (2), 793-798 (2000)

[0106] Of particular note are Class I HDACs. All Class I HDACs appear to be sensitive to inhibition by trichostatin A (TSA). Of particular note HDAC2 and HDAC8, proteins whose crystal structures Applicants determined and used in conjunction with arriving at the present invention.

[0107] HDAC2 is a 488 residue, 55 kDa protein localized to the nucleus of a wide array of tissues, as well as several human tumor cell lines. The wild-type form of full length HDAC2 is described in GenBank Accession Number NM 001527, Furukawa, Y. et al., Cryogenet. Cell Genet., 73 (1-2), 130-133 (1996). Zn^{2+} is likely native to the protein and required for HDAC2 activity.

[0108] HDAC8 is a 377 residue, 42kDa protein localized to the nucleus of a wide array of tissues, as well as several human tumor cell lines. The wild-type form of full length HDAC8 is described in GenBank Accession Number NP 060956; Buggy, J.J. et al., Biochem. J., 350 (Pt 1), 199-205 (2000). Zn^{2+} is likely native to the protein and required for HDAC8 activity.

[0109] It is noted that the compounds of the present invention may also possess inhibitory activity for other HDAC family members and thus may be used to address disease states associated with these other family members.

Crystal Structure of Histone Deacetylase

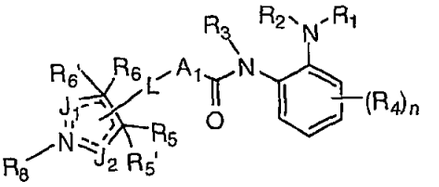
[0110] Syrrx, Inc. (now Takeda San Diego, Inc.) in San Diego, California solved the crystal structure for HDAC2. HDAC2 was found to adopt an open-faced α/β structure consisting of 8 central parallel β-sheets sandwiched between 12 α-helices. The ligand binding cleft lies almost in the plane of the central β-sheet, and is formed primarily by loops emanating from the carboxy-terminal ends of the β-strands comprising the sheet. Residues which form loop regions extending between β-strand 1 and α-helix 1 and between α-helix 4 and α-helix 5, provide key surface interactions with bound ligands. Residues which form loop regions extending between β-strand 3 and α-helix 6 and between β-strand 4 and α-helix 7 and between β-strand 8 and α-helix 10 play important roles in defining the shape of the ligand binding pocket, and are involved in a number of key interactions with the bound ligands.

[0111] HDAC8 was found to have a single domain structure belonging to the open α/β class of folds. The structure consists of a central 8-stranded parallel β-sheet sandwiched between layers of α-helices. The ligand binding clefts lie almost in the plane of the central β-sheet, and are formed primarily by loops emanating from the carboxy-terminal ends of the β-strands comprising the sheet. There are two large structural extensions, which occur beyond the core of the α/β motif, off the second and last β-strands of the central β-sheet. Residues contained in the extension off the second β-strand form a globular "cap" over the core of the protein, play an important role in defining the shape of the ligand binding pockets, and are involved in a number of key interactions with the bound ligands.

[0112] Knowledge of the crystal structures was used to guide the design of the HDAC inhibitors provided herein.

HDAC Inhibitors

[0113] In one embodiment, HDAC inhibitors of the present invention comprise:



wherein:

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atom to which L is attached;

J_1 is selected from the group consisting of $-CR_7R_7'$- and $-NR_{19}$-;

J_2 is selected from the group consisting of $-CR_{20}R_{20}'$ and $-NR_{10}$-;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 are taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl,

aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

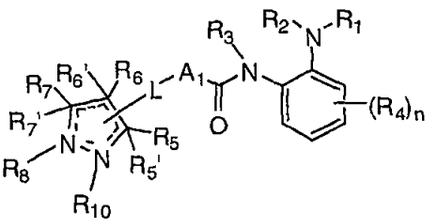
each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_5, R_5', R_6, R_6', R_7, and R_7', R_{20} and R_{20}' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' may be taken together to form a substituted or unsubstituted ring, provided that R_5, R_6, R_7 and R_{20}, are each independently absent when the C to which they are bound is bound to L, and R_5', R_6', R_7' and R_{20}', are each independently absent when the C to which they are bound form part of a double bond; and

R_8, R_{10} and R_{19} are each individually selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl,

carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}', R_{10} and R_{19} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}' and R_{19} may be taken together to form a substituted or unsubstituted ring, or R_{19} and any one of R_5, R_5', R_6, R_6', R_{20} and R_{20}', may be taken together to form a substituted or unsubstituted ring, provided that R_8, R_{10} and R_{19} are each independently absent when the N to which they are bound is bound to L, and R_8, R_{10} and R_{19} are each independently absent when the N to which they are bound form part of a double bond.

[0114] In another embodiment, HDAC inhibitors of the present invention comprise:



wherein:

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

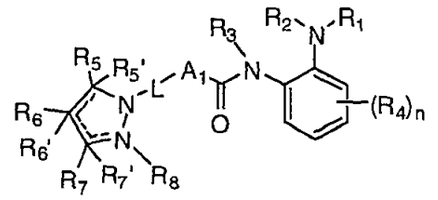
each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

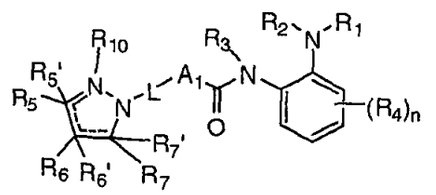
R_5, R_5', R_6, R_6', R_7 and R_7' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl,

(C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_5, R_6 and R_7 are each independently absent when the C to which they are bound is bound to L, and R_5', R_6' and R_7' are each independently absent when the C to which they are bound form part of a double bond; and

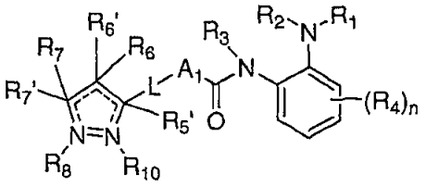
R_8 and R_{10} are each individually selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7' and R_{10} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_8 and R_{10} are each independently absent when the N to which they are bound is bound to L, and R_8 and R_{10} are absent when the N to which they are bound form part of a double bond.

[0115] In another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:





and



wherein:

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

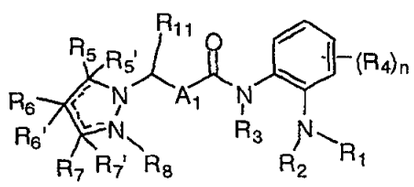
each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_5, R_5', R_6, R_6', R_7 and R_7' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_5', R_6' and R_7' are each independently absent when the C to which they are bound form part of a double bond; and

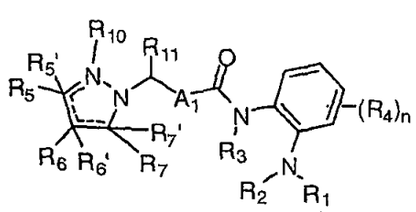
R_8 and R_{10} are each individually selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8

and any one of R_5, R_5', R_6, R_6', R_7, R_7' and R_{10} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_8 and R_{10} are each independently absent when the N to which they are bound form part of a double bond.

[0116] In yet another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



and



wherein:

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl,

(C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

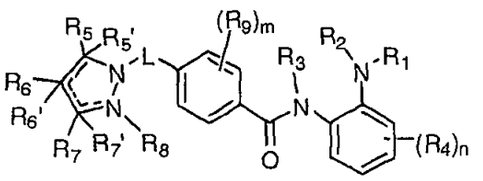
R_5, R_5', R_6, R_6', R_7 and R_7' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring,

provided that R_5', R_6' and R_7' are each independently absent when the C to which they are bound form part of a double bond;

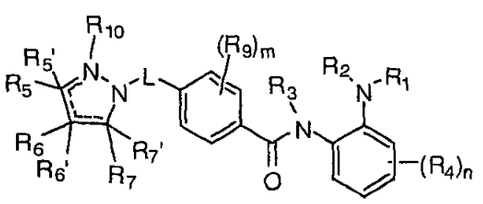
R_8 and R_{10} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7' and R_{10} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_8 and R_{10} are each independently absent when the N to which they are bound form part of a double bond; and

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0117] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

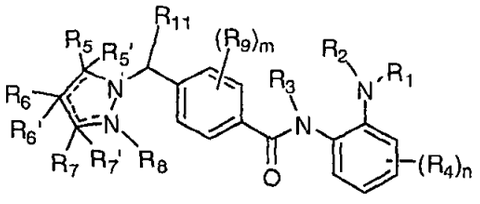
R_5, R_5', R_6, R_6', R_7 and R_7' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_5', R_6' and R_7' are each independently absent when the C to which they are bound form part of a double bond;

R_8 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl,

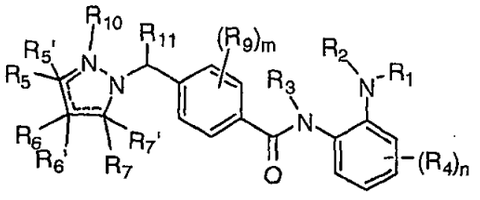
(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, $R_7'$and R_{10} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_8 and R_{10} are absent when the N to which they are bound form part of a double bond; and

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_3, R_5, R_5', R_7, R_7', R_8 and R_{10} may be taken together to form a substituted or unsubstituted ring.

[0118] In a further embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_5, R_5', R_6, R_6', R_7 and R_7' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_5', R_6' and R_7' are each independently absent when the C to which they are bound form part of a double bond;

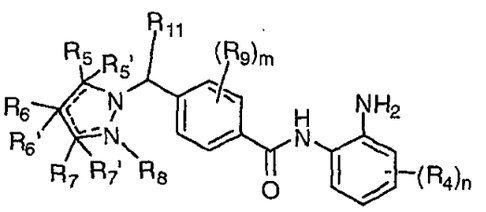
R_8 and R_{10} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7' and R_{10} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_8 or R_{10} are each independently absent when the N to which it is bound form part of a double bond;

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl,

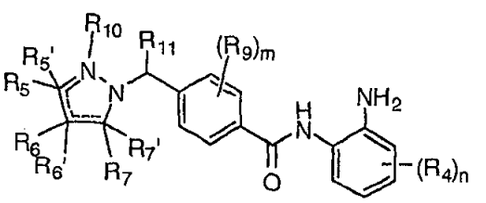
amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_3, R_5, R_5', R_7, R_7', R_8 and R_{10} may be taken together to form a substituted or unsubstituted ring; and

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring.

[0119] In still a further embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_5, R_5', R_6, R_6', R_7 and R_7' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_5', R_6' and R_7' are each independently absent when the C to which they are bound form part of a double bond;

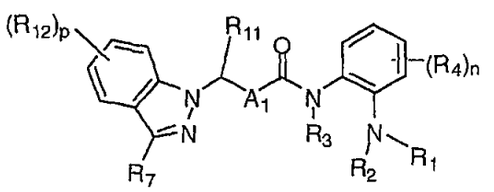
R_8 and R_{10} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7' and R_{10} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_8 is absent when the N to which it is bound forms part of a double bond;

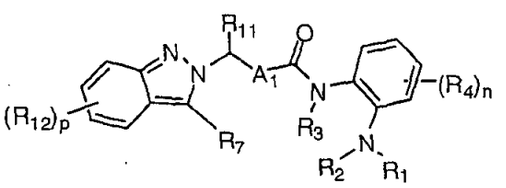
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_5, R_5', R_7, R_7', R_8 and R_{10} may be taken together to form a substituted or unsubstituted ring; and

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring.

[0120] In yet a further embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



and



wherein:

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl,

aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

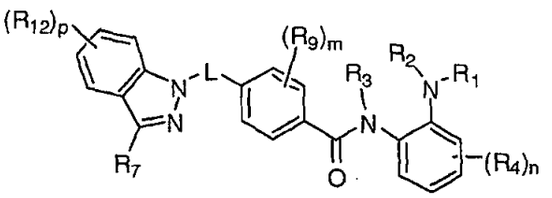
R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl,

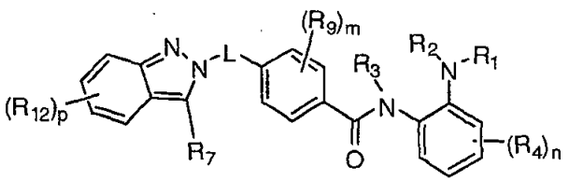
(C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_7 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0121] In another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

L is a linker providing a 0-6 atom separation between the two rings atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

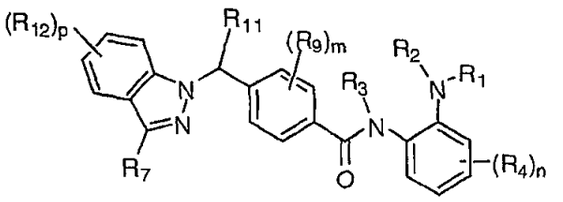
R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl,

(C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and R_3 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 may be taken together to form a substituted or unsubstituted ring.

[0122] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



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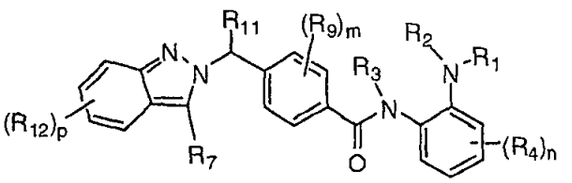


wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl,

(C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

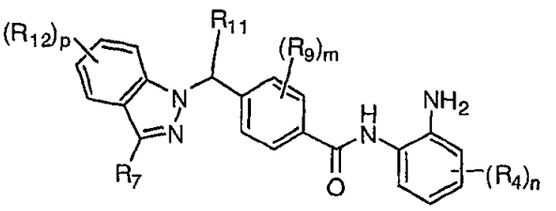
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or

any two R_9 or one R_9 and R_3 may be taken together to form a substituted or unsubstituted ring;

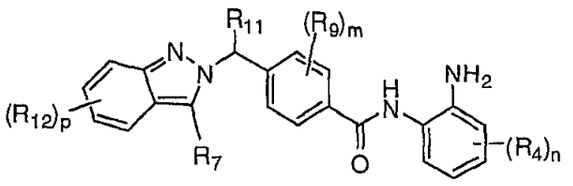
R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0123] In yet another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl,

amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 may be taken together to form a substituted or unsubstituted ring;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_7 or R_9 may be taken together to form a substituted or unsubstituted ring; and

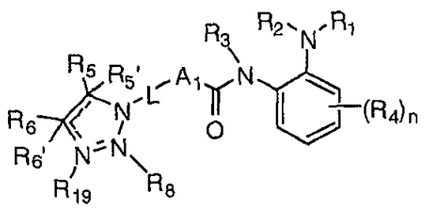
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

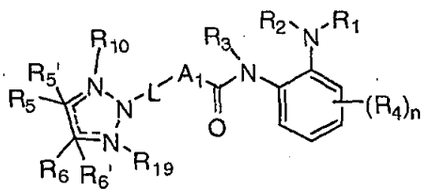
[0124] In one variation of each of the above embodiments, m is 0, R_{11} is hydrogen, and R_{12} is selected from the group consisting of hydroxy, alkoxy, halo, amido, carboxamido, and (C_{1-10})alkylamido, each substituted or unsubstituted.

[0125] In yet another variation, n is 0, p is 2, and R_{12} is selected from the group consisting of hydroxy, alkoxy, and halo.

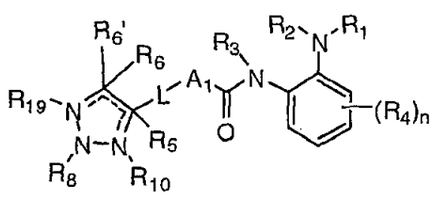
[0126] In still another variation, R_7 is hydrogen, and R_{12} is alkoxy.

[0127] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:





and



wherein:

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl,

(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

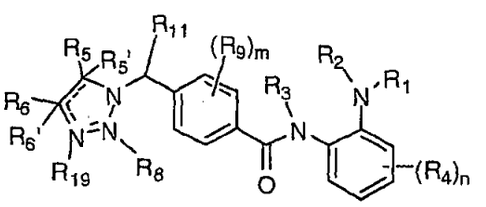
R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_5, R_5', R_6 and R_6' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and

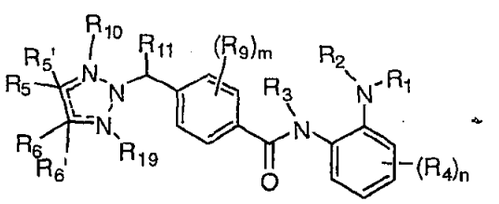
hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, and R_6' may be taken together to form a substituted or unsubstituted ring, provided that R_5' andR_6' are each independently absent when the C to which they are bound form part of a double bond; and

R_8, R_{10} and R_{19}, are each individually selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_{10} and R_{19} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6' and R_{19} may be taken together to form a substituted or unsubstituted ring, or R_{19} and any one of R_5, R_5', R_6 and R_6' may be taken together to form a substituted or unsubstituted ring, provided that R_8, R_{10} and R_{19} are each independently absent when the N to which they are bound forms part of a double bond.

[0128] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_5, R_5', R_6 and R_6' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6 and R_6' may be taken together to form a substituted or unsubstituted ring, provided that R_5' and R_6' are each independently absent when the C to which they are bound form part of a double bond;

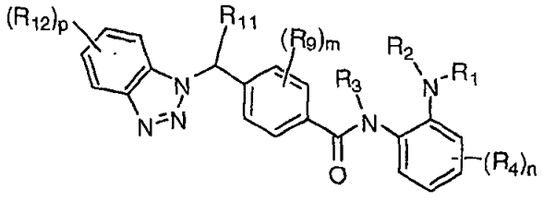
R_8, R_{10} and R_{19} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_{10} and R_{19} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6' and R_{19} may be taken together to form a substituted or unsubstituted ring, or R_{19} and any one of R_5, R_5', R_6 and R_6' may be taken together to form a substituted or unsubstituted ring, provided that R_8, R_{10} and R_{19} are each independently absent when the N to which they are bound forms part of a double bond.

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl,

carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_3, R_5, R_5', R_8, R_{10} and R_{19} may be taken together to form a substituted or unsubstituted ring; and

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring.

[0129] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



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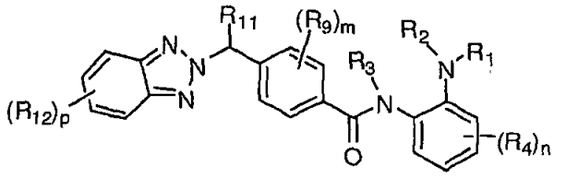


wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

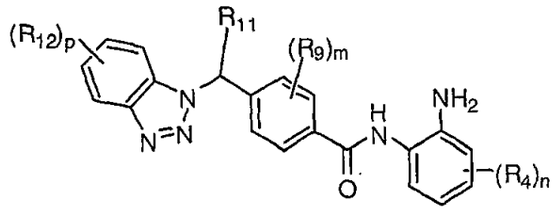
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and R_3 may be taken together to form a substituted or unsubstituted ring;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and

hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_{11} may be taken together to form a substituted or unsubstituted.

[0130] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:



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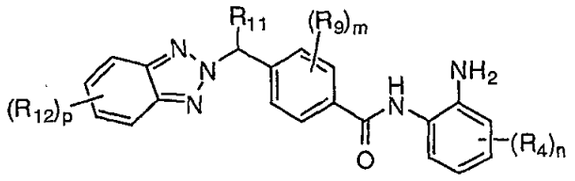


wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

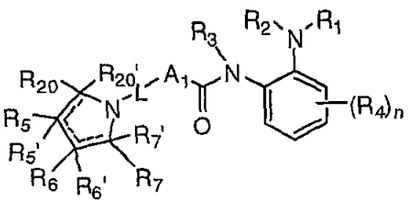
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl,

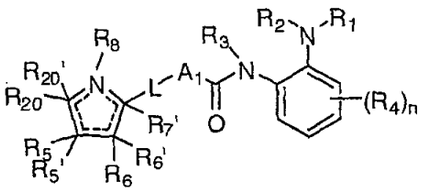
amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 may be taken together to form a substituted or unsubstituted ring;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamide, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_{11} may be taken together to form a substituted or unsubstituted ring.

[0131] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:





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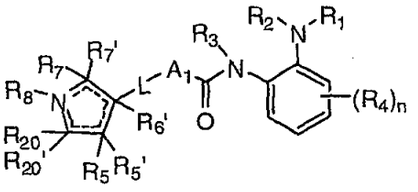


wherein:

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

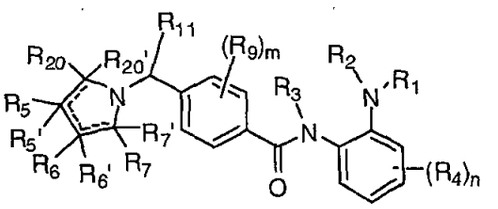
R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

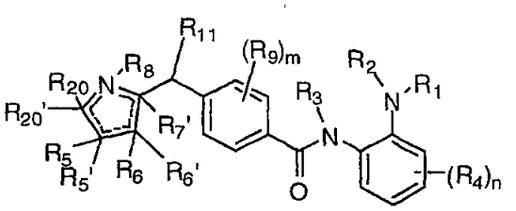
R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' may be taken together to form a substituted or unsubstituted ring, provided that R_5', R_6', R_7' and R_{20}', are each

independently absent when the C to which they are bound form part of a double bond; and

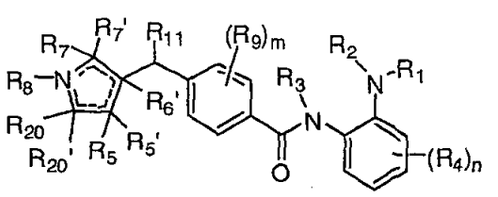
R_8 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' may be taken together to form a substituted or unsubstituted ring, provided that R_8 is absent when the N to which it is bound forms part of a double bond.

[0132] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:





and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' may be taken together to form a substituted or unsubstituted ring, provided that R_5', R_6', R_7' and R_{20}', are each independently absent when the C to which they are bound form part of a double bond; and

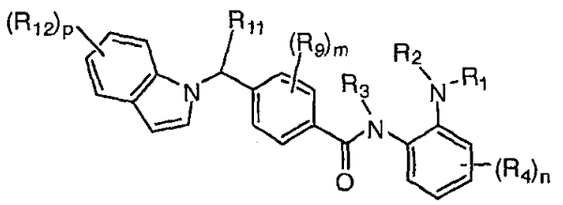
R_8 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' may be taken together to form a substituted or unsubstituted ring, provided that R_8 is absent when the N to which it is bound forms part of a double bond;

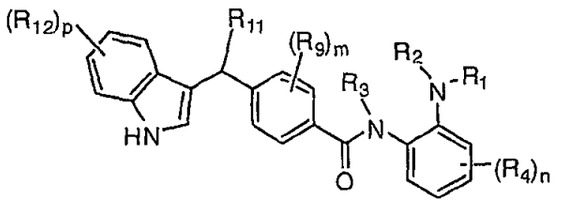
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_3, R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}' and R_8 may be taken together to form a substituted or unsubstituted ring; and

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring.

[0133] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:





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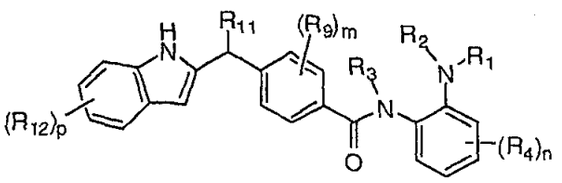


wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl,

amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

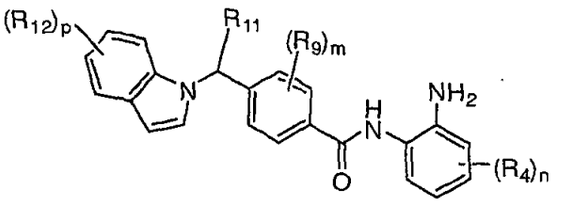
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and R_3 may be taken together to form a substituted or unsubstituted ring;

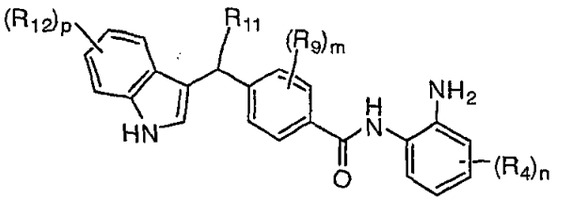
R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

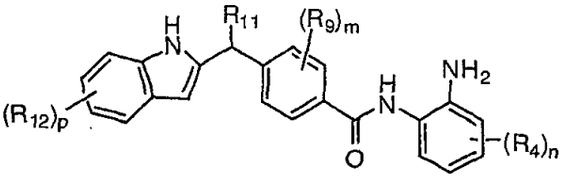
(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_{11} may be taken together to form a substituted or unsubstituted ring.

[0134] In still another embodiment, HDAC inhibitors of the present invention comprise a compound selected from the group consisting of:





and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl,

carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 may be taken together to form a substituted or unsubstituted ring;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_{11} may be taken together to form a substituted or unsubstituted ring.

[0135] In one variation of each of the above embodiments, R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl and imino(C_{1-3})alkyl, each substituted or unsubstituted.

[0136] In another variation of each of the above embodiments and variations, R_1 is hydrogen or a substituent convertible in vivo to hydrogen. In still another variation of each of the above embodiments and variations, R_2 is hydrogen or a substituent convertible in vivo to hydrogen. In yet another variation of each of the above embodiments and variations, R_3 is hydrogen or a substituent convertible in vivo to hydrogen.

[0137] In a further variation of each of the above embodiments and variations, R_4 is selected from the group consisting of hydrogen, halo, aryl and heteroaryl, each substituted or unsubstituted. In yet a further variation of each of the above embodiments and variations, R_4 is selected from the group consisting of phenyl, oxazolyl, thiazolyl, morpholinyl and thiomorpholinyl, each substituted or unsubstituted.

[0138] In still a further variation of each of the above embodiments and variations, R_5, R_6, R_7 and R_{20} are independently selected from the group consisting of carbonyl, oxo, amino, (C_{1-10})alkylamino, amido, carboxamido, cyano, alkoxy, (C_{1-10})alkyl, aryl, and heteroaryl, each substituted or unsubstituted.

[0139] In another variation of each of the above embodiments and variations, R_5 and R_6 are taken together to form a substituted or unsubstituted ring. In one variation, the ring is an aryl or heteroaryl, each substituted or unsubstituted. In another variation, the ring is substituted with a substituent selected from the group consisting of halo, alkoxy, amino(C_{1-10})alkoxy, amino(C_{1-10})alkylamino, amino(C_{1-10})alkylsulfanyl, halo(C_{1-10})alkyl,

aryl and heteroaryl, each substituted or unsubstituted. In yet another variation, the ring is substituted with a substituent selected from the group consisting of thiopheneyl, pyridinyl, furanyl and pyrimidinyl, each substituted or unsubstituted.

[0140] In still another variation, the ring is substituted with -O-CH_2CH_2-$NR_{13}R_{14}$. In a further variation, the ring is substituted with -NH-CH_2CH_2-$NR_{13}R_{14}$. In yet a further variation, the ring is substituted with -S-CH_2CH_2-$NR_{13}R_{14}$. In each of these variations, R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero (C_{8-12})bicycloaryl (C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{13} and R_{14} may be taken together to form a substituted or unsubstituted ring. In other embodiments, R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, and heteroaryl, each substituted or unsubstituted. In still other embodiments, R_{13} and R_{14} are taken together to form a ring selected from the group consisting of morpholinyl, pyrrolidinyl, piperazinyl and thiomorpholinyl, each substituted or unsubstituted.

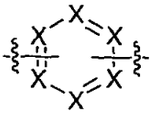
[0141] In another variation of each of the above embodiments and variations, R_8, R_{10} and R_{19} are selected from the group consisting of hydrogen and substituted or unsubstituted (C_{1-10})alkyl.

[0142] In still another variation of each of the above embodiments and variations, L is a linker providing a 1-5 atom separation between the two ring atoms to which L is attached. In yet another variation of each of the above embodiments and variations, L is a linker providing a 1-3 atom separation between the two ring atoms to which L is attached. In a further variation of each of the above embodiments and variations, L is a substituted or unsubstituted alkylene. In yet a further variation of each of the above embodiments and variations, wherein L is -CH_2-. In another variation of each of the above embodiments and

variations, L is selected from the group consisting of $-NR_{15}-$; $-NR_{15}-CH_2-$; $-O-CH_2-$; $-S-CH_2-$; $-CH_2-NR_{15}-$; $-CH_2-O-$ and $-CH_2-S-$, wherein R_{15} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0143] In still another variation of each of the above embodiments and variations, A_1 is selected from the group consisting of aryl and heteroaryl, each substituted or unsubstituted. In yet another variation of each of the above embodiments and variations, A_1 is a substituted or unsubstituted phenylene. In a further variation of each of the above embodiments and variations, A_1 is a substituted or unsubstituted 1,4-phenylene. In still a further variation of each of the above embodiments and variations, A_1 is selected from the group consisting of a thiophenediyl, furandiyl, pyrrolediyl, thiazolediyl, oxazolediyl, imidazolediyl and pyridinediyl, each substituted or unsubstituted.

[0144] In another variation of each of the above embodiments and variations, A_1 comprises:



wherein:

each X is independently selected from the group consisting of CR_{16} and N; and

each R_{16} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl,

heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{16} is absent when the C to which it is bound is further bound to L or the carbonyl adjacent to A_1.

[0145] Particular examples of compounds according to the present invention include, but are not limited to:

4-((1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-acetamido-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-acetamido-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((5-nitro-1H-indazol-1-yl)methyl)benzamide;

4-((5-benzamido-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-amino-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((5-nitro-2H-indazol-2-yl)methyl)benzamide;

4-((5-amino-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-benzamido-2H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

2-Methoxyethyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2H-indazol-5-ylcarbamate;

Methyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2H-indazol-5-ylcarbamate;

2-Methoxyethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-indazol-5-ylcarbamate;

Methyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-indazol-5-ylcarbamate;

Benzyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-indazol-5-ylcarbamate;

Benzyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2H-indazol-5-ylcarbamate;

N-(4-Amino-biphenyl-3-yl)-4-(5-nitro-indazol-2-ylmethyl)-benzamide;

N-(2-(4-((2-Aminophenyl)carbamoyl)benzyl)-2H-indazol-5-yl)morpholine-4-carboxamide;

5-((2H-Indazol-2-yl)methyl)-N-(2-aminophenyl)thiophene-2-carboxamide;

N-(2-Aminophenyl)-5-((5-nitro-2H-indazol-2-yl)methyl)thiophene-2-carboxamide;

N-(1-(4-((2-Aminophenyl)carbamoyl)benzyl)-1H-indazol-5-yl)morpholine-4-carboxamide;

2-Morpholinoethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-indazol-5-ylcarbamate;

Pyridin-3-ylmethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-indazol-5-ylcarbamate;

5-((1H-Indazol-1-yl)methyl)-N-(2-aminophenyl)thiophene-2-carboxamide;

4-((2H-Pyrazolo[3,4-b]pyridin-2-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(4-Amino-biphenyl-3-yl)-4-pyrazolo[3,4-b]pyridin-2-ylmethyl-benzamide;

N-(4-Amino-biphenyl-3-yl)-4-indazol-2-ylmethyl-benzamide;

N-(2-Aminophenyl)-4-((3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-Aminophenyl)-4-((3-methyl-2H-indazol-2-yl)methyl)benzamide;

4-((1H-indazol-3-ylamino)methyl)-N-(2-aminophenyl)benzamide;

4-((1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-(4-((2-Aminophenyl)carbamoyl)benzyl)-2H-indazol-5-yl)morpholine-4-carboxamide;

Methyl 3-(4-((2H-indazol-2-yl)methyl)benzamido)-4-aminobenzoate;

N-(2-aminophenyl)-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-fluoro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-fluoro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-fluoro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-fluoro-2H-indazol-2-yl)methyl)benzamide;

4-(1-(1H-indazol-1-yl)propan-2-yl)-N-(2-aminophenyl)benzamide;

4-(2-(1H-indazol-1-yl)ethyl)-N-(2-aminophenyl)benzamide;

4-(2-(2H-indazol-2-yl)ethyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((4-chloro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-chloro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4,6-difluoro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4,6-difluoro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((7-fluoro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((7-fluoro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-fluoro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-fluoro-2H-indazol-2-yl)methyl)benzamide;

(R)-4-(1-(2H-indazol-2-yl)ethyl)-N-(2-aminophenyl)benzamide;

(S)-4-(1-(2H-indazol-2-yl)ethyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((7-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((7-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-difluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-difluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-methoxy-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-methoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-chloro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-chloro-2H-indazol-2-yl)methyl)benzamide;

4-((3-amino-5-(trifluoromethyl)-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((3-amino-5-(trifluoromethyl)-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((3-oxo-2,3-dihydro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-oxo-1H-indazol-2(3H)-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-methoxy-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-methoxy-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-ethyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-ethyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-hydroxy-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-hydroxy-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-phenyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-phenyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-methoxy-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-methoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3,5-dimethyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3,5-dimethyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((7-methoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-methoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((7-methoxy-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-methoxy-1H-indazol-1-yl)methyl)benzamide;

4-((6-acetamido-3-methyl-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((6-acetamido-3-methyl-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((3-amino-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((6-acetamido-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((6-acetamido-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((3-methyl-7-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-methyl-6-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-methyl-6-(trifluoromethyl)-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-methyl-5-(trifluoromethyl)-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-methyl-5-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide;

4-((3-amino-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((5-hydroxy-6-methoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-dimethoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-dimethoxy-1H-indazol-1-yl)methyl)benzamide;

4-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;

4-((2*H*-benzo[*d*][1,2,3]triazol-2-yl)methyl)-*N*-(2-aminophenyl)benzamide;

4-((5-acetamido-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(piperazin-1-yl)ethyl)-1H-pyrazole-4-carboxamide;

4-((2*H*-indazol-2-yl)methyl)-*N*-(4-aminopyrimidin-5-yl)benzamide;

4-((5-acetamido-3-amino-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;

4-((5-acetamido-3-methyl-2*H*-indazol-2-yl)methyl)-*N*-(2-aminophenyl)benzamide;

4-((5-acetamido-3-methyl-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;

4-(1-(1*H*-indazol-1-yl)ethyl)-*N*-(2-aminophenyl)benzamide;

4-(1-(2*H*-indazol-2-yl)ethyl)-*N*-(2-aminophenyl)benzamide;

5-((5-acetamido-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)thiophene-2-carboxamide;

4-((2*H*-indazol-2-yl)methyl)-*N*-(2-amino-5-(thiophen-2-yl)phenyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4,6-difluoro-2*H*-indazol-2-yl)methyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4,6-difluoro-1*H*-indazol-1-yl)methyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((6-methoxy-3-methyl-1*H*-indazol-1-yl)methyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-methyl-1*H*-pyrazol-1-yl)methyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((6-methoxy-3-methyl-2*H*-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-(trifluoromethyl)-1*H*-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-(trifluoromethyl)-1*H*-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-1H-pyrazole-4-carboxylic acid;

N-(2-aminophenyl)-4-((3-methyl-1H-pyrazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzamide;

Ethyl 1-(4-(2-aminophenylcarbamoyl)benzyl)-1H-pyrazole-4-carboxylate;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-phenyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-benzyl-1H-pyrazole-4-carboxamide;

N-(2-aminophenyl)-4-((4,5,6,7-tetrahydro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4,5,6,7-tetrahydro-1H-indazol-1-yl)methyl)benzamide;

4-((1H-pyrazol-3-ylamino)methyl)-N-(2-aminophenyl)benzamide;

4-((5-amino-1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((3-amino-1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-methyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-ethyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N,N-dimethyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-isopropyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-cyclopropyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(cyclopropylmethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(dimethylamino)ethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-hydroxyethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-(dimethylamino)propyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridin-3-ylmethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridin-4-ylmethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-morpholinoethyl)-1H-pyrazole-4-carboxamide;

N-(2-aminophenyl)-4-((5-methyl-1H-pyrazol-1-yl)methyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-propyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-isobutyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-methoxyethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-methoxypropyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-hydroxypropyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-morpholinopropyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(piperidin-1-yl)ethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-(4-methylpiperazin-1-yl)propyl)-1H-pyrazole-4-carboxamide;

4-((1*H*-Pyrrolo[2,3-b]pyridin-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((1*H*-Indol-3-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((1H-indazol-1-yl)methyl)-N-(2-amino-5-fluorophenyl)benzamide;

4-((2H-indazol-2-yl)methyl)-N-(2-amino-5-fluorophenyl)benzamide;

4-((1H-indazol-1-yl)methyl)-N-(2-amino-5-fluorophenyl)-3-methylbenzamide;

4-((2H-indazol-2-yl)methyl)-N-(2-amino-5-fluorophenyl)-3-methylbenzamide;

N-(2-aminophenyl)-3-methyl-4-((3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-3-methyl-4-((3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-cyano-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-cyano-2H-indazol-2-yl)methyl)benzamide;

1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-indazole-3-carboxylic acid;

2-(4-((2-aminophenyl)carbamoyl)benzyl)-2H-indazole-3-carboxylic acid;

N-(2-aminophenyl)-4-((5-cyano-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-cyano-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-(pyridin-2-yl)-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-(pyridin-2-yl)-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-(dimethylamino)-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-(dimethylamino)-2H-indazol-2-yl)methyl)benzamide;
4-((1H-indazol-1-yl)methyl)-N-(2-amino-5-(furan-2-yl)phenyl)benzamide;
4-((2H-indazol-2-yl)methyl)-N-(2-amino-5-(furan-2-yl)phenyl)benzamide;
N-(2-aminophenyl)-4-((3-methoxy-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-methoxy-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-(methoxymethylamino)-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-(methoxymethylamino)-2H-indazol-2-yl)methyl)benzamide;
4-((1H-pyrazol-1-yl)methyl)-N-(2-amino-5-fluorophenyl)benzamide;
N-(2-amino-5-fluorophenyl)-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide;
4-((1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)-3-methylbenzamide;
N-(2-amino-5-fluorophenyl)-3-methyl-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-(furan-2-yl)-1H-pyrazol-1-yl)methyl)benzamide;
1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-pyrazole-4-carboxylic acid;
N-(2-aminophenyl)-4-((3-ethyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5-ethyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-phenyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-3-methyl-4-((5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-cyano-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzamide;
4-((1H-pyrazol-1-yl)methyl)-N-(2-amino-5-(furan-2-yl)phenyl)benzamide;
N-(2-amino-5-(furan-2-yl)phenyl)-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide;
(S)-4-(1-(1H-pyrazol-1-yl)ethyl)-N-(2-aminophenyl)benzamide;
(R)-4-(1-(1H-pyrazol-1-yl)ethyl)-N-(2-aminophenyl)benzamide;
N-(2-aminophenyl)-4-((3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5-methoxy-1H-pyrazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-(methoxymethylamino)-1H-pyrazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-(methoxymethylamino)-1H-pyrazol-1-yl)methyl)benzamide; and

N-(2-aminophenyl)-4-((3-methoxy-1H-pyrazol-1-yl)methyl)benzamide.

[0146] It is noted that the compounds of the present invention may be in the form of a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, solvate, hydrate or prodrug thereof. For example, the compound optionally comprises a substituent that is convertible in vivo to a different substituent such as a hydrogen.

[0147] It is further noted that the compound may be present in a mixture of stereoisomers (including tautomers), or the compound may comprise a single stereoisomer.

[0148] The present invention also provides a pharmaceutical composition comprising as an active ingredient a compound according to any one of the above embodiments and variations. In one particular variation, the composition is a solid formulation adapted for oral administration. In another particular variation, the composition is a liquid formulation adapted for oral administration. In yet another particular variation, the composition is a tablet. In still another particular variation, the composition is a liquid formulation adapted for parenteral administration.

[0149] In another of its aspects, there is provided a pharmaceutical composition comprising a compound according to any one of the above embodiments and variations, wherein the composition is adapted for administration by a route selected from the group consisting of orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, and intrathecally.

[0150] In yet another of its aspects, there is provided a kit comprising a compound of any one of the above embodiments and variations; and instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the composition is to be administered, storage information for the composition,

dosing information and instructions regarding how to administer the composition. In one particular variation, the kit comprises the compound in a multiple dose form.

[0151] In still another of its aspects, there is provided an article of manufacture comprising a compound of any one of the above embodiments and variations; and packaging materials. In one variation, the packaging material comprises a container for housing the compound. In one particular variation, the container comprises a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the compound. In another variation, the article of manufacture comprises the compound in a multiple dose form.

[0152] In a further of its aspects, there is provided a therapeutic method comprising administering a compound of any one of the above embodiments and variations to a subject.

[0153] In another of its aspects, there is provided a method of inhibiting HDAC comprising contacting HDAC with a compound of any one of the above embodiments and variations.

[0154] In yet another of its aspects, there is provided a method of inhibiting HDAC comprising causing a compound of any one of the above embodiments and variations to be present in a subject in order to inhibit HDAC in vivo.

[0155] In a further of its aspects, there is provided a method of inhibiting HDAC comprising administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits HDAC in vivo, the second compound being a compound according to any one of the above embodiments and variations.

[0156] In another of its aspects, there is provided a method of treating a disease state for which HDAC possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising causing a compound of any one of the above embodiments and variations to be present in a subject in a therapeutically effective amount for the disease state.

[0157] In yet another of its aspects, there is provided a method of treating a disease state for which HDAC possesses activity that contributes to the pathology and/or

symptomology of the disease state, the method comprising administering a compound of any one of the above embodiments and variations to a subject, wherein the compound is present in the subject in a therapeutically effective amount for the disease state.

[0158] In a further of its aspects, there is provided a method of treating a disease state for which HDAC possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits HDAC in vivo, the second compound being a compound according to any one of the above embodiments and variations.

[0159] In still another embodiment, the present invention relates to a method for treating cancer comprising administering a compound according to any one of the above embodiments and variations to a mammalian species in need thereof. In one variation, the cancer is selected from the group consisting of squamous cell carcinoma, astrocytoma, Kaposi's sarcoma, glioblastoma, non small-cell lung cancer, bladder cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, breast cancer, small-cell lung cancer, glioma, colorectal cancer, genitourinary cancer and gastrointestinal cancer.

[0160] In another embodiment, the present invention relates to a method for treating inflammation, inflammatory bowel disease, psoriasis, or transplant rejection, comprising administering a compound according to any one of the above embodiments and variations to a mammalian species in need thereof.

[0161] In a further embodiment, the present invention relates to a method for treating arthritis comprising administering a compound according to any one of the above embodiments and variations to a mammalian species in need thereof.

[0162] In yet another embodiment, the present invention relates to a method for treating degenerative diseases of the eye comprising administering a compound according to any one of the above embodiments and variations to a mammalian species in need thereof.

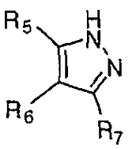
[0163] In still another embodiment, the present invention relates to a method for treating multiple sclerosis, amyotrophic lateral sclerosis, thyroid neoplasm or Alzheimer's disease comprising administering a compound according to any one of the above embodiments and variations to a mammalian species in need thereof.

[0164] In a further embodiment, the present invention relates to a method for treating hyperproliferative skin diseases or inflammatory cutaneous disorders comprising administering a compound according to any one of the above embodiments and variations to a mammalian species in need thereof.

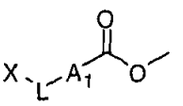
[0165] In each of the above embodiments and variations, the histone deacetylase is optionally a Class I histone deacetylase. In particular variations of each of the above embodiments and variations, the histone deacetylase is HDAC2 and/or HDAC8.

[0166] In still other of its aspects, the present invention relates to methods of making the HDAC inhibitors of the present invention, as well as intermediates useful for the preparation of such HDAC inhibitors. In one embodiment, the processes comprise:

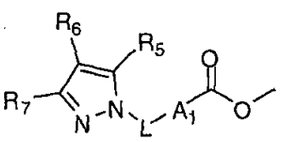
reacting a compound comprising the formula



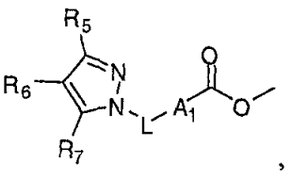
with a compound comprising the formula



under conditions that form a reaction product comprising a formula selected from the group consisting of



and



wherein

X is a leaving group;

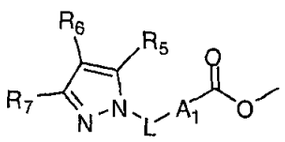
A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached; and

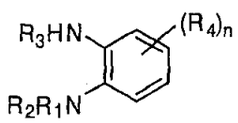
R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

[0167] In another embodiment, the processes comprise:

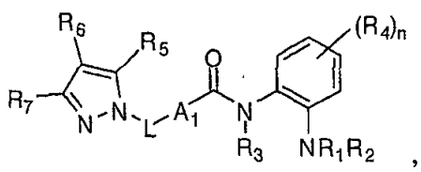
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising a formula



wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

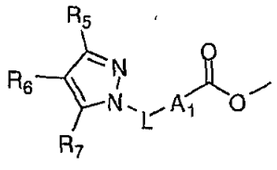
each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

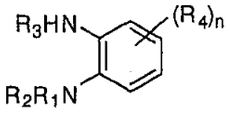
R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

[0168] In still another embodiment, the processes comprise:

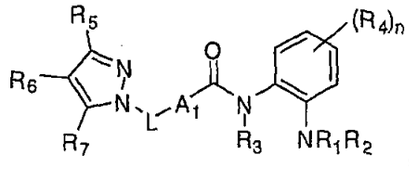
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising a formula



wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

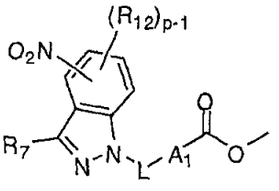
each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

[0169] In yet another embodiment, the processes comprise:

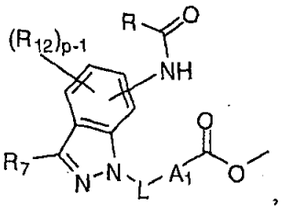
reacting a compound comprising the formula



with a compound comprising the formula

R-C(O)-X

under conditions that form a reaction product comprising a formula



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

X is a leaving group;

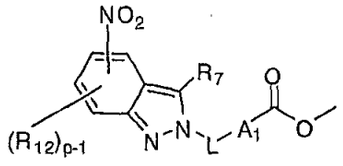
R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl,

heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0170] In a further embodiment, the processes comprise:

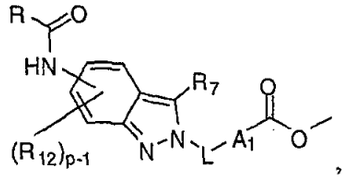
reacting a compound comprising the formula



with a compound comprising the formula

R-C(O)-X

under conditions that form a reaction product comprising a formula



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl,

imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

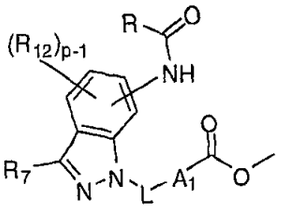
X is a leaving group;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

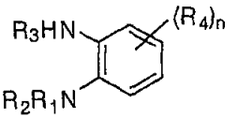
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0171] In still a further embodiment, the processes comprise:

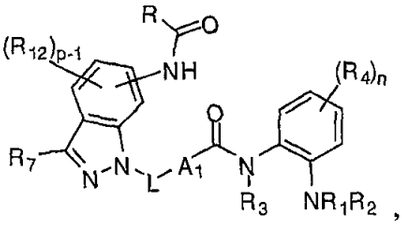
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising a formula



wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl,

(C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

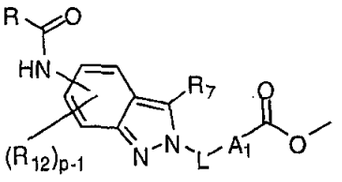
each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

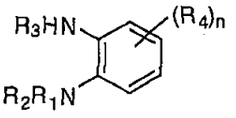
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0172] In yet a further embodiment, the processes comprise:

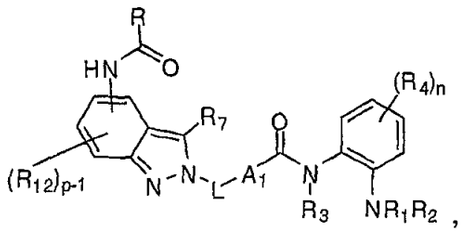
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising a formula



wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

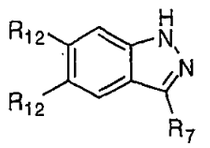
each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

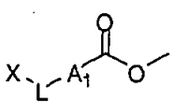
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0173] In another embodiment, the processes comprise:

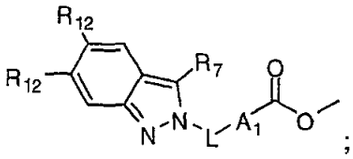
reacting a compound comprising the formula



with a compound comprising the formula

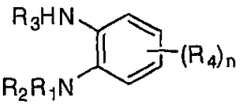


under conditions that form a first reaction product comprising a formula

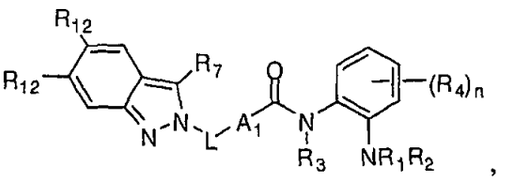


; and

reacting the first reaction product with a compound comprising the formula



under conditions that form a second reaction product comprising a formula



wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

X is a leaving group;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

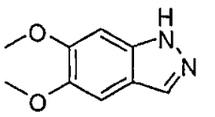
each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

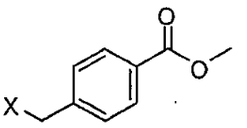
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0174] In another embodiment, the processes comprise:

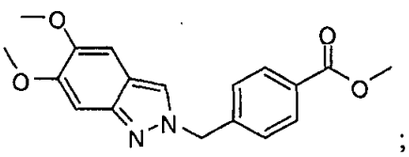
reacting a compound comprising the formula



with a compound comprising the formula

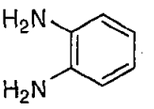


under conditions that form a first reaction product comprising a formula

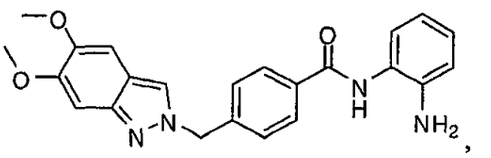


; and

reacting the first reaction product with a compound comprising the formula



under conditions that form a second reaction product comprising a formula



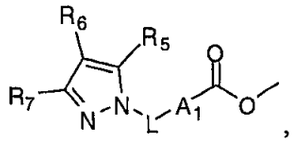
,

wherein

X is a leaving group.

[0175] In one variation of the above embodiments, X is halo. In one particular variation, X is bromo. In another particular variation, X is chloro.

[0176] In yet other of its aspects, the present invention relates to compounds useful in the preparation of the HDAC inhibitors of the present invention. In one embodiment, the compounds comprise:



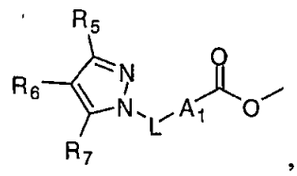
wherein

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached; and

R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

[0177] In another embodiment, the compounds comprise:



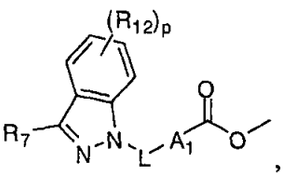
wherein

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached; and

R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

[0178] In still another embodiment, the compounds comprise:



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

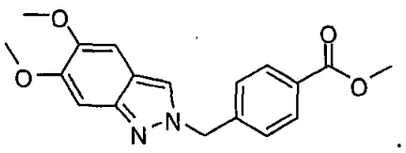
L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl,

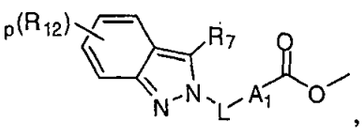
heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0179] In one particular variation of the above embodiment, the compounds comprise:



[0180] In yet another embodiment, the compounds comprise:



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

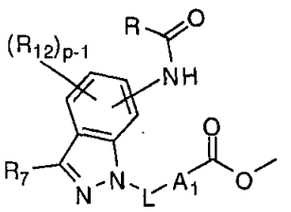
A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0181] In a further embodiment, the compounds comprise:



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

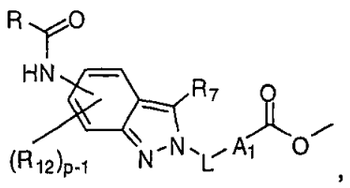
R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl,

(C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

[0182] In still a further embodiment, the compounds comprise:



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

Salts, Hydrates, and Prodrugs of HDAC Inhibitors

[0183] It should be recognized that the compounds of the present invention may be present and optionally administered in the form of salts, hydrates and prodrugs that are converted in vivo into the compounds of the present invention. For example, it is within the scope of the present invention to convert the compounds of the present invention into and use them in the form of their pharmaceutically acceptable salts derived from various organic and inorganic acids and bases in accordance with procedures well known in the art.

[0184] When the compounds of the present invention possess a free base form, the compounds 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, e.g., hydrohalides such as hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding salts such as sulfate, nitrate, phosphate, etc.; and alkyl and monoarylsulfonates such as ethanesulfonate, toluenesulfonate and benzenesulfonate; and other organic acids and their corresponding salts such as acetate,

tartrate, maleate, succinate, citrate, benzoate, salicylate and ascorbate. Further acid addition salts of the present invention include, but are not limited to: adipate, alginate, arginate, aspartate, bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptaoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, iso-butyrate, lactate, lactobionate, malate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate and phthalate. It should be recognized that the free base forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base forms for the purposes of the present invention.

[0185] When the compounds of the present invention possess a free acid form, a pharmaceutically acceptable base addition salt can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Examples of such bases are alkali metal hydroxides including potassium, sodium and lithium hydroxides; alkaline earth metal hydroxides such as barium and calcium hydroxides; alkali metal alkoxides, e.g., potassium ethanolate and sodium propanolate; and various organic bases such as ammonium hydroxide, piperidine, diethanolamine and N-methylglutamine. Also included are the aluminum salts of the compounds of the present invention. Further base salts of the present invention include, but are not limited to: copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium and zinc salts. Organic base salts include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, e.g., arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine,

histidine, hydrabamine, iso-propylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)-methylamine (tromethamine). It should be recognized that the free acid forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid forms for the purposes of the present invention.

[0186] Compounds of the present invention that comprise basic nitrogen-containing groups may be quaternized with such agents as (C_{1-4}) alkyl halides, e.g., methyl, ethyl, iso-propyl and tert-butyl chlorides, bromides and iodides; di (C_{1-4}) alkyl sulfates, e.g., dimethyl, diethyl and diamyl sulfates; (C_{10-18}) alkyl halides, e.g., decyl, dodecyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aryl (C_{1-4}) alkyl halides, e.g., benzyl chloride and phenethyl bromide. Such salts permit the preparation of both water-soluble and oil-soluble compounds of the present invention.

[0187] N-oxides of compounds according to the present invention can be prepared by methods known to those of ordinary skill in the art. For example, N-oxides can be prepared by treating an unoxidized form of the compound with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, meta-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0 °C. Alternatively, the N-oxides of the compounds can be prepared from the N-oxide of an appropriate starting material.

[0188] Prodrug derivatives of compounds according to the present invention can be prepared by modifying substituents of compounds of the present invention that are then converted in vivo to a different substituent. It is noted that in many instances, the prodrugs themselves also fall within the scope of the range of compounds according to the present invention. For example, prodrugs can be prepared by reacting a compound with a carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, para-nitrophenyl carbonate, or the like) or an acylating agent. Further examples of methods of making prodrugs are described in Saulnier et al.(1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985.

[0189] Protected derivatives of compounds of the present invention can also be made. Examples of techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, Protecting Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, Inc. 1999.

[0190] Compounds of the present invention may also be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0191] A "pharmaceutically acceptable salt", as used herein, is intended to encompass any compound according to the present invention that is utilized in the form of a salt thereof, especially where the salt confers on the compound improved pharmacokinetic properties as compared to the free form of compound or a different salt form of the compound. The pharmaceutically acceptable salt form may also initially confer desirable pharmacokinetic properties on the compound that it did not previously possess, and may even positively affect the pharmacodynamics of the compound with respect to its therapeutic activity in the body. An example of a pharmacokinetic property that may be favorably affected is the manner in which the compound is transported across cell membranes, which in turn may directly and positively affect the absorption, distribution, biotransformation and excretion of the compound. While the route of administration of the pharmaceutical composition is important, and various anatomical, physiological and pathological factors can critically affect bioavailability, the solubility of the compound is usually dependent upon the character of the particular salt form thereof, which it utilized. One of skill in the art will appreciate that an aqueous solution of the compound will provide the most rapid absorption of the compound into the body of a subject being treated, while lipid solutions and suspensions, as well as solid dosage forms, will result in less rapid absorption of the compound.

Preparation Of HDAC Inhibitors

[0192] Various methods may be developed for synthesizing compounds according to the present invention. Representative methods for synthesizing these compounds are

provided in the Examples. It is noted, however, that compounds of the present invention may also be synthesized by other synthetic routes that others may devise.

[0193] It will be readily recognized that certain compounds according to the present invention have atoms with linkages to other atoms that confer a particular stereochemistry to the compound (e.g., chiral centers). It is recognized that synthesis of compounds according to the present invention may result in the creation of mixtures of different stereoisomers (i.e., enantiomers and diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

[0194] Various methods for separating mixtures of different stereoisomers are known in the art. For example, a racemic mixture of a compound may be reacted with an optically active resolving agent to form a pair of diastereoisomeric compounds. The diastereomers may then be separated in order to recover the optically pure enantiomers. Dissociable complexes may also be used to resolve enantiomers (e.g., crystalline diastereoisomeric salts). Diastereomers typically have sufficiently distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) that they can be readily separated by taking advantage of these dissimilarities. For example, diastereomers can typically be separated by chromatography or by separation/resolution techniques based upon differences in solubility. A more detailed description of techniques that can be used to resolve stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

Compositions Comprising HDAC Inhibitors

[0195] A wide variety of compositions and administration methods may be used in conjunction with the compounds of the present invention. Such compositions may include, in addition to the compounds of the present invention, conventional pharmaceutical excipients, and other conventional, pharmaceutically inactive agents. Additionally, the compositions may include active agents in addition to the compounds of the present invention. These additional active agents may include additional compounds according to the invention, and/or one or more other pharmaceutically active agents.

[0196] The compositions may be in gaseous, liquid, semi-liquid or solid form, formulated in a manner suitable for the route of administration to be used. For oral administration, capsules and tablets are typically used. For parenteral administration, reconstitution of a lyophilized powder, prepared as described herein, is typically used.

[0197] Compositions comprising compounds of the present invention may be administered or coadministered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, or intrathecally. The compounds and/or compositions according to the invention may also be administered or coadministered in slow release dosage forms.

[0198] The HDAC inhibitors and compositions comprising them may be administered or coadministered in any conventional dosage form. Co-administration in the context of this invention is intended to mean the administration of more than one therapeutic agent, one of which includes a HDAC inhibitor, in the course of a coordinated treatment to achieve an improved clinical outcome. Such co-administration may also be coextensive, that is, occurring during overlapping periods of time.

[0199] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application may optionally include one or more of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; agents for the adjustment of tonicity such as sodium chloride or dextrose, and agents for adjusting the acidity or alkalinity of the composition, such as alkaline or acidifying agents or buffers like carbonates, bicarbonates, phosphates, hydrochloric acid, and organic acids like acetic and citric acid. Parenteral preparations may optionally be enclosed in ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

[0200] When compounds according to the present invention exhibit insufficient solubility, methods for solubilizing the compounds may be used. Such methods are

known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

[0201] Upon mixing or adding compounds according to the present invention to a composition, a solution, suspension, emulsion or the like may be formed. The form of the resulting composition will depend upon a number of factors, including the intended mode of administration, and the solubility of the compound in the selected carrier or vehicle. The effective concentration needed to ameliorate the disease being treated may be empirically determined.

[0202] Compositions according to the present invention are optionally provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, dry powders for inhalers, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds, particularly the pharmaceutically acceptable salts, preferably the sodium salts, thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms, as used herein, refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes individually packaged tablet or capsule. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pint or gallons. Hence, multiple dose form is a multiple of unit-doses that are not segregated in packaging.

[0203] In addition to one or more compounds according to the present invention, the composition may comprise: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and

talc; and a binder such as starch, natural gums, such as gum acaciagelatin, glucose, molasses, polvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known in the art, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a sufficient quantity of a inhibitor of the present invention to reduce HDAC activity in vivo, thereby treating the disease state of the subject.

[0204] Dosage forms or compositions may optionally comprise one or more compounds according to the present invention in the range of 0.005% to 100% (weight/weight) with the balance comprising additional substances such as those described herein. For oral administration, a pharmaceutically acceptable composition may optionally comprise any one or more commonly employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate, sodium saccharin, talcum. Such compositions include solutions, suspensions, tablets, capsules, powders, dry powders for inhalers and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparing these formulations are known to those skilled in the art. The compositions may optionally

contain 0.01%-100% (weight/weight) of one or more HDAC inhibitors, optionally 0.1-95%, and optionally 1-95%.

[0205] Salts, preferably sodium salts, of the inhibitors may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. The formulations may further include other active compounds to obtain desired combinations of properties.

Formulations For Oral Administration

[0206] Oral pharmaceutical dosage forms may be as a solid, gel or liquid. Examples of solid dosage forms include, but are not limited to tablets, capsules, granules, and bulk powders. More specific examples of oral tablets include compressed, chewable lozenges and tablets that may be enteric-coated, sugar-coated or film-coated. Examples of capsules include hard or soft gelatin capsules. Granules and powders may be provided in non-effervescent or effervescent forms. Each may be combined with other ingredients known to those skilled in the art.

[0207] In certain embodiments, compounds according to the present invention are provided as solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like may optionally contain one or more of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

[0208] Examples of binders that may be used include, but are not limited to, microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste.

[0209] Examples of lubricants that may be used include, but are not limited to, talc, starch, magnesium or calcium stearate, lycopodium and stearic acid.

[0210] Examples of diluents that may be used include, but are not limited to, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate.

[0211] Examples of glidants that may be used include, but are not limited to, colloidal silicon dioxide.

[0212] Examples of disintegrating agents that may be used include, but are not limited to, crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose.

[0213] Examples of coloring agents that may be used include, but are not limited to, any of the approved certified water-soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate.

[0214] Examples of sweetening agents that may be used include, but are not limited to, sucrose, lactose, mannitol and artificial sweetening agents such as sodium cyclamate and saccharin, and any number of spray-dried flavors.

[0215] Examples of flavoring agents that may be used include, but are not limited to, natural flavors extracted from plants such as fruits and synthetic blends of compounds that produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate.

[0216] Examples of wetting agents that may be used include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether.

[0217] Examples of anti-emetic coatings that may be used include, but are not limited to, fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates.

[0218] Examples of film coatings that may be used include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0219] If oral administration is desired, the salt of the compound may optionally be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

[0220] When the dosage unit form is a capsule, it may optionally additionally comprise a liquid carrier such as a fatty oil. In addition, dosage unit forms may optionally additionally comprise various other materials that modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents.

[0221] Compounds according to the present invention may also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may optionally comprise, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0222] The compounds of the present invention may also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. For example, if a compound is used for treating asthma or hypertension, it may be used with other bronchodilators and antihypertensive agents, respectively.

[0223] Examples of pharmaceutically acceptable carriers that may be included in tablets comprising compounds of the present invention include, but are not limited to binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets may be compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets may be compressed tablets that have been coated with polymers or other suitable coating. Multiple compressed tablets may be compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in tablets. Flavoring and sweetening agents may be used in tablets, and are especially useful in the formation of chewable tablets and lozenges.

[0224] Examples of liquid oral dosage forms that may be used include, but are not limited to, aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules.

[0225] Examples of aqueous solutions that may be used include, but are not limited to, elixirs and syrups. As used herein, elixirs refer to clear, sweetened, hydroalcoholic preparations. Examples of pharmaceutically acceptable carriers that may be used in elixirs include, but are not limited to solvents. Particular examples of solvents that may be used include glycerin, sorbitol, ethyl alcohol and syrup. As used herein, syrups refer to

[0236] Sources of carbon dioxide that may be used in effervescent compositions include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof.

[0237] Particular examples of flavoring agents that may be used include natural flavors extracted from plants such fruits, and synthetic blends of compounds that produce a pleasant taste sensation.

[0238] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, e.g., for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be easily measured for administration.

[0239] Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (e.g., propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Pat. Nos. Re 28,819 and 4,358,603.

Injectables, Solutions, and Emulsions

[0240] The present invention is also directed to compositions designed to administer the compounds of the present invention by parenteral administration, generally characterized by subcutaneous, intramuscular or intravenous injection. Injectables may be prepared in any conventional form, for example as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions.

[0241] Examples of excipients that may be used in conjunction with injectables according to the present invention include, but are not limited to water, saline, dextrose, glycerol or ethanol. The injectable compositions may also optionally comprise minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for

example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, e.g., U.S. Pat. No. 3,710,795) is also contemplated herein. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

[0242] Parenteral administration of the formulations includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as the lyophilized powders described herein, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[0243] When administered intravenously, examples of suitable carriers include, but are not limited to physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[0244] Examples of pharmaceutically acceptable carriers that may optionally be used in parenteral preparations include, but are not limited to aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[0245] Examples of aqueous vehicles that may optionally be used include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection.

[0246] Examples of nonaqueous parenteral vehicles that may optionally be used include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil.

[0247] Antimicrobial agents in bacteriostatic or fungistatic concentrations may be added to parenteral preparations, particularly when the preparations are packaged in multiple-dose containers and thus designed to be stored and multiple aliquots to be removed. Examples of antimicrobial agents that may be used include phenols or cresols,

mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride.

[0248] Examples of isotonic agents that may be used include sodium chloride and dextrose. Examples of buffers that may be used include phosphate and citrate. Examples of antioxidants that may be used include sodium bisulfate. Examples of local anesthetics that may be used include procaine hydrochloride. Examples of suspending and dispersing agents that may be used include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Examples of emulsifying agents that may be used include Polysorbate 80 (TWEEN 80). A sequestering or chelating agent of metal ions include EDTA.

[0249] Pharmaceutical carriers may also optionally include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[0250] The concentration of an inhibitor in the parenteral formulation may be adjusted so that an injection administers a pharmaceutically effective amount sufficient to produce the desired pharmacological effect. The exact concentration of an inhibitor and/or dosage to be used will ultimately depend on the age, weight and condition of the patient or animal as is known in the art.

[0251] Unit-dose parenteral preparations may be packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration should be sterile, as is known and practiced in the art.

[0252] Injectables may be designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the HDAC inhibitor to the treated tissue(s). The inhibitor may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment will be a function of the location of where the composition is parenterally administered, the carrier and other variables that may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further

understood that for any particular subject, specific dosage regimens may need to be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations. Hence, the concentration ranges set forth herein are intended to be exemplary and are not intended to limit the scope or practice of the claimed formulations.

[0253] The HDAC inhibitor may optionally be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease state and may be empirically determined.

Lyophilized Powders

[0254] The compounds of the present invention may also be prepared as lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. The lyophilized powders may also be formulated as solids or gels.

[0255] Sterile, lyophilized powder may be prepared by dissolving the compound in a sodium phosphate buffer solution containing dextrose or other suitable excipient. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Briefly, the lyophilized powder may optionally be prepared by dissolving dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent, about 1-20%, preferably about 5 to 15%, in a suitable buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Then, a HDAC inhibitor is added to the resulting mixture, preferably above room temperature, more preferably at about 30-35 oC, and stirred until it dissolves. The resulting mixture is diluted by adding more buffer to a desired concentration. The resulting mixture is sterile filtered or treated to remove particulates and to insure sterility, and apportioned into vials for lyophilization. Each vial may contain a single dosage or multiple dosages of the inhibitor.

Topical Administration

[0256] The compounds of the present invention may also be administered as topical mixtures. Topical mixtures may be used for local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[0257] The HDAC inhibitors may be formulated as aerosols for topical application, such as by inhalation (see, U.S. Pat. Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

[0258] The inhibitors may also be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the HDAC inhibitor alone or in combination with other pharmaceutically acceptable excipients can also be administered.

Formulations For Other Routes of Administrations

[0259] Depending upon the disease state being treated, other routes of administration, such as topical application, transdermal patches, and rectal administration, may also be used. For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum that melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or

vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax, (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm. Tablets and capsules for rectal administration may be manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

Examples of Formulations

[0260] The following are particular examples of oral, intravenous and tablet formulations that may optionally be used with compounds of the present invention. It is noted that these formulations may be varied depending on the particular compound being used and the indication for which the formulation is going to be used.

ORAL FORMULATION	
Compound of the Present Invention	10-100 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 100 mL

INTRAVENOUS FORMULATION	
Compound of the Present Invention	0.1-10 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION	
Compound of the Present Invention	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.

Kits Comprising HDAC Inhibitors

[0261] The invention is also directed to kits and other articles of manufacture for treating diseases associated with HDACs. It is noted that diseases are intended to cover all

conditions for which the HDACs possess activity that contributes to the pathology and/or symptomology of the condition.

[0262] In one embodiment, a kit is provided that comprises a composition comprising at least one inhibitor of the present invention in combination with instructions. The instructions may indicate the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also comprise packaging materials. The packaging material may comprise a container for housing the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0263] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one inhibitor of the present invention in combination with packaging materials. The packaging material may comprise a container for housing the composition. The container may optionally comprise a label indicating the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0264] It is noted that the packaging material used in kits and articles of manufacture according to the present invention may form a plurality of divided containers such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container that is employed will depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle that is in turn contained within a box. Typically the kit includes directions for the administration of the separate components. The kit form is particularly advantageous

when the separate components are preferably administered in different dosage forms (e.g., oral, topical, transdermal and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

[0265] One particular example of a kit according to the present invention is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[0266] Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time in the order of their intended use. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter that indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

Combination Therapy

[0267] A wide variety of therapeutic agents may have a therapeutic additive or synergistic effect with HDAC inhibitors according to the present invention. Such

therapeutic agents may additively or synergistically combine with the HDAC inhibitors to inhibit undesirable cell growth, such as inappropriate cell growth resulting in undesirable benign conditions or tumor growth.

[0268] In one embodiment, a method is provided for treating a cell proliferative disease state comprising treating cells with a compound according to the present invention in combination with an anti-proliferative agent, wherein the cells are treated with the compound according to the present invention before, at the same time, and/or after the cells are treated with the anti-proliferative agent, referred to herein as combination therapy. It is noted that treatment of one agent before another is referred to herein as sequential therapy, even if the agents are also administered together. It is noted that combination therapy is intended to cover when agents are administered before or after each other (sequential therapy) as well as when the agents are administered at the same time.

[0269] Examples of therapeutic agents that may be used in combination with HDAC inhibitors include, but are not limited to, anticancer agents, alkylating agents, antibiotic agents, antimetabolic agents, hormonal agents, plant-derived agents, and biologic agents.

[0270] Alkylating agents are polyfunctional compounds that have the ability to substitute alkyl groups for hydrogen ions. Examples of alkylating agents include, but are not limited to, bischloroethylamines (nitrogen mustards, e.g. chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard), aziridines (e.g. thiotepa), alkyl alkone sulfonates (e.g. busulfan), nitrosoureas (e.g. carmustine, lomustine, streptozocin), nonclassic alkylating agents (altretamine, dacarbazine, and procarbazine), platinum compounds (carboplastin and cisplatin). These compounds react with phosphate, amino, hydroxyl, sulfihydryl, carboxyl, and imidazole groups. Under physiological conditions, these drugs ionize and produce positively charged ion that attach to susceptible nucleic acids and proteins, leading to cell cycle arrest and/or cell death. Combination therapy including a HDAC inhibitor and an alkylating agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0271] Antibiotic agents are a group of drugs that produced in a manner similar to antibiotics as a modification of natural products. Examples of antibiotic agents include,

but are not limited to, anthracyclines (e.g. doxorubicin, daunorubicin, epirubicin, idarubicin and anthracenedione), mitomycin C, bleomycin, dactinomycin, plicatomycin. These antibiotic agents interfere with cell growth by targeting different cellular components. For example, anthracyclines are generally believed to interfere with the action of DNA topoisomerase II in the regions of transcriptionally active DNA, which leads to DNA strand scissions. Bleomycin is generally believed to chelate iron and forms an activated complex, which then binds to bases of DNA, causing strand scissions and cell death. Combination therapy including a HDAC inhibitor and an antibiotic agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0272] Antimetabolic agents are a group of drugs that interfere with metabolic processes vital to the physiology and proliferation of cancer cells. Actively proliferating cancer cells require continuous synthesis of large quantities of nucleic acids, proteins, lipids, and other vital cellular constituents. Many of the antimetabolites inhibit the synthesis of purine or pyrimidine nucleosides or inhibit the enzymes of DNA replication. Some antimetabolites also interfere with the synthesis of ribonucleosides and RNA and/or amino acid metabolism and protein synthesis as well. By interfering with the synthesis of vital cellular constituents, antimetabolites can delay or arrest the growth of cancer cells. Examples of antimetabolic agents include, but are not limited to, fluorouracil (5-FU), floxuridine (5-FUdR), methotrexate, leucovorin, hydroxyurea, thioguanine (6-TG), mercaptopurine (6-MP), cytarabine, pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, and gemcitabine. Combination therapy including a HDAC inhibitor and a antimetabolic agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0273] Hormonal agents are a group of drug that regulate the growth and development of their target organs. Most of the hormonal agents are sex steroids and their derivatives and analogs thereof, such as estrogens, androgens, and progestins. These hormonal agents may serve as antagonists of receptors for the sex steroids to down regulate receptor expression and transcription of vital genes. Examples of such hormonal agents are synthetic estrogens (e.g. diethylstibestrol), antiestrogens (e.g. tamoxifen, toremifene, fluoxymesterol and raloxifene), antiandrogens (bicalutamide, nilutamide, flutamide),

aromatase inhibitors (e.g., aminoglutethimide, anastrozole and tetrazole), ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone. Combination therapy including a HDAC inhibitor and a hormonal agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0274] Plant-derived agents are a group of drugs that are derived from plants or modified based on the molecular structure of the agents. Examples of plant-derived agents include, but are not limited to, vinca alkaloids (e.g., vincristine, vinblastine, vindesine, vinzolidine and vinorelbine), podophyllotoxins (e.g., etoposide (VP-16) and teniposide (VM-26)), taxanes (e.g., paclitaxel and docetaxel). These plant-derived agents generally act as antimitotic agents that bind to tubulin and inhibit mitosis. Podophyllotoxins such as etoposide are believed to interfere with DNA synthesis by interacting with topoisomerase II, leading to DNA strand scission. Combination therapy including a HDAC inhibitor and a plant-derived agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0275] Biologic agents are a group of biomolecules that elicit cancer/tumor regression when used alone or in combination with chemotherapy and/or radiotherapy. Examples of biologic agents include, but are not limited to, immuno-modulating proteins such as cytokines, monoclonal antibodies against tumor antigens, tumor suppressor genes, and cancer vaccines. Combination therapy including a HDAC inhibitor and a biologic agent may have therapeutic synergistic effects on cancer, enhance the patient's immune responses to tumorigenic signals, and reduce potential sides affects associated with this chemotherapeutic agent.

[0276] Cytokines possess profound immunomodulatory activity. Some cytokines such as interleukin-2 (IL-2, aldesleukin) and interferon have demonstrated antitumor activity and have been approved for the treatment of patients with metastatic renal cell carcinoma and metastatic malignant melanoma. IL-2 is a T-cell growth factor that is central to T-cell-mediated immune responses. The selective antitumor effects of IL-2 on some patients are believed to be the result of a cell-mediated immune response that discriminate between self and nonself. Examples of interleukins that may be used in conjunction with HDAC inhibitor include, but are not limited to, interleukin 2 (IL-2), and interleukin 4 (IL-4), interleukin 12 (IL-12).

[0277] Interferon include more than 23 related subtypes with overlapping activities, all of the IFN subtypes within the scope of the present invention. IFN has demonstrated activity against many solid and hematologic malignancies, the later appearing to be particularly sensitive.

[0278] Other cytokines that may be used in conjunction with a HDAC inhibitor include those cytokines that exert profound effects on hematopoiesis and immune functions. Examples of such cytokines include, but are not limited to erythropoietin, granulocyte-CSF (filgrastin), and granulocyte, macrophage-CSF (sargramostim). These cytokines may be used in conjunction with a HDAC inhibitor to reduce chemotherapy-induced myelopoietic toxicity.

[0279] Other immuno-modulating agents other than cytokines may also be used in conjunction with a HDAC inhibitor to inhibit abnormal cell growth. Examples of such immuno-modulating agents include, but are not limited to bacillus Calmette-Guerin, levamisole, and octreotide, a long-acting octapeptide that mimics the effects of the naturally occurring hormone somatostatin.

[0280] Monoclonal antibodies against tumor antigens are antibodies elicited against antigens expressed by tumors, preferably tumor-specific antigens. For example, monoclonal antibody HERCEPTIN® (Trastruzumab) is raised against human epidermal growth factor receptor2 (HER2) that is overexpressed in some breast tumors including metastatic breast cancer. Overexpression of HER2 protein is associated with more aggressive disease and poorer prognosis in the clinic. HERCEPTIN® is used as a single agent for the treatment of patients with metastatic breast cancer whose tumors over express the HER2 protein. Combination therapy including HDAC inhibitor and HERCEPTIN® may have therapeutic synergistic effects on tumors, especially on metastatic cancers.

[0281] Another example of monoclonal antibodies against tumor antigens is RITUXAN® (Rituximab) that is raised against CD20 on lymphoma cells and selectively deplete normal and malignant CD20+ pre-B and mature B cells. RITUXAN® is used as single agent for the treatment of patients with relapsed or refractory low-grade or follicular, CD20+, B cell non-Hodgkin's lymphoma. Combination therapy including

HDAC inhibitor and RITUXAN® may have therapeutic synergistic effects not only on lymphoma, but also on other forms or types of malignant tumors.

[0282] Tumor suppressor genes are genes that function to inhibit the cell growth and division cycles, thus preventing the development of neoplasia. Mutations in tumor suppressor genes cause the cell to ignore one or more of the components of the network of inhibitory signals, overcoming the cell cycle check points and resulting in a higher rate of controlled cell growth-cancer. Examples of the tumor suppressor genes include, but are not limited to, DPC-4, NF-1, NF-2, RB, p53, WT1, BRCA1 and BRCA2.

[0283] DPC-4 is involved in pancreatic cancer and participates in a cytoplasmic pathway that inhibits cell division. NF-1 codes for a protein that inhibits Ras, a cytoplasmic inhibitory protein. NF-1 is involved in neurofibroma and pheochromocytomas of the nervous system and myeloid leukemia. NF-2 encodes a nuclear protein that is involved in meningioma, schwanoma, and ependymoma of the nervous system. RB codes for the pRB protein, a nuclear protein that is a major inhibitor of cell cycle. RB is involved in retinoblastoma as well as bone, bladder, small cell lung and breast cancer. P53 codes for p53 protein that regulates cell division and can induce apoptosis. Mutation and/or inaction of p53 is found in a wide ranges of cancers. WT1 is involved in Wilms tumor of the kidneys. BRCA1 is involved in breast and ovarian cancer, and BRCA2 is involved in breast cancer. The tumor suppressor gene can be transferred into the tumor cells where it exerts its tumor suppressing functions. Combination therapy including a HDAC inhibitor and a tumor suppressor may have therapeutic synergistic effects on patients suffering from various forms of cancers.

[0284] Cancer vaccines are a group of agents that induce the body's specific immune response to tumors. Most of cancer vaccines under research and development and clinical trials are tumor-associated antigens (TAAs). TAA are structures (i.e. proteins, enzymes or carbohydrates) which are present on tumor cells and relatively absent or diminished on normal cells. By virtue of being fairly unique to the tumor cell, TAAs provide targets for the immune system to recognize and cause their destruction. Example of TAAs include, but are not limited to gangliosides (GM2), prostate specific antigen (PSA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) (produced by colon cancers and other adenocarcinomas, e.g. breast, lung, gastric, and pancreas cancer s), melanoma associated

antigens (MART-1, gp100, MAGE 1,3 tyrosinase), papillomavirus E6 and E7 fragments, whole cells or portions/lysates of antologous tumor cells and allogeneic tumor cells.

[0285] An adjuvant may be used to augment the immune response to TAAs. Examples of adjuvants include, but are not limited to, bacillus Calmette-Guerin (BCG), endotoxin lipopolysaccharides, keyhole limpet hemocyanin (GKLH), interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF) and cytoxan, a chemotherapeutic agent which is believe to reduce tumor-induced suppression when given in low doses.

EXAMPLES

Preparation of HDAC Inhibitors

[0286] Various methods may be developed for synthesizing compounds according to the present invention. Representative methods for synthesizing these compounds are provided in the Examples. It is noted, however, that the compounds of the present invention may also be synthesized by other synthetic routes that others may devise.

[0287] It will be readily recognized that certain compounds according to the present invention have atoms with linkages to other atoms that confer a particular stereochemistry to the compound (e.g., chiral centers). It is recognized that synthesis of compounds according to the present invention may result in the creation of mixtures of different stereoisomers (i.e., enantiomers and diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

[0288] Various methods for separating mixtures of different stereoisomers are known in the art. For example, a racemic mixture of a compound may be reacted with an optically active resolving agent to form a pair of diastereoisomeric compounds. The diastereomers may then be separated in order to recover the optically pure enantiomers. Dissociable complexes may also be used to resolve enantiomers (e.g., crystalline diastereoisomeric salts). Diastereomers typically have sufficiently distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. For example, diastereomers can typically be separated by chromatography or by separation/resolution techniques based upon differences in solubility. A more detailed description of techniques that can be

used to resolve stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

[0289] Compounds according to the present invention can also 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 can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds can be prepared using salts of the starting materials or intermediates.

[0290] The free acid or free base forms of the compounds can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound 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 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).

[0291] The N-oxides of compounds according to the present invention can be prepared by methods known to those of ordinary skill in the art. For example, N-oxides can be prepared by treating an unoxidized form of the compound with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, meta-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0 C. Alternatively, the N-oxides of the compounds can be prepared from the N-oxide of an appropriate starting material.

[0292] Compounds in an unoxidized form can be prepared from N-oxides of compounds by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80 oC.

[0293] Prodrug derivatives of the compounds 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 with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, para-nitrophenyl carbonate, or the like).

[0294] Protected derivatives of the compounds can be made by methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, Protecting Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, Inc. 1999.

[0295] Compounds according to the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0296] Compounds according to the present invention can also 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 enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds, dissociable complexes are preferred (e.g., crystalline diastereoisomeric 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 & Sons, Inc. (1981).

[0297] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or thee-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

μL (microliters)	Ac (acetyl)
atm (atmosphere)	ATP (Adenosine Triphophatase)
BOC (tert-butyloxycarbonyl)	BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride)
BSA (Bovine Serum Albumin)	CBZ (benzyloxycarbonyl)
CDI (1,1-carbonyldiimidazole)	DCC (dicyclohexylcarbodiimide)
DCE (dichloroethane)	DCM (dichloromethane)
DMAP (4-dimethylaminopyridine)	DME (1,2-dimethoxyethane)
DMF (N,N-dimethylformamide)	DMPU (N,N'-dimethylpropyleneurea)
DMSO (dimethylsulfoxide)	EDCI (ethylcarbodiimide hydrochloride)
EDTA (Ethylenediaminetetraacetic acid)	Et (ethyl)
Et_2O (diethyl ether)	EtOAc (ethyl acetate)
FMOC (9-fluorenylmethoxycarbonyl)	g (grams)
h (hours)	HOAc or AcOH (acetic acid)
HOBT (1-hydroxybenzotriazole)	HOSu (N-hydroxysuccinimide)
HPLC (high pressure liquid chromatography)	Hz (Hertz)
i.v. (intravenous)	IBCF (isobutyl chloroformate)
i-PrOH (isopropanol)	L (liters)
M (molar)	mCPBA (meta-chloroperbenzoic acid)
Me (methyl)	MeOH (methanol)
mg (milligrams)	MHz (megahertz)
min (minutes)	mL (milliliters)
mM (millimolar)	mmol (millimoles)
mol (moles)	MOPS (Morpholinepropanesulfonic acid)
mp (melting point)	NaOAc (sodium acetate)
OMe (methoxy)	psi (pounds per square inch)
RP (reverse phase)	RT (ambient temperature)
SPA (Scintillation Proximity Assay)	TBAF (tetra-n-butylammonium fluoride)
TBS (t-butyldimethylsilyl)	tBu (tert-butyl)
TEA (triethylamine)	TFA (trifluoroacetic acid)

TFAA (trifluoroacetic anhydride)	THF (tetrahydrofuran)
TIPS (triisopropylsilyl)	TLC (thin layer chromatography)
TMS (trimethylsilyl)	TMSE (2-(trimethylsilyl)ethyl)
Tr (retention time)	

[0298] All references to ether or Et2O are to diethyl ether; and brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at RT unless otherwise noted.

[0299] 1H NMR spectra were recorded on a Bruker Avance 400. Chemical shifts are expressed in parts per million (ppm). Coupling constants are in units of Hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

[0300] Low-resolution mass spectra (MS) and compound purity data were acquired on a Waters ZQ LC/MS single quadrupole system equipped with electrospray ionization (ESI) source, UV detector (220 and 254 nm), and evaporative light scattering detector (ELSD). Thin-layer chromatography was performed on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid, Ninhydrin or p-anisaldehyde solution. Flash column chromatography was performed on silica gel (230-400 mesh, Merck).

[0301] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as the Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), or may be prepared by methods well known to a person of ordinary skill in the art, following procedures described in such standard references as Fieser and Fieser's Reagents for Organic Synthesis, vols. 1-17, John Wiley and Sons, New York, NY, 1991; Rodd's Chemistry of Carbon Compounds, vols. 1-5 and supps., Elsevier Science Publishers, 1989; Organic Reactions, vols. 1-40, John Wiley and Sons, New York, NY, 1991; March J.: Advanced Organic Chemistry, 4th ed., John Wiley and Sons, New York, NY; and Larock: Comprehensive Organic Transformations, VCH Publishers, New York, 1989.

[0302] The entire disclosure of all documents cited throughout this application are incorporated herein by reference.

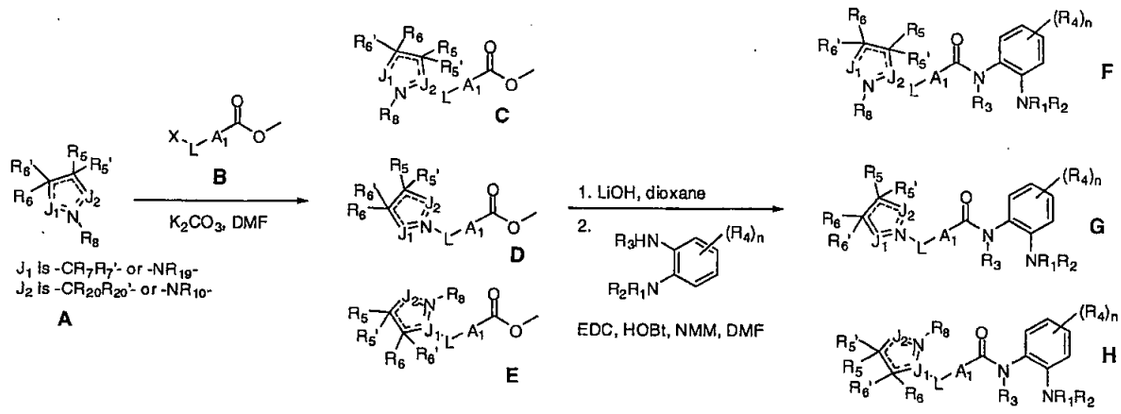
Synthetic Schemes For Compounds of the Present Invention

[0303] Compounds according to the present invention may be synthesized according to the reaction schemes shown below. Other reaction schemes could be readily devised by those skilled in the art. It should also be appreciated that a variety of different solvents, temperatures and other reaction conditions can be varied to optimize the yields of the reactions.

[0304] In the reactions described hereinafter it may 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 may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

[0305] General synthetic routes for producing compounds of the present invention are shown in the schemes below.

Scheme 1



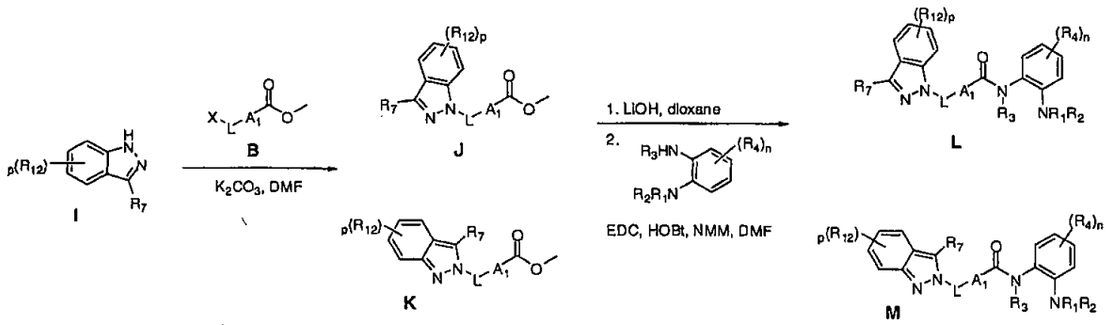
[0306] A solution of **B** (0.5 mmol) in DMF (2.5 mL) is treated with an appropriate heterocycle **A** (0.5 mmol) and solid K_2CO_3 (0.6 mmol). After stirring at 23 °C for 18 h, the reaction is poured into water (10 mL) and the resulting solid isolated by filtration. The filter cake can be rinsed with water and allowed to dry in vacuo to yield a mixture of regioisomeric alkylation products **C**, **D** and **E**, which can be separated by flash chromatography. If no solid is formed, the DMF/water mixture can be extracted with

ethylacetate. The combined extracts can be dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography.

[0307] A solution of the alkylation products **C**, **D** and/or **E** (0.25 mmol) in dioxane (1 mL) is treated with aqueous LiOH (1 M, 1.0 mL). After stirring at 23 °C for 2 h, the reaction is neutralized with aqueous HCl (1 M, 2.0 mL) and the resulting solid isolated by filtration. The filter cake can be rinsed with water and allowed to dry in vacuo to yield the corresponding carboxylic acid.

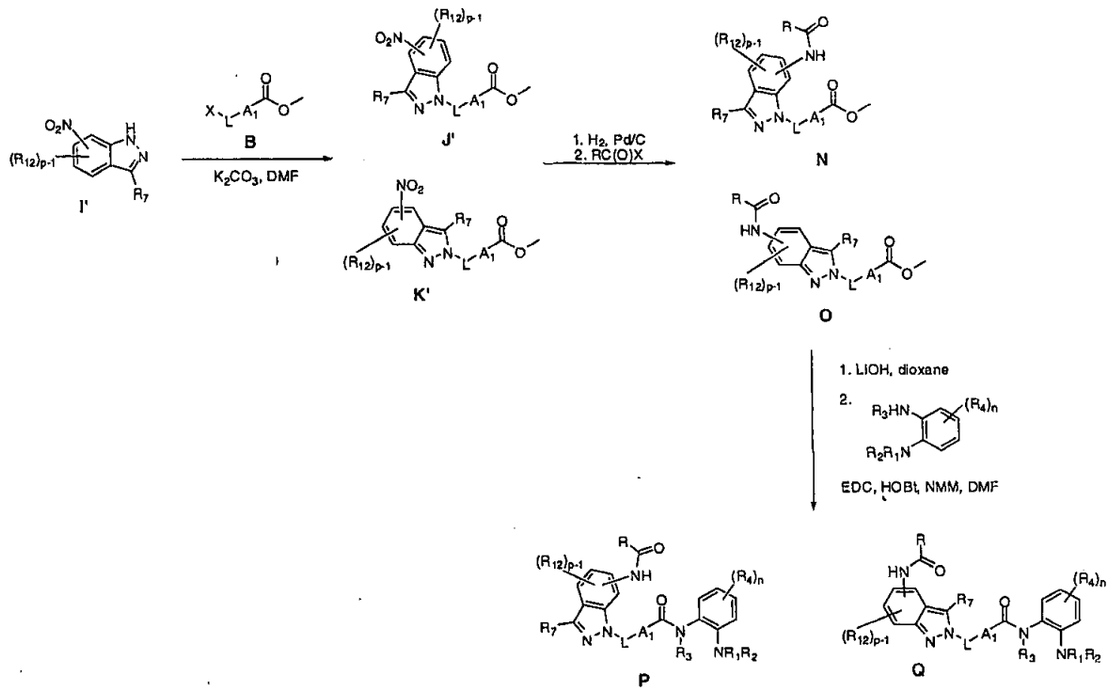
[0308] A solution of the carboxylic acid formed above (0.1 mmol) in DMF (1 mL) is sequentially treated with EDC (0.12 mmol), HOBt (0.12 mmol), a substituted or unsubstituted 1,2-phenylenediamine (0.12 mmol) and NMM (0.3 mmol). After stirring at 23 °C for 4 h, the reaction is poured into water (10 mL) and the resulting solid isolated by filtration. The filter cake can be rinsed with water and allowed to dry in vacuo to yield the corresponding amide **F**, **G** and/or **H**.

Scheme 2



[0309] In relation to Scheme 2, the alkylation of **I** with **B**, hydrolysis of **J** and/or **K**, and coupling with the 1,2-phenylenediamine to provide **L** and/or **M** proceed as described in Scheme 1.

Scheme 3



[0310] In relation to Scheme 3, nitrobenzenes **J'** and **K'** may be prepared as described in connection with Schemes 1 and 2.

[0311] A solution of the nitrobenzene (**J'** and/or **K'**) (1.0 mmol) in MeOH (10 mL) with Pd/C (10 wt%, 50 mg) is stirred vigorously under hydrogen for 4 h. The reaction is filtered and concentrated in vacuo to give the corresponding aniline that can be carried forward.

[0312] A solution of the aniline (1.0 mmol) in dichloromethane (10 mL) is treated sequentially with the appropriate acid chloride or chloroformate (RC(O)Cl, wherein R is, for example, an optionally substituted alkoxy, alkyl, heterocycloalkyl or aryl) (1.1 mmol) and triethylamine (2.2 mmol). After stirring at 23 °C for 4 h, the reaction is concentrated in vacuo to yield the corresponding acylation product (**N** and/or **O**). If necessary, purification can be carried out by flash chromatography or recrystallization.

[0313] Compounds **N** and/or **O** can be coupled with a substituted or unsubstituted 1,2-phenylenediamine to yield **P** and/or **Q**, as described in connection with Schemes 1 and 2.

[0314] Chiral components can be separated and purified using any of a variety of techniques known to those skilled in the art. For example, chiral components can be purified using supercritical fluid chromatography (SFC). In one particular variation, chiral analytical SFC/MS analyses are conducted using a Berger analytical SFC system (AutoChem, Newark, DE) which consists of a Berger SFC dual pump fluid control module with a Berger FCM 1100/1200 supercritical fluid pump and FCM 1200 modifier fluid pump, a Berger TCM 2000 oven, and an Alcott 718 autosampler. The integrated system can be controlled by BI-SFC Chemstation software version 3.4. Detection can be accomplished with a Watrers ZQ 2000 detector operated in positive mode with an ESI interface and a scan range from 200-800 Da with 0.5 second per scan. Chromatographic separations can be performed on a ChiralPak AD-H, ChiralPak AS-H, ChiralCel OD-H, or ChiralCel OJ-H column (5μ, 4.6 x 250 mm; Chiral Technologies, Inc. West Chester, PA) with 10 to 40% methanol as the modifier and with or without ammonium acetate (10 mM). Any of a variety of flow rates can be utilized including, for example, 1.5 or 3.5 mL/min with an inlet pressure set at 100 bar. Additionally, a variety of sample injection conditions can be used including, for example, sample injections of either 5 or 10μL in methanol at 0.1 mg/mL in concentration.

[0315] In another variation, preparative chiral separations are performed using a Berger MultiGram II SFC purification system. For example, samples can be loaded onto a ChiralPak AD column (21 x 250 mm, 10μ). In particular variations, the flow rate for separation can be 70 mL/min, the injection volume up to 2 mL, and the inlet pressure set at 130 bar. Stacked injections can be applied to increase the efficiency.

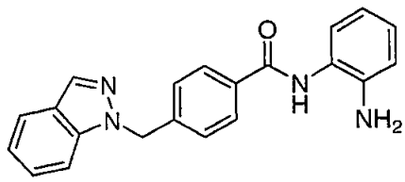
[0316] In each of the above reaction procedures or schemes, the various substituents may be selected from among the various substituents otherwise taught herein.

[0317] Descriptions of the syntheses of particular compounds according to the present invention based on the above reaction scheme are set forth herein.

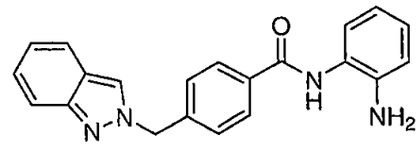
Examples of HDAC Inhibitors

[0318] The present invention is further exemplified, but not limited by, the following examples that describe the synthesis of particular compounds according to the invention.

Examples 1 and 2: 4-((1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide *and* 4-((2*H*-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide



Example 1



Example 2

[0319] The title compounds were prepared using the procedure described in Scheme 2. In particular, a solution of methyl 4-bromomethylbenzoate (0.5 mmol) in DMF (2.5 mL) was treated with the indazole (0.5 mmol) and solid K_2CO_3 (0.6 mmol). After stirring at 23 °C for 18 h, the reaction was poured into water (10 mL) and the resulting solid was isolated by filtration. The filter cake was rinsed with water and allowed to dry in vacuo to yield a mixture of regioisomeric alkylation products, which were separated by flash chromatography.

[0320] A solution of the methyl ester (0.25 mmol) in dioxane (1 mL) was treated with aqueous LiOH (1 M, 1.0 mL). After stirring at 23 °C for 2 h, the reaction was neutralized with aqueous HCl (1 M, 2.0 mL) and the resulting solid was isolated by filtration. The filter cake was rinsed with water and allowed to dry in vacuo to yield the corresponding benzoic acid.

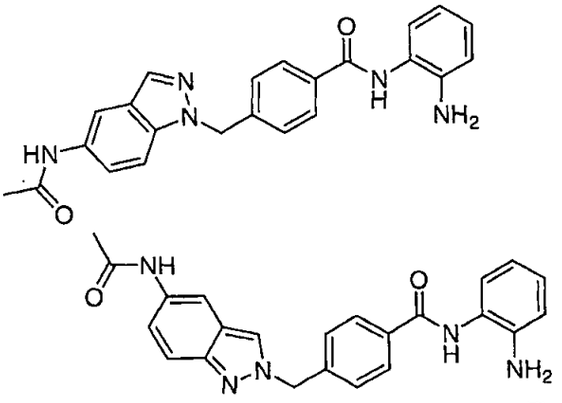
[0321] A solution of the appropriate benzoic acid (0.1 mmol) in DMF (1 mL) was sequentially treated with EDC (0.12 mmol), HOBt (0.12 mmol), 1,2-phenylenediame (0.12 mmol) and NMM (0.3 mmol). After stirring at 23 °C for 4 h, the reaction was poured into water (10 mL) and the resulting solid was isolated by filtration. The filter cake was rinsed with water and allowed to dry in vacuo to yield the corresponding amide.

[0322] Example 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.85 (s, 2 H) 5.74 (s, 2 H) 6.53 - 6.58 (m, 1 H) 6.73 (dd, J=7.83, 1.26 Hz, 1 H) 6.91 - 6.96 (m, 1 H) 7.09 - 7.16 (m, 2 H) 7.28 - 7.39 (m, 3 H) 7.70 (d, J=8.34 Hz, 1 H) 7.77 (d, J=8.34 Hz, 1 H) 7.87 (d, J=8.08 Hz, 2 H) 8.13 (s, 1 H) 9.56 (s, 1 H). ESI-MS: m/z 343.4 $(M + H)^+$.

[0323] Example 2: ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.94 (s, 2 H) 5.72 (s, 2 H) 6.57 (t, J=7.58 Hz, 1 H) 6.74 - 6.77 (m, 1 H) 6.95 (td, J=7.58, 1.52 Hz, 1 H) 7.00 - 7.05 (m, 1 H) 7.13 (d, J=7.58 Hz, 1 H) 7.22 (dd, J=8.21, 7.20 Hz, 1 H) 7.41 (d, J=8.08 Hz, 2 H)

7.58 (d, J=8.59 Hz, 1 H) 7.71 (d, J=8.59 Hz, 1 H) 7.93 (d, J=8.08 Hz, 2 H) 8.51 (s, 1 H) 9.62 (s, 1 H). ESI-MS: m/z 343.4 $(M + H)^+$.

Examples 3 and 4: 4-((5-acetamido-1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide *and* 4-((5-acetamido-2*H*-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide



Example 3 Example 4

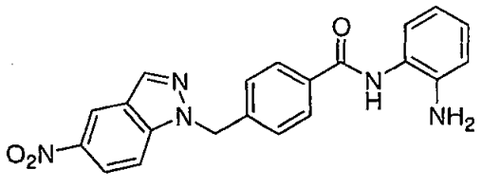
[0324] The title compounds were prepared using a procedure analogous to that described in Examples 1 and 2 except that the nitrobenzene was reduced and the aniline acylated as further described in Scheme 2. Specifically, the alkylation with methyl 4-bromomethylbenzoate, hydrolysis of methyl benzoate, and coupling with 1,2-phenylenediamine proceed as described in connection with Examples 1 and 2. A solution of the nitrobenzene (1.0 mmol) in MeOH (10 mL) with Pd/C (10 wt%, 50 mg) was then stirred vigorously under hydrogen for 4 h. The reaction was filtered and concentrated in vacuo to give the corresponding aniline that was carried forward. A solution of the aniline (1.0 mmol) in dichloromethane (10 mL) was treated sequentially with the appropriate acid chloride or chloroformate (1.1 mmol) and triethylamine (2.2 mmol). After stirring at 23 °C for 4 h, the reaction was concentrated in vacuo to yield the corresponding acylation product. If necessary, purification can be carried out by flash chromatography or recrystallization.

[0325] Example 3: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.02 (s, 3 H) 4.85 (s, 2 H) 5.69 (s, 2 H) 6.49 - 6.60 (m, 1 H) 6.73 (d, J=8.08 Hz, 1 H) 6.87 - 6.99 (m, 2 H) 7.11 (d, J=8.08 Hz, 1 H) 7.29 (d, J=8.08 Hz, 2 H) 7.39 (dd, J=9.09, 1.77 Hz, 1 H) 7.61 (d, J=8.84

Hz, 1 H) 7.87 (d, J=8.08 Hz, 2 H) 8.06 (s, 1 H) 8.12 (s, 1 H) 9.56 (s, 1 H). ESI-MS: m/z 400.5 $(M + H)^+$.

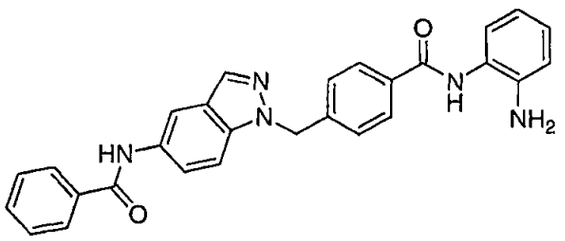
[0326] Example 4: ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 2.03 (s, 3 H) 4.87 (s, 2 H) 5.67 (s, 2 H) 6.45 - 6.65 (m, 1 H) 6.74 (d, J=8.08 Hz, 1 H) 6.86 - 7.02 (m, 1 H) 7.13 (d, J=7.33 Hz, 1 H) 7.20 (dd, J=9.35, 1.77 Hz, 1 H) 7.39 (d, J=8.08 Hz, 2 H) 7.52 (d, J=9.09 Hz, 1 H) 7.92 (d, J=8.08 Hz, 2 H) 8.12 (s, 1 H) 8.41 (s, 1 H) 9.61 (s, 1 H) 9.85 (s, 1 H). ESI-MS: m/z 400.5 $(M + H)^+$.

Example 5: N-(2-aminophenyl)-4-((5-nitro-1H-indazol-1-yl)methyl)benzamide



[0327] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) of the trifluoroacetic acid salt: δ ppm 5.86 (s, 2 H) 6.96 (s, 1 H) 7.05 (d, J=7.58 Hz, 1 H) 7.13 (d, J=7.33 Hz, 1 H) 7.25 (d, J=7.83 Hz, 1 H) 7.37 (d, J=8.08 Hz, 2 H) 7.92 (d, J=8.34 Hz, 2 H) 7.96 (d, J=9.09 Hz, 1 H) 8.24 (dd, J=9.35, 2.27 Hz, 1 H) 8.47 (s, 1 H) 8.85 (d, J=2.02 Hz, 1 H) 9.99 (s, 1 H). ESI-MS: m/z 388.4 $(M + H)^+$.

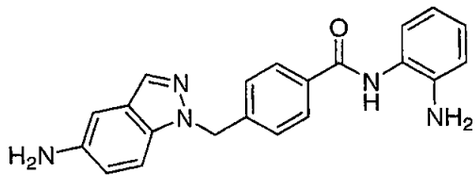
Example 6: 4-((5-benzamido-1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



[0328] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.86 (s, 2 H) 5.73 (s, 2 H) 6.49 - 6.62 (m, 1 H) 6.73 (d, J=7.83 Hz, 1 H) 6.85 - 6.97 (m, 1 H) 7.11 (d, J=7.83 Hz, 1 H) 7.30 (d, J=8.08 Hz, 2 H) 7.45 - 7.62 (m, 3 H) 7.61 - 7.74 (m, 2 H) 7.88 (d, J=8.34 Hz, 2 H)

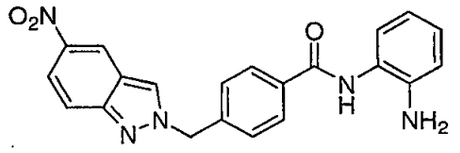
7.96 (d, J=6.82 Hz, 2 H) 8.12 (s, 1 H) 8.26 (s, 1 H) 9.57 (s, 1 H) 10.28 (s, 1 H). ESI-MS: m/z 462.5 $(M + H)^+$.

Example 7: 4-((5-amino-1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



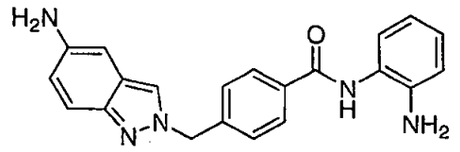
[0329] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.85 (bs, 4 H) 5.59 (s, 2 H) 6.55 (s, 1 H) 6.71 - 6.80 (m, 3 H) 6.93 (d, J=6.32 Hz, 1 H) 7.11 (d, J=6.82 Hz, 1 H) 7.26 (d, J=7.58 Hz, 2 H) 7.30 - 7.40 (m, 1 H) 7.73 - 7.83 (m, 1 H) 7.86 (d, J=7.58 Hz, 2 H) 9.56 (s, 1 H). ESI-MS: m/z 358.4 $(M + H)^+$.

Example 8: N-(2-aminophenyl)-4-((5-nitro-2*H*-indazol-2-yl)methyl)benzamide



[0330] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.87 (br. s., 2 H) 5.75 - 5.88 (m, 2 H) 6.51 - 6.61 (m, 1 H) 6.74 (d, J=7.33 Hz, 1 H) 6.90 - 6.98 (m, 1 H) 7.13 (d, J=7.58 Hz, 1 H) 7.46 (d, J=8.08 Hz, 2 H) 7.77 (d, J=9.60 Hz, 1 H) 7.94 (d, J=8.08 Hz, 2 H) 7.97 - 8.04 (m, 1 H) 8.91 (d, 1 H) 8.94 - 9.01 (m, 1 H) 9.62 (s, 1 H). ESI-MS: m/z 388.4 $(M + H)^+$.

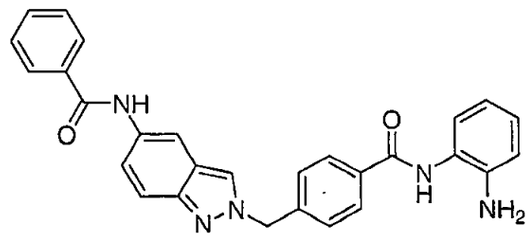
Example 9: 4-((5-amino-2*H*-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide



[0331] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) of the trifluoroacetic acid salt: δ

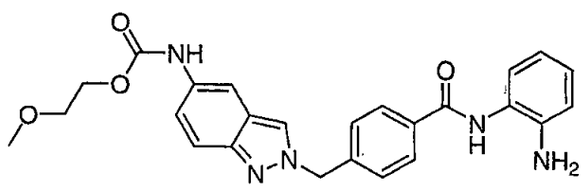
ppm 5.76 (s, 2 H) 6.84 - 6.95 (m, 1 H) 7.01 (d, J=7.83 Hz, 1 H) 7.08 - 7.20 (m, 2 H) 7.24 (s, 1 H) 7.44 (d, J=8.08 Hz, 2 H) 7.69 - 7.79 (m, 2 H) 7.96 (d, J=7.83 Hz, 2 H) 8.64 (s, 1 H) 9.96 (s, 1 H). ESI-MS: m/z 358.4 $(M + H)^+$

Example 10: 4-((5-benzamido-2*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



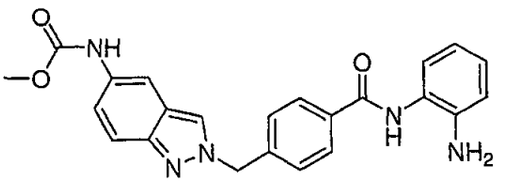
[0332] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.87 (s, 2 H) 5.61 - 5.76 (s, 2 H) 6.56 (t, J=7.33 Hz, 1 H) 6.75 (d, J=8.08 Hz, 1 H) 6.88 - 7.00 (m, 1 H) 7.13 (d, J=8.08 Hz, 1 H) 7.41 (d, J=7.07 Hz, 2 H) 7.45 - 7.63 (m, 3 H) 7.83 - 8.02 (m, 4 H) 8.26 (s, 1 H) 8.49 (s, 1 H) 9.61 (s, 1 H) 10.20 (s, 1 H). ESI-MS: m/z 462.5 $(M + H)^+$.

Example 11: 2-Methoxyethyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-ylcarbamate



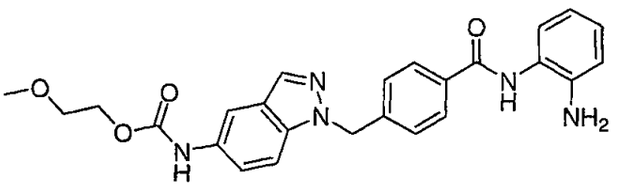
[0333] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3.52 - 3.60 (m, 2 H) 4.13 - 4.22 (m, 2 H) 4.86 (bs, 2 H) 5.66 (s, 2 H) 6.56 (m, 1 H) 6.75 (m, 1 H) 6.93 (d, J=6.82 Hz, 1 H) 7.13 (m, 1 H) 7.21 (d, J=2.02 Hz, 1 H) 7.39 (d, J=7.83 Hz, 2 H) 7.52 (s, 1 H) 7.82 - 7.89 (m, 2 H) 7.91 (s, 1 H) 8.40 (s, 1 H) 9.60 (s, 1 H) 9.64 (s, 1 H). ESI-MS: m/z 460.5 $(M + H)^+$.

Example 12: Methyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-ylcarbamate



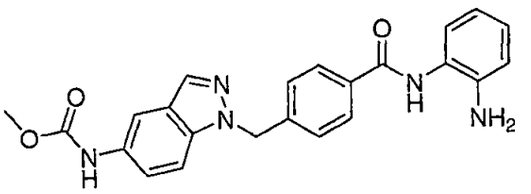
[0334] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3.32 (s, 3 H) 4.87 (s, 2 H) 5.58 - 5.73 (m, 2 H) 6.48 - 6.62 (m, 1 H) 6.74 (d, J=8.08 Hz, 1 H) 6.88 - 7.00 (m, 1 H) 7.07 - 7.17 (m, 1 H) 7.18 - 7.24 (m, 1 H) 7.39 (dd, J=8.08, 4.55 Hz, 2 H) 7.46 - 7.57 (m, 1 H) 7.88 - 8.00 (m, 2 H) 8.39 (d, J=6.32 Hz, 1 H) 8.56 (s, 1 H) 9.54 (s, 1 H) 9.61 (s, 1 H). ESI-MS: m/z 416.5 $(M + H)^+$.

Example 13: 2-Methoxyethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate



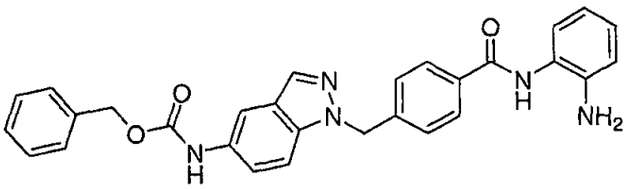
[0335] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3.31 (s, 3 H) 3.47 - 3.61 (m, 2 H) 4.12 - 4.23 (m, 2 H) 4.85 (s, 2 H) 5.69 (s, 2 H) 6.55 (t, J=7.58 Hz, 1 H) 6.69 - 6.78 (m, 1 H) 6.86 - 7.01 (m, 1 H) 7.11 (d, J=7.83 Hz, 1 H) 7.28 (d, J=8.34 Hz, 2 H) 7.33 - 7.45 (m, 1 H) 7.61 (d, J=9.09 Hz, 1 H) 7.87 (m, 3 H) 8.05 (s, 1 H) 9.56 (s, 1 H) 9.71 (s, 1 H). ESI-MS: m/z 460.5 $(M + H)^+$.

Example 14: Methyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate



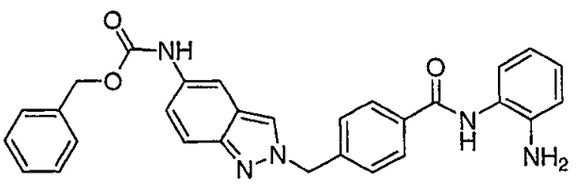
[0336] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) of the trifluoroacetic acid salt: δ ppm 3.65 (s, 3 H) 5.70 (s, 2 H) 6.90 (s, 1 H) 6.99 (s, 1 H) 7.11 (s, 1 H) 7.23 (d, J=7.83 Hz, 1 H) 7.31 (d, J=8.08 Hz, 2 H) 7.38 (s, 1 H) 7.61 (d, J=9.09 Hz, 1 H) 7.89 (d, J=7.83 Hz, 3 H) 8.06 (s, 1 H) 9.61 (s, 1 H) 9.91 (s, 1 H). ESI-MS: m/z 416.5 $(M + H)^+$.

Example 15: Benzyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate



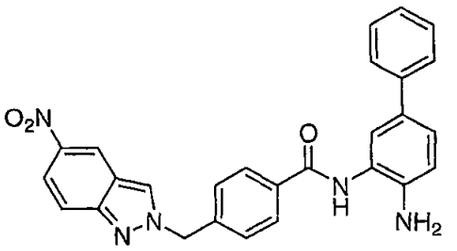
[0337] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) of the trifluoroacetic acid salt: δ ppm 4.85 (s, 2 H) 5.14 (s, 2 H) 5.69 (s, 2 H) 6.55 (s, 1 H) 6.73 (d, J=8.08 Hz, 1 H) 6.93 (s, 1 H) 7.04 - 7.18 (m, 1 H) 7.22 - 7.49 (m, 7 H) 7.61 (s, 1 H) 7.79 - 8.00 (m, 4 H) 8.05 (s, 1 H) 9.56 (s, 1 H) 9.74 (s, 1 H). ESI-MS: m/z 492.5 $(M + H)^+$.

Example 16: Benzyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-ylcarbamate



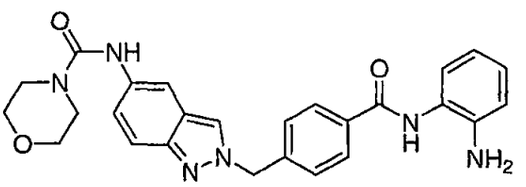
[0338] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) of the trifluoroacetic acid salt: δ ppm 5.14 (s, 2 H) 5.68 (s, 2 H) 6.81 - 6.94 (m, 1 H) 6.95 - 7.05 (m, 1 H) 7.10 (s, 1 H) 7.22 (dd, J=9.35, 1.77 Hz, 2 H) 7.29 - 7.47 (m, 7 H) 7.51 (d, J=9.35 Hz, 2 H) 7.94 (d, J=8.08 Hz, 2 H) 8.41 (s, 1 H) 9.68 (s, 1 H) 9.94 (s, 1 H). ESI-MS: m/z 492.5 $(M + H)^+$.

Example 17: *N*-(4-Amino-biphenyl-3-yl)-4-(5-nitro-indazol-2-ylmethyl)-benzamide



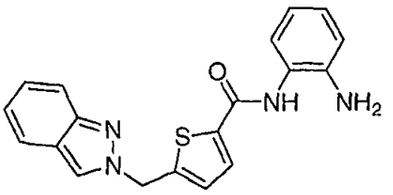
[0339] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) of the trifluoroacetic acid salt: δ ppm 5.84 (s, 2 H) 6.97 (s, 1 H) 7.25 (s, 1 H) 7.39 (s, 3 H) 7.44 - 7.62 (m, 5 H) 7.79 (s, 1 H) 7.99 (s, 3 H) 8.98 (s, 2 H) 9.89 (s, 1 H). ESI-MS: m/z 464.5 $(M + H)^+$.

Example 18: N-(2-(4-((2-Aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-yl)morpholine-4-carboxamide



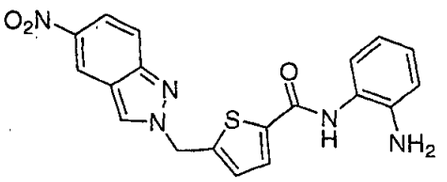
[0340] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) of the trifluoroacetic acid salt: δ ppm 3.34 - 3.45 (m, 4 H) 3.59 (m, 4 H) 4.86 (s, 2 H) 5.66 (s, 2 H) 6.75 (m, 1 H) 6.86 - 6.98 (m, 1 H) 7.06 - 7.16 (m, 1 H) 7.20 - 7.30 (m, 1 H) 7.38 (d, 2 H) 7.46 (m, 1 H) 7.78 (s, 1 H) 7.91 (d, 2 H) 8.36 (s, 1 H) 8.40 - 8.48 (m, 1 H) 9.61 (s, 1 H). ESI-MS: m/z 471.5 $(M + H)^+$.

Example 19: 5-((2*H*-Indazol-2-yl)methyl)-N-(2-aminophenyl)thiophene-2-carboxamide



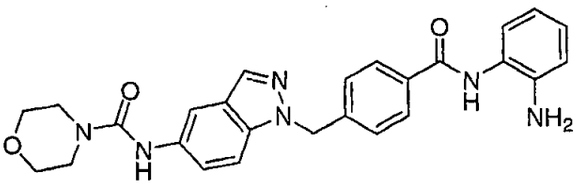
[0341] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.88 (s, 2 H) 5.89 (s, 2 H) 6.54 - 6.60 (m, 1 H) 6.75 (d, J=8.08 Hz, 1 H) 6.94 - 6.99 (m, 1 H) 7.02 - 7.10 (m, 2 H) 7.22 - 7.30 (m, 2 H) 7.62 (d, J=8.84 Hz, 1 H) 7.72 (d, J=8.59 Hz, 1 H) 7.83 (d, J=3.03 Hz, 1 H) 8.51 (s, 1 H) 9.68 (s, 1 H). ESI-MS: m/z 349.4 $(M + H)^+$.

Example 20: N-(2-Aminophenyl)-5-((5-nitro-2*H*-indazol-2-yl)methyl)thiophene-2-carboxamide



[0342] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.89 (s, 2 H) 6.01 (s, 2 H) 6.55 - 6.59 (m, 1 H) 6.75 (d, J=8.08 Hz, 1 H) 6.95 (d, J=7.83 Hz, 1H) 7.07 (d, J=7.83 Hz, 1 H) 7.30 (s, 1 H) 7.82 (d, J=9.35 Hz, 2 H) 8.01 - 8.05 (m, 1 H) 8.93 - 8.97 (m, 2 H) 9.70 (s, 1 H). ESI-MS: m/z 394.4 $(M + H)^+$.

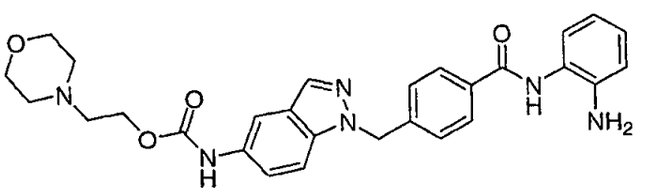
Example 21: N-(1-(4-((2-Aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-yl)morpholine-4-carboxamide



[0343] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3.37 - 3.47 (m, 4 H) 3.50 -

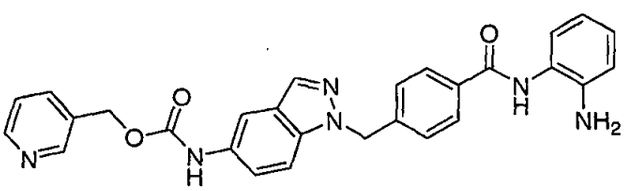
3.66 (m, 4 H) 5.62 (s, 2 H) 6.56 (m, 1 H) 6.74 (d, J=8.59 Hz, 1 H) 6.94 (m, 1 H) 7.11 (m, 1 H) 7.29 (d, J=8.08 Hz, 2 H) 7.39 (dd, J=9.09, 1.77 Hz, 1 H) 7.57 (d, J=9.09 Hz, 1 H) 7.74 - 7.89 (m, 3 H) 7.96 - 8.05 (m, 1 H) 8.52 (s, 1 H) 9.57 (s, 1 H). ESI-MS: m/z 471.5 $(M + H)^+$.

Example 22: 2-Morpholinoethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate



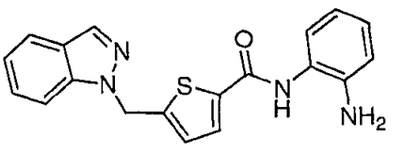
[0344] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 2.41 (m, 2 H) 2.56 (m, 2 H) 3.55 (m, 4 H) 4.18 (m, 4 H) 4.85 (s, 2 H) 5.68 (s, 2 H) 6.47 - 6.63 (m, 1 H) 6.73 (d, J=8.08 Hz, 1 H) 6.85 - 6.99 (m, 1 H) 7.10 (s, 1 H) 7.28 (d, J=8.34 Hz, 2 H) 7.39 (d, J=8.84 Hz, 1 H) 7.61 (d, J=9.09 Hz, 1 H) 7.87 (d, J=8.08 Hz, 3 H) 8.04 (s, 1 H) 9.55 (s, 1 H) 9.60 - 9.71 (m, 1 H). ESI-MS: m/z 515.6 $(M + H)^+$.

Example 23: Pyridin-3-ylmethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate



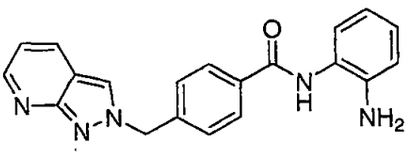
[0345] The title compound was prepared using a procedure analogous to that described in Examples 3 and 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.85 (bs, 2 H) 5.18 (s, 2 H) 5.69 (s, 2 H) 6.48 - 6.59 (m, 1 H) 6.73 (dd, J=8.08, 1.26 Hz, 1 H) 6.87 - 6.98 (m, 1 H) 7.11 (d, J=7.33 Hz, 1 H) 7.28 (d, J=8.34 Hz, 2 H) 7.34 - 7.47 (m, 2 H) 7.62 (d, J=9.09 Hz, 2 H) 7.77 - 7.94 (m, 3 H) 8.03 - 8.08 (m, 1 H) 8.54 (dd, J=4.80, 1.52 Hz, 1 H) 8.65 (d, J=1.77 Hz, 1 H) 9.56 (s, 1 H) 9.78 (s, 1 H). ESI-MS: m/z 493.5 $(M + H)^+$.

Example 24: 5-((1*H*-Indazol-1-yl)methyl)-N-(2-aminophenyl)thiophene-2-carboxamide



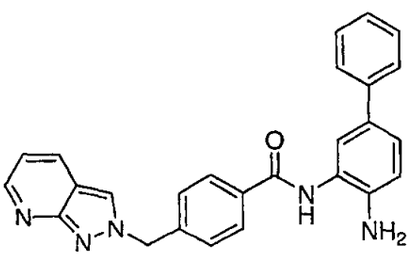
[0346] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.86 (s, 2 H) 5.90 (s, 2 H) 6.52 - 6.59 (m, 1 H) 6.74 (d, J=7.33 Hz, 1 H) 6.91 - 6.99 (m, 1 H) 7.05 (d, J=7.33 Hz, 1 H) 7.13 - 7.23 (m, 2 H) 7.42 (s, 1 H) 7.79 (m, 3 H) 8.15 (s, 1 H) 9.62 (s, 1 H). ESI-MS: m/z 349.4 $(M + H)^+$.

Example 25: 4-((2*H*-Pyrazolo[3,4-b]pyridin-2-yl)methyl)-N-(2-aminophenyl)benzamide



[0347] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) of the *bis*-trifluoroacetic acid salt: δ ppm 6.11 (s, 2 H) 6.79 (d, J=8.08 Hz, 1 H) 6.92 (d, J=8.08 Hz, 1 H) 7.02 - 7.10 (m, 1 H) 7.19 (d, J=7.58 Hz, 1 H) 7.63 (d, J=8.08 Hz, 2H) 7.79 (dd, J=8.08, 5.81 Hz, 1 H) 7.97 (d, J=8.34 Hz, 2 H) 9.11 - 9.19 (m, 1 H) 9.23 (d, J=7.83 Hz, 1 H) 9.40 (d, J=4.80 Hz, 1 H) 9.86 (s, 1 H). ESI-MS: m/z 344.4 $(M + H)^+$.

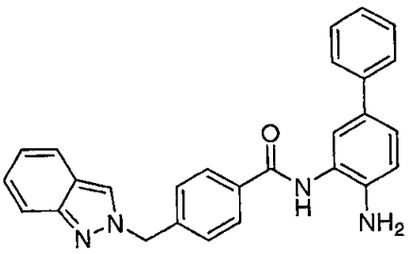
Example 26: *N*-(4-Amino-biphenyl-3-yl)-4-pyrazolo[3,4-*b*]pyridin-2-ylmethyl-benzamide



[0348] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) of the *bis*-trifluoroacetic acid salt:

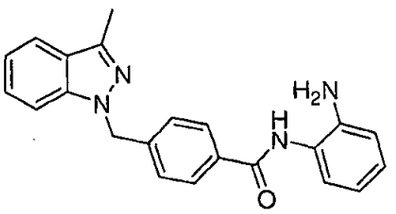
δ ppm 6.11 (s, 2H) 6.91 (d, J=8.34 Hz, 1 H) 7.24 (t, J=7.33 Hz, 1 H) 7.33 - 7.41 (m, 3 H) 7.48 - 7.56 (m, 3 H) 7.64 (d, J=8.34 Hz, 2 H) 7.79 (dd, J=8.08, 5.81 Hz, 1 H) 8.00 (d, J=8.34 Hz, 2 H) 9.16 (br. s., 1 H) 9.23 (d, J=7.83 Hz, 1 H) 9.35 - 9.45 (m, 1 H) 9.82 (s, 1 H). ESI-MS: m/z 420.5 $(M + H)^+$.

Example 27: *N*-(4-Amino-biphenyl-3-yl)-4-indazol-2-ylmethyl-benzamide



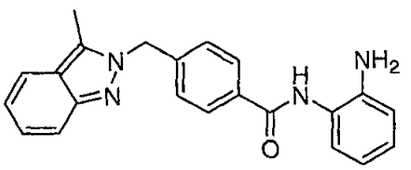
[0349] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) of the trifluoroacetic acid salt: δ ppm 5.74 (s, 2 H) 6.98 - 7.06 (m, 1 H) 7.08 (d, J=8.34 Hz, 1 H) 7.18 - 7.25 (m, 1 H) 7.28 (t, 1 H) 7.35 - 7.48 (m, 5 H) 7.58 (m, 4 H) 7.71 (d, J=8.34 Hz, 1 H) 7.98 (d, J=8.08 Hz, 2 H) 8.53 (s, 1 H) 10.02 (s, 1 H). ESI-MS: m/z 419.5 $(M + H)^+$.

Example 28: N-(2-Aminophenyl)-4-((3-methyl-1*H*-indazol-1-yl)methyl)benzamide



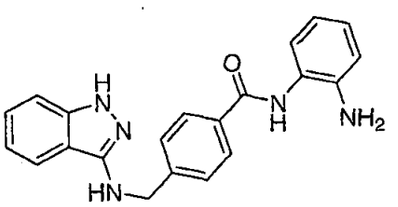
[0350] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 2.48 (s, 3 H) 4.87 (s, 2 H) 5.66 (s, 2 H) 6.54 - 6.61 (m, 1 H) 6.76 (dd, J=7.83, 1.26 Hz, 1 H) 6.91 - 6.99 (m, 1 H) 7.09 - 7.17 (m, 2 H) 7.31 (d, J=8.34 Hz, 2 H) 7.34 - 7.40 (m, 1 H) 7.64 (d, J=8.34 Hz, 1 H) 7.73 (d, J=8.08 Hz, 1 H) 7.89 (d, J=8.34 Hz, 2 H) 9.57 (s, 1 H). ESI-MS: m/z 357.4 $(M + H)^+$.

Example 29: N-(2-Aminophenyl)-4-((3-methyl-2*H*-indazol-2-yl)methyl)benzamide



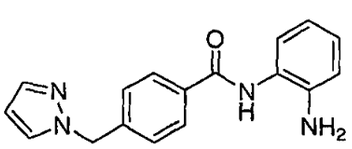
[0351] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 2.61 (s, 3 H) 4.88 (s, 2 H) 5.72 (s, 2 H) 6.50 - 6.64 (m, 1 H) 6.72 - 6.82 (m, 1 H) 6.93 - 7.03 (m, 2 H) 7.12 - 7.17 (m, 1 H) 7.20 - 7.31 (m, 3 H) 7.55 (d, J=8.59 Hz, 1 H) 7.68 (d, J=8.59 Hz, 1 H) 7.93 (d, J=8.08 Hz, 2 H) 9.62 (s, 1 H). ESI-MS: m/z 357.4 $(M + H)^+$.

Example 30: 4-((1H-indazol-3-ylamino)methyl)-N-(2-aminophenyl)benzamide



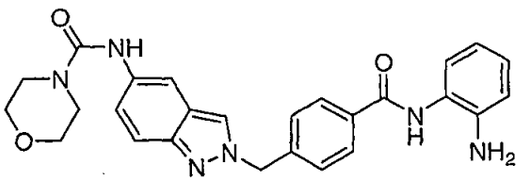
[0352] The title compound was prepared using a procedure analogous to that described in Examples 1 and 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.56 (d, J=6.15 Hz, 2 H) 4.88 (s, 2 H) 6.49 - 6.63 (m, 1 H) 6.63 - 6.73 (m, 1 H) 6.77 (d, J=7.98 Hz, 1 H) 6.84 - 7.01 (m, 2 H) 7.16 (d, J=7.48 Hz, 1 H) 7.20 - 7.29 (m, 2 H) 7.52 (d, J=8.14 Hz, 2 H) 7.77 (d, J=8.14 Hz, 1 H) 7.92 (d, J=8.14 Hz, 2 H) 9.60 (s, 1 H) 11.40 (s, 1 H). ESI-MS: m/z 358.4 $(M + H)^+$.

Example 31: 4-((1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



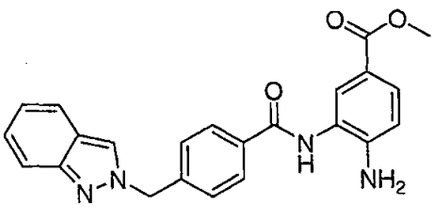
[0353] ^{1}H NMR (499 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 5.38 (s, 2 H), 6.25 - 6.33 (m, 2 H), 7.18 - 7.26 (m, 3 H), 7.31 - 7.38 (m, 3 H), 7.46 - 7.53 (m, 1 H), 7.84 - 7.89 (m, 1 H), 7.92 - 7.99 (m, 1 H), 10.09 (s, 1 H). ESI-MS: *m/z* 293.3 $(M + H)^+$.

Example 32: N-(2-(4-((2-Aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-yl)morpholine-4-carboxamide



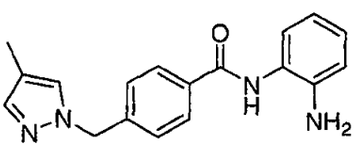
[0354] ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3.36 - 3.47 (m, 4 H) 3.61 (m, 4 H) 4.85 (s, 2 H) 5.69 (s, 2 H) 6.77 (m, 1 H) 6.94 (m, 1 H) 7.12 (m, 1 H) 7.27 (m, 1 H) 7.37 (d, 2 H) 7.46 (m, 1 H) 7.78 (s, 1 H) 7.87 (d, 2 H) 8.36 (s, 1 H) 8.46 (m, 1 H) 9.56 (s, 1 H). ESI-MS: *m/z* 471.5 $(M + H)^+$.

Example 33: Methyl 3-(4-((2H-indazol-2-yl)methyl)benzamido)-4-aminobenzoate



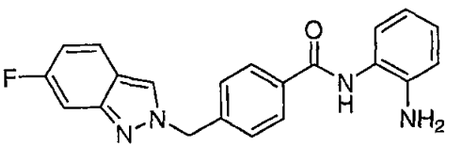
[0355] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.73 (s, 14 H), 5.72 (s, 10 H), 5.81 (s, 10 H), 6.74 (d, *J*=8.59 Hz, 6 H), 6.98 - 7.07 (m, 6 H), 7.17 - 7.26 (m, 6 H), 7.41 (d, *J*=8.34 Hz, 10 H), 7.51 - 7.61 (m, 11 H), 7.67 - 7.77 (m, 11 H), 7.94 (d, *J*=8.08 Hz, 10 H), 8.52 (s, 6 H), 9.60 (s, 1 H). ESI-MS: *m/z* 401.4 $(M + H)^+$.

Example 34: N-(2-aminophenyl)-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide



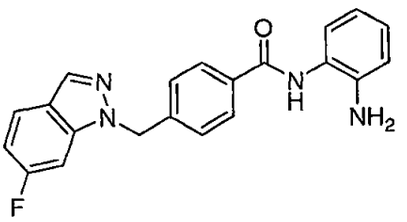
[0356] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (s, 3 H), 4.87 (s, 2 H), 5.29 - 5.33 (m, 2 H), 6.54 - 6.60 (m, 1 H), 6.73 - 6.78 (m, 1 H), 6.92 - 6.97 (m, 1 H), 7.13 (d, *J*=7.58 Hz, 1 H), 7.25 - 7.30 (m, 3 H), 7.58 (s, 1 H), 7.91 (d, *J*=8.08 Hz, 2 H), 9.60 (s, 1 H). ESI-MS: *m/z* 307.4 $(M + H)^+$.

Example 35: N-(2-aminophenyl)-4-((6-fluoro-2H-indazol-2-yl)methyl)benzamide



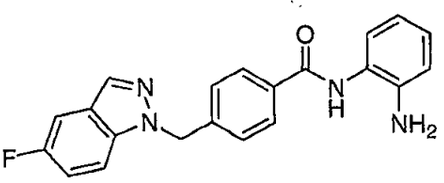
[0357] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 2 H), 5.70 (s, 2 H), 6.53 - 6.60 (m, 1 H), 6.75 (d, *J*=8.08 Hz, 1 H), 6.91 - 6.99 (m, 2 H), 7.13 (d, *J*=8.08 Hz, 1 H), 7.31 (d, *J*=10.36 Hz, 1 H), 7.41 (d, *J*=8.08 Hz, 2 H), 7.76 - 7.83 (m, 1 H), 7.93 (d, *J*=8.08 Hz, 2 H), 8.58 (s, 1 H), 9.61 (s, 1 H). ESI-MS: *m/z* 361.4 $(M + H)^+$.

Example 36: N-(2-aminophenyl)-4-((6-fluoro-1H-indazol-1-yl)methyl)benzamide



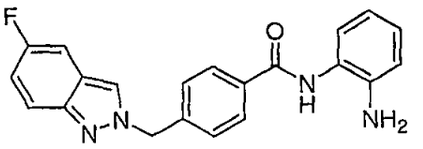
[0358] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.86 (s, 2 H), 5.67 - 5.72 (m, 2 H), 6.53 - 6.59 (m, 1 H), 6.74 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.91 - 6.96 (m, 1 H), 6.99 - 7.06 (m, 1 H), 7.11 (d, *J*=7.33 Hz, 1 H), 7.33 (d, *J*=8.08 Hz, 2 H), 7.59 - 7.66 (m, 1 H), 7.81 (dd, *J*=8.84, 5.31 Hz, 1 H), 7.88 (d, *J*=8.08 Hz, 2 H), 8.13 - 8.16 (m, 1 H), 9.57 (s, 1 H). ESI-MS: *m/z* 361.4 $(M + H)^+$.

Example 37: N-(2-aminophenyl)-4-((5-fluoro-1H-indazol-1-yl)methyl)benzamide



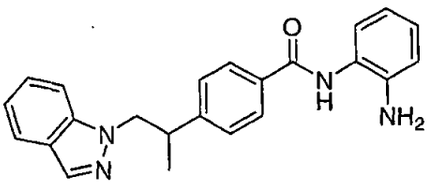
[0359] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.86 (s, 2 H), 5.75 (s, 2 H), 6.55 (s, 1 H), 6.74 (d, *J*=7.83 Hz, 1 H), 6.92 (d, *J*=7.58 Hz, 1 H), 7.10 (s, 1 H), 7.23 - 7.33 (m, 3 H), 7.49 - 7.59 (m, 1 H), 7.75 (s, 1 H), 7.87 (s, 2 H), 8.11 (s, 1 H), 9.57 (s, 1 H). ESI-MS: *m/z* 361.4 $(M + H)^+$.

Example 38: N-(2-aminophenyl)-4-((5-fluoro-2H-indazol-2-yl)methyl)benzamide



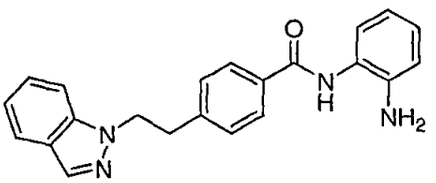
[0360] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 2 H), 5.68 (s, 2 H), 6.52 - 6.59 (m, 1 H), 6.71 - 6.77 (m, 1 H), 6.91 - 6.98 (m, 1 H), 7.09 - 7.17 (m, 2 H), 7.37 - 7.48 (m, 3 H), 7.62 - 7.68 (m, 1 H), 7.93 (d, *J*=8.34 Hz, 2 H), 8.50 (s, 1 H), 9.60 (s, 1 H). ESI-MS: *m/z* 361.4 $(M + H)^+$.

Example 39: 4-(1-(1H-indazol-1-yl)propan-2-yl)-N-(2-aminophenyl)benzamide



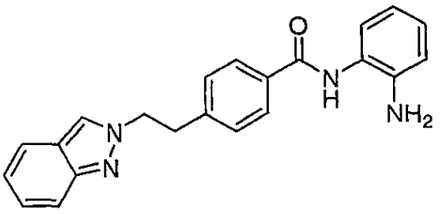
[0361] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 1.20 (d, *J*=6.82 Hz, 3 H), 3.51 - 3.62 (m, 1 H), 4.54 - 4.65 (m, 2 H), 6.95 (s, 2 H), 7.01 - 7.13 (m, 3 H), 7.25 (d, *J*=7.58 Hz, 1 H), 7.29 - 7.35 (m, 1 H), 7.44 (d, *J*=8.34 Hz, 2 H), 7.65 - 7.72 (m, 2 H), 7.85 (d, *J*=8.08 Hz, 2 H), 8.02 (s, 1 H), 9.84 - 10.01 (m, 1 H). ESI-MS: *m/z* 371.4 $(M + H)^+$.

Example 40: 4-(2-(1H-indazol-1-yl)ethyl)-N-(2-aminophenyl)benzamide



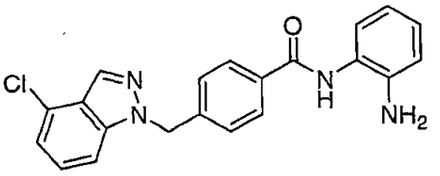
[0362] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.17 - 3.28 (m, 2 H), 4.68 (t, *J*=7.07 Hz, 2 H), 4.85 (s, 2 H), 6.51 - 6.62 (m, 1 H), 6.75 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.88 - 7.00 (m, 1 H), 7.03 - 7.18 (m, 2 H), 7.26 - 7.38 (m, 3 H), 7.62 (d, *J*=8.34 Hz, 1 H), 7.72 (d, *J*=8.08 Hz, 1 H), 7.78 - 7.86 (m, 2 H), 8.04 (s, 1 H), 9.56 (s, 1 H). ESI-MS: *m/z* 357.4 $(M + H)^+$.

Example 41: 4-(2-(2H-indazol-2-yl)ethyl)-N-(2-aminophenyl)benzamide



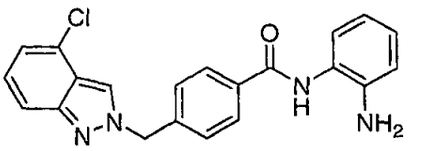
[0363] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.34 (t, *J*=7.07 Hz, 2 H), 4.72 (t, *J*=7.07 Hz, 2 H), 4.85 (s, 2 H), 6.51 - 6.62 (m, 1 H), 6.74 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.88 - 7.03 (m, 2 H), 7.11 (d, *J*=7.33 Hz, 1 H), 7.15 - 7.25 (m, 1 H), 7.29 (d, *J*=8.08 Hz, 2 H), 7.54 - 7.68 (m, 2 H), 7.84 (d, *J*=8.08 Hz, 2 H), 8.19 - 8.30 (m, 1 H), 9.56 (s, 1 H). ESI-MS: *m/z* 357.4 $(M + H)^+$.

Example 42: N-(2-aminophenyl)-4-((4-chloro-1H-indazol-1-yl)methyl)benzamide



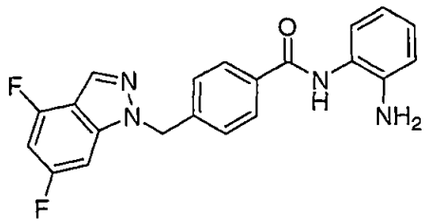
[0364] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.85 (s, 2 H), 5.74 - 5.81 (m, 2 H), 6.52 - 6.59 (m, 1 H), 6.71 - 6.77 (m, 1 H), 6.90 - 6.97 (m, 1 H), 7.11 (d, *J*=7.07 Hz, 1 H), 7.23 (d, *J*=7.58 Hz, 1 H), 7.31 (d, *J*=8.34 Hz, 2 H), 7.35 - 7.42 (m, 1 H), 7.74 (d, *J*=8.59 Hz, 1 H), 7.89 (d, *J*=8.08 Hz, 2 H), 8.18 - 8.23 (m, 1 H), 9.57 (s, 1 H). ESI-MS: *m/z* 377.8 $(M + H)^+$.

Example 43: N-(2-aminophenyl)-4-((4-chloro-2H-indazol-2-yl)methyl)benzamide



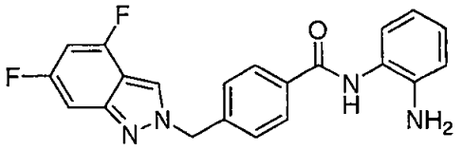
[0365] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 2 H), 5.70 - 5.78 (m, 2 H), 6.53 - 6.61 (m, 1 H), 6.75 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.91 - 6.98 (m, 1 H), 7.13 (d, *J*=7.07 Hz, 2 H), 7.22 (dd, *J*=8.59, 7.07 Hz, 1 H), 7.41 - 7.49 (m, 2 H), 7.58 (d, *J*=8.59 Hz, 1 H), 7.93 (d, *J*=8.08 Hz, 2 H), 8.67 - 8.71 (m, 1 H), 9.61 (s, 1 H). ESI-MS: *m/z* 377.8 $(M + H)^+$.

Example 44: N-(2-aminophenyl)-4-((4,6-difluoro-1H-indazol-1-yl)methyl)benzamide



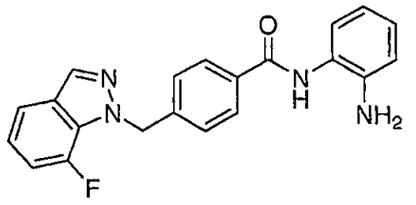
[0366] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.86 (s, 2 H), 5.67 - 5.75 (m, 2 H), 6.52 - 6.59 (m, 1 H), 6.74 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.91 - 6.96 (m, 1 H), 7.00 - 7.07 (m, 1 H), 7.12 (d, *J*=7.58 Hz, 1 H), 7.34 (d, *J*=8.08 Hz, 2 H), 7.60 (d, *J*=9.35 Hz, 1 H), 7.89 (d, *J*=8.08 Hz, 2 H), 8.25 - 8.30 (m, 1 H), 9.58 (s, 1 H). ESI-MS: *m/z* 379.4 $(M + H)^+$.

Example 45: N-(2-aminophenyl)-4-((4,6-difluoro-2H-indazol-2-yl)methyl)benzamide



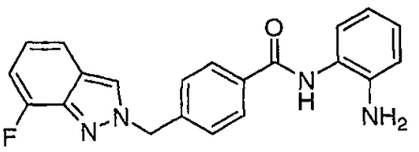
[0367] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 2 H), 5.67 - 5.74 (m, 2 H), 6.52 - 6.61 (m, 1 H), 6.75 (dd, *J*=7.83, 1.26 Hz, 1 H), 6.88 - 6.98 (m, 2 H), 7.13 (d, *J*=7.07 Hz, 1 H), 7.25 (d, *J*=8.84 Hz, 1 H), 7.44 (d, *J*=8.34 Hz, 2 H), 7.93 (d, *J*=8.08 Hz, 2 H), 8.82 (s, 1 H), 9.61 (s, 1 H). ESI-MS: *m/z* 379.4 $(M + H)^+$.

Example 46: N-(2-aminophenyl)-4-((7-fluoro-1H-indazol-1-yl)methyl)benzamide



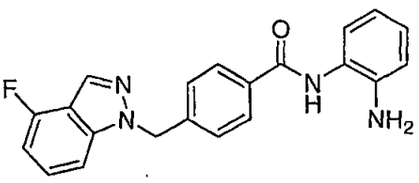
[0368] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.86 (s, 2 H), 5.78 (s, 2 H), 6.51 - 6.58 (m, 1 H), 6.71 - 6.76 (m, 1 H), 6.89 - 6.96 (m, 1 H), 7.07 - 7.14 (m, 2 H), 7.17 - 7.25 (m, 3 H), 7.61 (d, *J*=7.83 Hz, 1 H), 7.88 (d, *J*=8.08 Hz, 2 H), 8.24 (d, *J*=2.53 Hz, 1 H), 9.56 (s, 1 H). ESI-MS: *m/z* 361.4 $(M + H)^+$.

Example 47: N-(2-aminophenyl)-4-((7-fluoro-2H-indazol-2-yl)methyl)benzamide



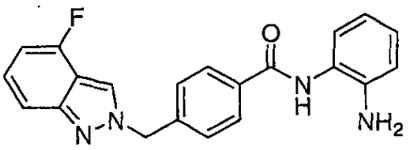
[0369] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 2 H), 5.72 - 5.78 (m, 2 H), 6.52 - 6.60 (m, 1 H), 6.75 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.92 - 7.04 (m, 3 H), 7.13 (d, *J*=7.33 Hz, 1 H), 7.43 (d, *J*=8.08 Hz, 2 H), 7.51 - 7.57 (m, 1 H), 7.94 (d, *J*=8.08 Hz, 2 H), 8.66 (d, *J*=2.78 Hz, 1 H), 9.62 (s, 1 H). ESI-MS: *m/z* 361.4 $(M + H)^+$.

Example 48: N-(2-aminophenyl)-4-((4-fluoro-1H-indazol-1-yl)methyl)benzamide



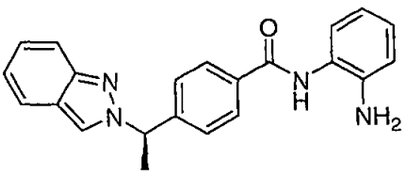
[0370] ^{1}H NMR (400 MHz, DMSO-d6) □ ppm 4.86 (s, 2 H), 5.77 (s, 2 H), 6.50 - 6.60 (m, 1 H), 6.73 (d, J=8.34 Hz, 1 H), 6.88 - 6.97 (m, 2 H), 7.11 (d, J=7.58 Hz, 1 H), 7.32 (d, J=8.08 Hz, 2 H), 7.34 - 7.42 (m, 1 H), 7.58 (d, J=8.34 Hz, 1 H), 7.89 (d, J=7.83 Hz, 2 H), 8.25 (s, 1 H), 9.57 (s, 1 H). ESI-MS: m/z 361.4 (M + H)+.

Example 49: N-(2-aminophenyl)-4-((4-fluoro-2H-indazol-2-yl)methyl)benzamide



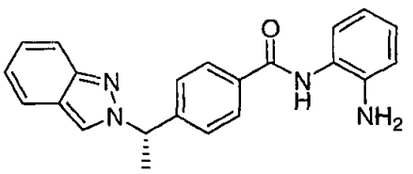
[0371] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 2 H), 5.69 - 5.75 (m, 2 H), 6.52 - 6.60 (m, 1 H), 6.72 - 6.82 (m, 2 H), 6.91 - 6.97 (m, 1 H), 7.12 (d, *J*=7.33 Hz, 1 H), 7.17 - 7.24 (m, 1 H), 7.39 - 7.46 (m, 3 H), 7.93 (d, *J*=8.08 Hz, 2 H), 8.74 (s, 1 H), 9.61 (s, 1 H). ESI-MS: *m/z* 361.4 $(M + H)^+$.

Example 50: (R)-4-(1-(2H-indazol-2-yl)ethyl)-N-(2-aminophenyl)benzamide



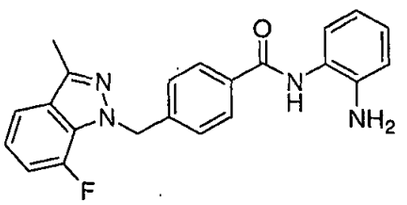
[0372] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (d, *J*=7.07 Hz, 4 H), 3.36 (d, *J*=5.05 Hz, 2 H), 4.29 (q, 1 H), 5.07 (s, 2 H), 6.24 (d, *J*=7.07 Hz, 1 H), 6.76 (s, 1 H), 6.96 (s, 1 H), 7.13 (s, 1 H), 7.24 (d, *J*=8.59 Hz, 2 H), 7.32 (s, 1 H), 7.39 - 7.44 (m, 1 H), 7.63 (d, *J*=8.08 Hz, 3 H), 7.80 (d, *J*=8.84 Hz, 2 H), 7.90 (d, *J*=8.34 Hz, 1 H), 8.11 (d, *J*=8.34 Hz, 3 H), 8.75 (s, 1 H), 9.79 (s, 1 H). ESI-MS: *m/z* 357.4 $(M + H)^+$.

Example 51: (S)-4-(1-(2H-indazol-2-yl)ethyl)-N-(2-aminophenyl)benzamide



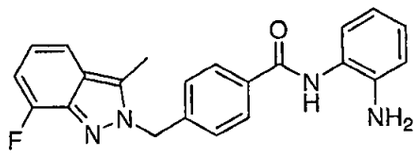
[0373] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (d, *J*=7.07 Hz, 4 H), 3.36 (d, *J*=5.05 Hz, 2 H), 4.29 (q, 1 H), 5.07 (s, 2 H), 6.24 (d, *J*=7.07 Hz, 1 H), 6.76 (s, 1 H), 6.96 (s, 1 H), 7.13 (s, 1 H), 7.24 (d, *J*=8.59 Hz, 2 H), 7.32 (s, 1 H), 7.39 - 7.44 (m, 1 H), 7.63 (d, *J*=8.08 Hz, 3 H), 7.80 (d, *J*=8.84 Hz, 2 H), 7.90 (d, *J*=8.34 Hz, 1 H), 8.11 (d, *J*=8.34 Hz, 3 H), 8.75 (s, 1 H), 9.79 (s, 1 H). ESI-MS: *m/z* 357.4 $(M + H)^+$.

Example 52: N-(2-aminophenyl)-4-((7-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide



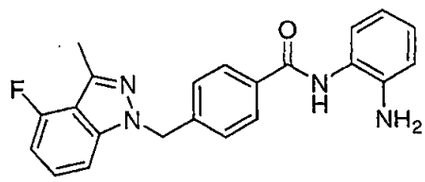
[0374] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 (s, 3 H), 4.86 (s, 2 H), 5.62 - 5.71 (m, 2 H), 6.51 - 6.59 (m, 1 H), 6.73 (d, *J*=7.83 Hz, 1 H), 6.89 - 6.97 (m, 1 H), 7.04 - 7.14 (m, 2 H), 7.15 - 7.25 (m, 3 H), 7.56 (d, *J*=8.08 Hz, 1 H), 7.87 (d, *J*=7.83 Hz, 2 H), 9.56 (s, 1 H). ESI-MS: *m/z* 375.4 $(M + H)^+$.

Example 53: N-(2-aminophenyl)-4-((7-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide



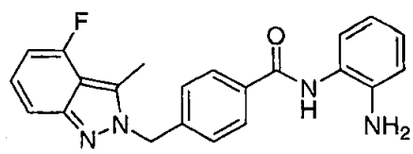
[0375] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.61 (s, 3 H), 4.87 (s, 2 H), 5.74 (s, 2 H), 6.53 - 6.59 (m, 1 H), 6.74 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.91 - 7.02 (m, 3 H), 7.12 (d, *J*=7.58 Hz, 1 H), 7.29 (d, *J*=8.08 Hz, 2 H), 7.51 (d, *J*=8.34 Hz, 1 H), 7.93 (d, *J*=8.08 Hz, 2 H), 9.61 (s, 1 H). ESI-MS: *m/z* 375.4 $(M + H)^+$.

Example 54: N-(2-aminophenyl)-4-((4-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide



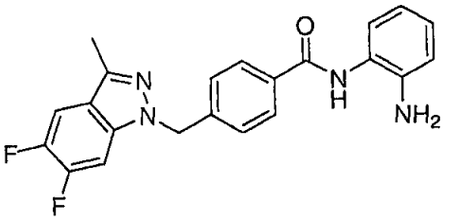
[0376] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.53 - 2.58 (m, 3 H), 4.86 (s, 2 H), 5.65 (s, 2 H), 6.51 - 6.59 (m, 1 H), 6.74 (dd, *J*=7.83, 1.26 Hz, 1 H), 6.84 (dd, *J*=10.86, 7.58 Hz, 1 H), 6.90 - 6.97 (m, 1 H), 7.11 (d, *J*=7.83 Hz, 1 H), 7.25 - 7.36 (m, 3 H), 7.48 (d, *J*=8.59 Hz, 1 H), 7.88 (d, *J*=8.08 Hz, 2 H), 9.56 (s, 1 H). ESI-MS: *m/z* 375.4 $(M + H)^+$.

Example 55: N-(2-aminophenyl)-4-((4-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide



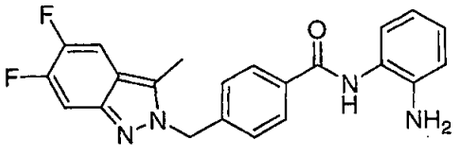
[0377] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.65 - 2.71 (m, 3 H), 4.87 (s, 2 H), 5.71 (s, 2 H), 6.53 - 6.60 (m, 1 H), 6.66 - 6.77 (m, 2 H), 6.91 - 6.98 (m, 1 H), 7.09 - 7.19 (m, 2 H), 7.29 (d, *J*=8.08 Hz, 2 H), 7.36 (d, *J*=8.59 Hz, 1 H), 7.92 (d, *J*=8.34 Hz, 2 H), 9.61 (s, 1 H). ESI-MS: *m/z* 375.4 $(M + H)^+$.

Example 56: N-(2-aminophenyl)-4-((5,6-difluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide



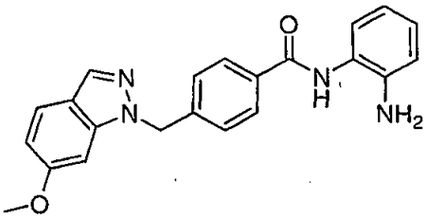
[0378] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.45 (s, 3 H), 4.86 (s, 2 H), 5.60 (s, 2 H), 6.51 - 6.60 (m, 1 H), 6.74 (d, *J*=8.08 Hz, 1 H), 6.89 - 6.98 (m, 1 H), 7.12 (d, *J*=7.83 Hz, 1 H), 7.32 (d, *J*=7.83 Hz, 2 H), 7.78 - 7.84 (m, 1 H), 7.85 - 7.91 (m, 3 H), 9.56 (s, 1 H). ESI-MS: *m/z* 393.4 $(M + H)^+$.

Example 57: N-(2-aminophenyl)-4-((5,6-difluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide



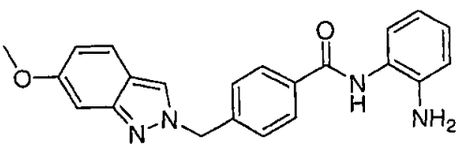
[0379] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.57 (s, 3 H), 4.98 (s, 1 H), 5.67 (s, 2 H), 6.58 (s, 1 H), 6.76 (s, 1 H), 6.95 (s, 1 H), 7.13 (s, 1 H), 7.27 (s, 2 H), 7.55 (s, 1 H), 7.75 (s, 1 H), 7.90 (s, 3 H), 9.62 (s, 1 H). ESI-MS: *m/z* 393.4 $(M + H)^+$.

Example 58: N-(2-aminophenyl)-4-((6-methoxy-1H-indazol-1-yl)methyl)benzamide



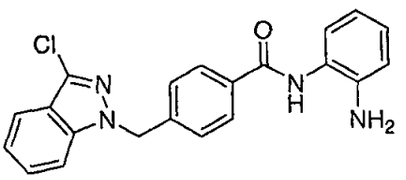
[0380] ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.31 (s, 3 H), 4.85 (s, 2 H), 5.68 (s, 2 H), 6.56 (s, 1 H), 6.72 - 6.79 (m, 2 H), 6.93 (s, 1 H), 7.11 (s, 1 H), 7.20 (s, 1 H), 7.30 (d, *J*=8.08 Hz, 2 H), 7.61 (s, 1 H), 7.88 (d, *J*=8.08 Hz, 2 H), 7.98 (s, 1 H), 9.56 (s, 1 H). ESI-MS: *m/z* 373.4 $(M + H)^+$.

Example 59: N-(2-aminophenyl)-4-((6-methoxy-2H-indazol-2-yl)methyl)benzamide



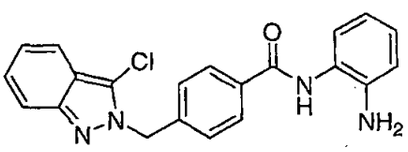
[0381] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.71 - 3.79 (m, 3 H), 4.87 (s, 2 H), 5.63 (s, 2 H), 6.51 - 6.62 (m, 1 H), 6.64 - 6.71 (m, 1 H), 6.72 - 6.78 (m, 1 H), 6.90 (d, *J*=1.77 Hz, 1 H), 6.91 - 6.97 (m, 1 H), 7.13 (d, *J*=7.83 Hz, 1 H), 7.38 (d, *J*=8.34 Hz, 2 H), 7.57 (d, *J*=9.09 Hz, 1 H), 7.92 (d, *J*=8.08 Hz, 2 H), 8.38 (s, 1 H), 9.60 (s, 1 H). ESI-MS: *m/z* 373.4 $(M + H)^+$.

Example 60: N-(2-aminophenyl)-4-((3-chloro-1H-indazol-1-yl)methyl)benzamide



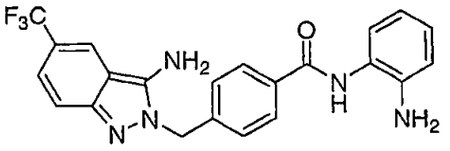
[0382] ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 4.86 (s, 2 H), 5.72 (s, 2 H), 6.52 - 6.59 (m, 1 H), 6.74 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.90 - 6.97 (m, 1 H), 7.11 (d, *J*=6.57 Hz, 1 H), 7.22 - 7.30 (m, 1 H), 7.35 (d, *J*=8.34 Hz, 2 H), 7.47 - 7.54 (m, 1 H), 7.68 (d, *J*=8.08 Hz, 1 H), 7.82 (d, J=8.59 Hz, 1 H), 7.89 (d, J=8.34 Hz, 2 H), 9.57 (s, 1 H). ESI-MS: m/z 377.8 (M + H)+.

Example 61: N-(2-aminophenyl)-4-((3-chloro-2H-indazol-2-yl)methyl)benzamide



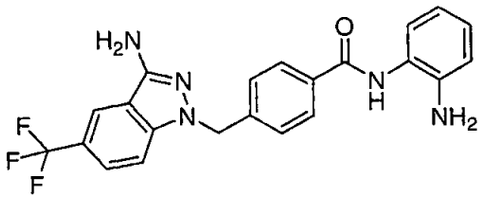
[0383] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 2 H), 5.73 - 5.82 (m, 2 H), 6.51 - 6.61 (m, 1 H), 6.74 (d, *J*=8.08 Hz, 1 H), 6.90 - 6.99 (m, 1 H), 7.10 - 7.19 (m, 2 H), 7.29 - 7.37 (m, 3 H), 7.53 (s, 1 H), 7.57 - 7.68 (m, 2 H), 7.93 (d, *J*=7.83 Hz, 2 H), 9.61 (s, 1 H). ESI-MS: *m/z* 377.8 $(M + H)^+$.

Example 62: 4-((3-amino-5-(trifluoromethyl)-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide



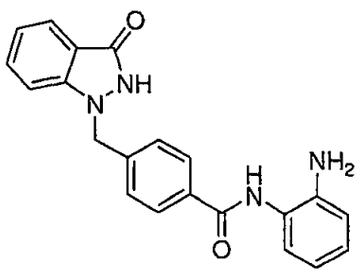
[0384] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.86 (s, 2 H), 5.47 (s, 2 H), 6.53 - 6.60 (m, 1 H), 6.73 - 6.80 (m, 3 H), 6.90 - 6.97 (m, 1 H), 7.13 (d, *J*=7.58 Hz, 1 H), 7.20 - 7.25 (m, 1 H), 7.25 - 7.34 (m, 3 H), 7.90 (d, *J*=8.08 Hz, 2 H), 8.17 (s, 1 H), 9.59 (s, 1 H). ESI-MS: *m/z* 425.5 $(M + H)^+$.

Example 63: 4-((3-amino-5-(trifluoromethyl)-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



[0385] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.85 (s, 2 H), 5.45 (s, 2 H), 5.85 (s, 2 H), 6.56 (td, *J*=7.58, 1.26 Hz, 1 H), 6.74 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.89 - 6.97 (m, 1 H), 7.10 (s, 1 H), 7.28 (d, *J*=8.08 Hz, 2 H), 7.50 - 7.57 (m, 1 H), 7.66 (d, *J*=8.84 Hz, 1 H), 7.87 (d, *J*=8.08 Hz, 2 H), 8.20 (s, 1 H), 9.55 (s, 1 H). ESI-MS: *m/z* 425.5 $(M + H)^+$.

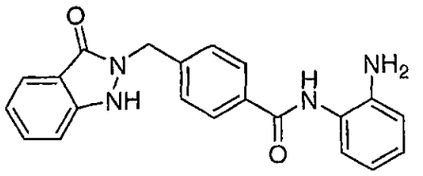
Example 64: N-(2-aminophenyl)-4-((3-oxo-2,3-dihydro-1H-indazol-1-yl)methyl)benzamide



[0386] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 5.46 (s, 2 H), 6.92 (s, 1 H), 7.01 (t, *J*=7.33 Hz, 2 H), 7.12 (s, 1 H), 7.25 (s, 1 H), 7.33 (d, *J*=7.83 Hz,

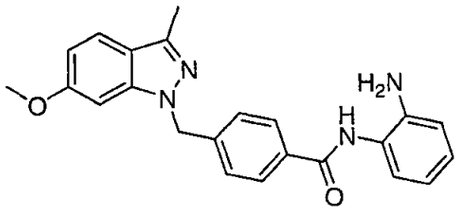
3 H), 7.55 (d, *J*=8.34 Hz, 1 H), 7.64 (d, *J*=8.08 Hz, 1 H), 7.90 (d, *J*=7.58 Hz, 2 H), 9.92 (s, 1 H). ESI-MS: *m/z* 359.3 $(M + H)^+$.

Example 65: N-(2-aminophenyl)-4-((3-oxo-1H-indazol-2(3H)-yl)methyl)benzamide



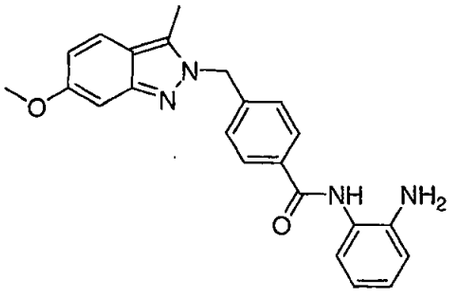
[0387] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 5.51 (s, 2 H), 6.89 (s, 1 H), 7.02 (s, 2 H), 7.15 (s, 1 H), 7.27 (s, 1 H), 7.37 (s, 2 H), 7.66 (s, 3 H), 8.02 (d, *J*=7.33 Hz, 2 H), 9.96 (s, 1 H), 11.98 (s, 1 H). ESI-MS: *m/z* 359.3 $(M + H)^+$.

Example 66: N-(2-aminophenyl)-4-((6-methoxy-3-methyl-1H-indazol-1-yl)methyl)benzamide



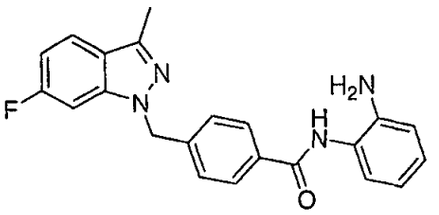
[0388] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.41 - 2.46 (m, 3 H), 3.78 - 3.84 (m, 3 H), 4.88 (s, 2 H), 5.60 (s, 2 H), 6.54 - 6.62 (m, 1 H), 6.72 - 6.79 (m, 2 H), 6.92 - 6.99 (m, 1 H), 7.11 - 7.18 (m, 2 H), 7.32 (d, *J*=8.34 Hz, 2 H), 7.58 (d, *J*=8.59 Hz, 1 H), 7.90 (d, *J*=8.34 Hz, 2 H), 9.58 (s, 1 H). ESI-MS: *m/z* 387.2 $(M + H)^+$.

Example 67: N-(2-aminophenyl)-4-((6-methoxy-3-methyl-2H-indazol-2-yl)methyl)benzamide



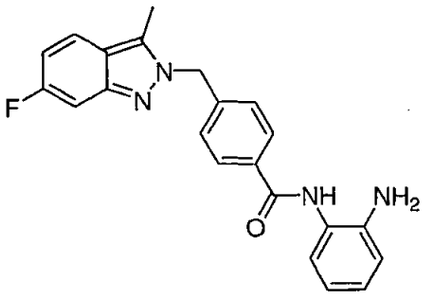
[0389] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.55 (s, 3 H), 3.79 (s, 3 H), 4.88 (s, 2 H), 5.63 (s, 2 H), 6.55 - 6.62 (m, 1 H), 6.62 - 6.68 (m, 1 H), 6.77 (dd, *J*=7.83, 1.26 Hz, 1 H), 6.86 (d, *J*=2.02 Hz, 1 H), 6.93 - 7.00 (m, 1 H), 7.14 (d, *J*=7.33 Hz, 1 H), 7.27 (d, *J*=8.34 Hz, 2 H), 7.55 (d, *J*=9.09 Hz, 1 H), 7.93 (d, *J*=8.08 Hz, 2 H), 9.62 (s, 1 H). ESI-MS: *m/z* 387.2 $(M + H)^+$.

Example 68: N-(2-aminophenyl)-4-((6-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide



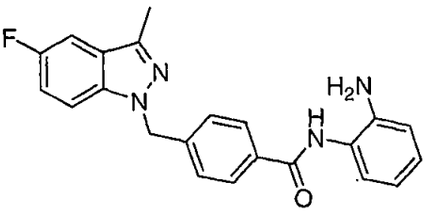
[0390] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.47 - 2.49 (m, 3 H), 4.87 (s, 2 H), 5.61 (s, 2 H), 6.55 - 6.61 (m, 1 H), 6.76 (dd, *J*=8.08, 1.52 Hz, 1 H), 6.93 - 7.02 (m, 2 H), 7.14 (d, *J*=7.83 Hz, 1 H), 7.34 (d, *J*=8.34 Hz, 2 H), 7.54 - 7.61 (m, 1 H), 7.77 (dd, *J*=8.84, 5.31 Hz, 1 H), 7.90 (d, *J*=8.34 Hz, 2 H), 9.57 (s, 1 H). ESI-MS: *m/z* 375.3 $(M + H)^+$.

Example 69: N-(2-aminophenyl)-4-((6-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide



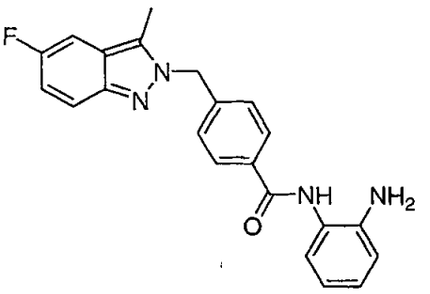
[0391] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.59 - 2.63 (m, 3 H), 4.88 (s, 2 H), 5.69 (s, 2 H), 6.53 - 6.62 (m, 1 H), 6.78 (dd, *J*=7.75, 1.52 Hz, 1 H), 6.87 - 6.99 (m, 2 H), 7.15 (d, *J*=7.33 Hz, 1 H), 7.24 - 7.35 (m, 3 H), 7.77 (dd, *J*=9.09, 5.56 Hz, 1 H), 7.94 (d, *J*=8.08 Hz, 2 H), 9.62 (s, 1 H). ESI-MS: *m/z* 375.3 $(M + H)^+$.

Example 70: N-(2-aminophenyl)-4-((5-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide



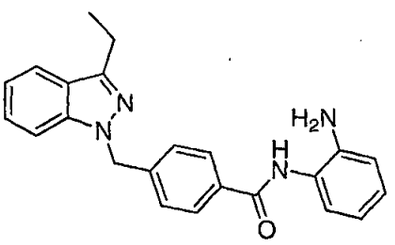
[0392] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.46 - 2.49 (m, 3 H), 4.87 (s, 2 H), 5.66 (s, 2 H), 6.53 - 6.62 (m, 1 H), 6.77 (d, *J*=1.26 Hz, 1 H), 6.91 - 7.01 (m, 1 H), 7.14 (d, *J*=7.07 Hz, 1 H), 7.25 - 7.35 (m, 3 H), 7.55 (d, *J*=2.27 Hz, 1 H), 7.70 (dd, *J*=9.09, 4.29 Hz, 1 H), 7.89 (d, *J*=8.08 Hz, 2 H), 9.57 (s, 1 H). ESI-MS: *m/z* 375.3 $(M + H)^+$.

Example 71: N-(2-aminophenyl)-4-((5-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide



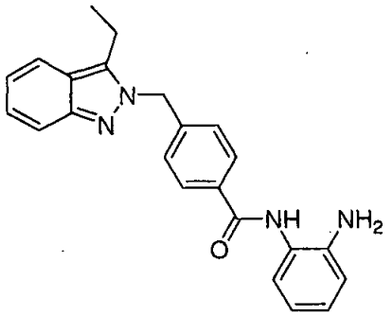
[0393] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.58 (s, 3 H), 4.88 (s, 2 H), 5.72 (s, 2 H), 6.55 - 6.62 (m, 1 H), 6.77 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.93 - 7.00 (m, 1 H), 7.14 (td, *J*=9.35, 2.53 Hz, 2 H), 7.29 (d, *J*=8.34 Hz, 2 H), 7.46 (dd, *J*=9.60, 2.02 Hz, 1 H), 7.62 (dd, *J*=9.35, 4.55 Hz, 1 H), 7.94 (d, *J*=8.34 Hz, 2 H), 9.62 (s, 1 H). ESI-MS: *m/z* 375.4 $(M + H)^+$.

Example 72: N-(2-aminophenyl)-4-((3-ethyl-1H-indazol-1-yl)methyl)benzamide



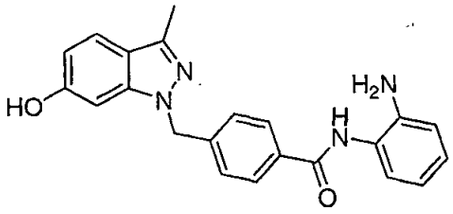
[0394] 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 - 1.36 (m, 3 H), 2.95 (q, *J*=7.58 Hz, 2 H), 4.87 (s, 2 H), 5.67 (s, 2 H), 6.53 - 6.62 (m, 1 H), 6.72 - 6.81 (m, 1 H), 6.91 - 7.00 (m, 1 H), 7.08 - 7.18 (m, 2 H), 7.27 - 7.39 (m, 3 H), 7.63 (d, *J*=8.34 Hz, 1 H), 7.77 (d, *J*=8.08 Hz, 1 H), 7.89 (d, *J*=8.08 Hz, 1 H), 9.57 (s, 1 H). ESI-MS: *m/z* 371.4 $(M + H)^+$.

Example 73: N-(2-aminophenyl)-4-((3-ethyl-2H-indazol-2-yl)methyl)benzamide



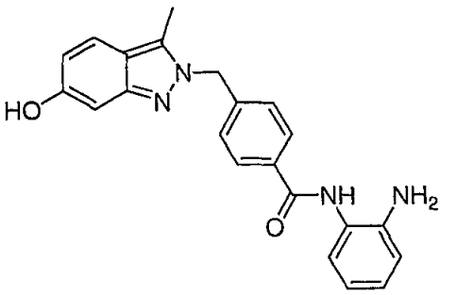
[0395] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 - 1.20 (m, 3 H), 3.09 (q, *J*=7.58 Hz, 2 H), 4.89 (s, 2 H), 5.75 (s, 2 H), 6.55 - 6.62 (m, 1 H), 6.74 - 6.80 (m, 1 H), 6.93 - 7.03 (m, 2 H), 7.14 (d, *J*=7.58 Hz, 1 H), 7.21 - 7.31 (m, 3 H), 7.56 (d, *J*=8.84 Hz, 1 H), 7.72 (d, *J*=8.59 Hz, 1 H), 7.93 (d, *J*=8.34 Hz, 2 H), 9.63 (s, 1 H). ESI-MS: *m/z* 371.4 $(M + H)^+$.

Example 74: N-(2-aminophenyl)-4-((6-hydroxy-3-methyl-1H-indazol-1-yl)methyl)benzamide



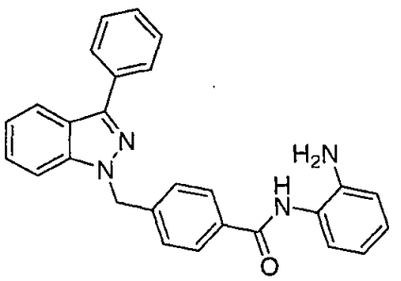
[0396] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.42 (s, 3 H), 5.52 (s, 2 H), 6.59 - 6.69 (m, 1 H), 6.74 (d, *J*=1.77 Hz, 1 H), 6.94 (s, 1 H), 7.04 (s, 1 H), 7.08 - 7.20 (m, 2 H), 7.23 - 7.34 (m, 3 H), 7.50 (d, *J*=8.84 Hz, 1 H), 7.92 (d, *J*=8.34 Hz, 2 H), 9.95 (s, 1 H). ESI-MS: *m/z* 373.3 $(M + H)^+$.

Example 75: N-(2-aminophenyl)-4-((6-hydroxy-3-methyl-2H-indazol-2-yl)methyl)benzamide



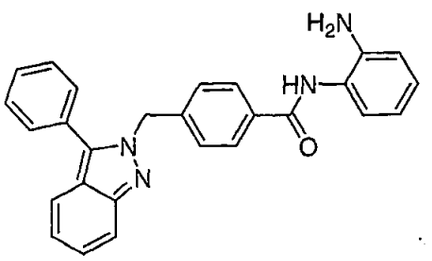
[0397] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 2.54 (s, 3 H), 3.97 (s, 1 H), 5.62 (s, 2 H), 6.56 - 6.65 (m, 1 H), 6.69 (d, *J*=1.52 Hz, 1 H), 7.01 (s, 1 H), 7.10 (d, *J*=7.83 Hz, 1 H), 7.14 - 7.23 (m, 1 H), 7.30 (d, *J*=8.08 Hz, 3 H), 7.52 (d, *J*=8.84 Hz, 1 H), 7.96 (d, *J*=8.34 Hz, 2 H), 10.07 (s, 1 H). ESI-MS: *m/z* 373.3 $(M + H)^+$.

Example 76: N-(2-aminophenyl)-4-((3-phenyl-1H-indazol-1-yl)methyl)benzamide



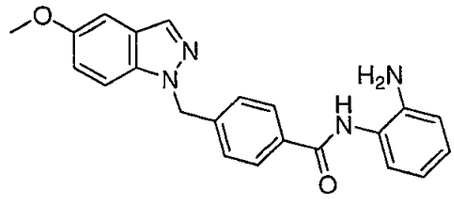
[0398] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.86 (s, 2 H), 5.78 - 5.87 (m, 2 H), 6.53 - 6.61 (m, 1 H), 6.75 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.91 - 6.99 (m, 1 H), 7.13 (d, *J*=7.83 Hz, 1 H), 7.22 - 7.30 (m, 1 H), 7.38 - 7.49 (m, 3 H), 7.50 - 7.57 (m, 2 H), 7.80 (d, *J*=8.34 Hz, 1 H), 7.91 (d, *J*=8.34 Hz, 2 H), 8.00 (d, *J*=7.07 Hz, 2 H), 8.11 (d, *J*=8.08 Hz, 1 H), 9.57 (s, 1 H). ESI-MS: *m/z* 419.4 $(M + H)^+$.

Example 77: N-(2-aminophenyl)-4-((3-phenyl-2H-indazol-2-yl)methyl)benzamide



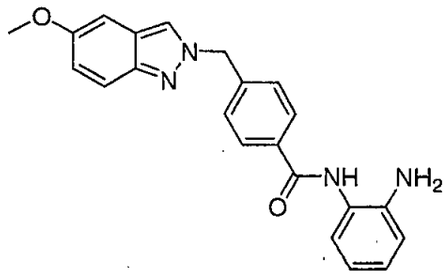
[0399] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 2 H), 5.77 (s, 2 H), 6.54 - 6.61 (m, 1 H), 6.76 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.92 - 6.99 (m, 1 H), 7.09 - 7.17 (m, 3 H), 7.30 - 7.37 (m, 1 H), 7.52 - 7.63 (m, 3 H), 7.69 (d, *J*=8.84 Hz, 1 H), 7.89 (d, *J*=8.08 Hz, 2 H), 9.60 (s, 1 H). ESI-MS: *m/z* 419.4 $(M + H)^+$.

Example 78: N-(2-aminophenyl)-4-((5-methoxy-1H-indazol-1-yl)methyl)benzamide



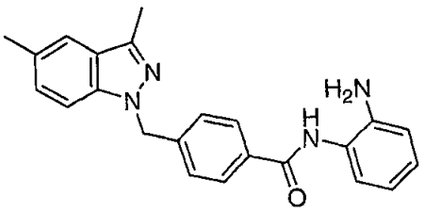
[0400] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 3.78 (s, 3 H), 5.71 (s, 2 H), 6.53 - 6.64 (m, 1 H), 6.78 (s, 1 H), 6.91 - 7.00 (m, 1 H), 7.01 - 7.08 (m, 1 H), 7.13 (s, 1 H), 7.20 (d, *J*=2.27 Hz, 1 H), 7.30 (d, *J*=8.08 Hz, 2 H), 7.61 (d, *J*=9.09 Hz, 1 H), 7.89 (d, *J*=8.08 Hz, 2 H), 8.01 (s, 1 H), 9.59 (s, 1 H). ESI-MS: *m/z* 373.3 $(M + H)^+$.

Example 79: N-(2-aminophenyl)-4-((5-methoxy-2H-indazol-2-yl)methyl)benzamide



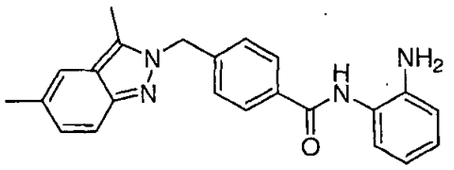
[0401] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.77 (s, 3 H), 5.69 (s, 2 H), 6.84 - 6.95 (m, 2 H), 6.95 - 7.05 (m, 2 H), 7.07 - 7.15 (m, 1 H), 7.26 (d, *J*=7.58 Hz, 1 H), 7.42 (d, *J*=8.34 Hz, 2 H), 7.51 (d, *J*=9.09 Hz, 1 H), 7.96 (d, *J*=8.34 Hz, 2 H), 8.35 (s, 1 H), 9.91 (s, 1 H). ESI-MS: *m/z* 373.3 $(M + H)^+$.

Example 80: N-(2-aminophenyl)-4-((3,5-dimethyl-1H-indazol-1-yl)methyl)benzamide



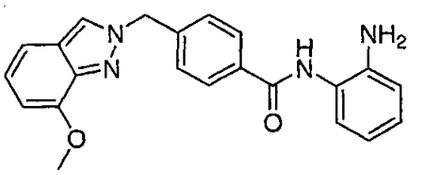
[0402] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3 H), 2.44 - 2.48 (m, 3 H), 4.87 (s, 2 H), 5.62 (s, 2 H), 6.54 - 6.61 (m, 1 H), 6.76 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.92 - 6.99 (m, 1 H), 7.13 (d, *J*=7.07 Hz, 1 H), 7.20 (dd, *J*=8.59, 1.26 Hz, 1 H), 7.28 (d, *J*=8.08 Hz, 2 H), 7.49 (s, 1 H), 7.52 (d, *J*=8.59 Hz, 1 H), 7.88 (d, *J*=8.08 Hz, 2 H), 9.57 (s, 1 H). ESI-MS: *m/z* 371.4 $(M + H)^+$.

Example 81: N-(2-aminophenyl)-4-((3,5-dimethyl-2H-indazol-2-yl)methyl)benzamide



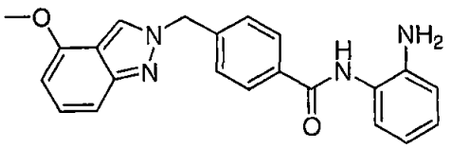
[0403] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H), 2.56 (s, 3 H), 4.88 (s, 2 H), 5.69 (s, 2 H), 6.54 - 6.62 (m, 1 H), 6.77 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.93 - 7.00 (m, 1 H), 7.07 (dd, *J*=8.84, 1.52 Hz, 1 H), 7.14 (d, *J*=7.07 Hz, 1 H), 7.26 (d, *J*=8.34 Hz, 2 H), 7.41 (s, 1 H), 7.45 (d, *J*=8.84 Hz, 1 H), 7.93 (d, *J*=8.08 Hz, 2 H), 9.62 (s, 1 H). ESI-MS: *m/z* 371.4 $(M + H)^+$.

Example 82: N-(2-aminophenyl)-4-((7-methoxy-2H-indazol-2-yl)methyl)benzamide



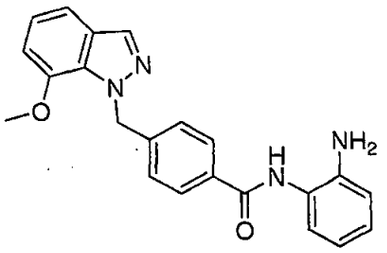
[0404] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.88 (s, 3 H), 4.89 (s, 2 H), 5.70 (s, 2 H), 6.54 - 6.65 (m, 2 H), 6.76 (d, *J*=7.58 Hz, 1 H), 6.90 - 7.01 (m, 2 H), 7.15 (s, 1 H), 7.24 (d, *J*=8.34 Hz, 1 H), 7.41 (d, *J*=7.58 Hz, 2 H), 7.95 (d, *J*=8.08 Hz, 2 H), 8.47 (s, 1 H), 9.62 (s, 1 H). ESI-MS: *m/z* 373.1 $(M + H)^+$.

Example 83: N-(2-aminophenyl)-4-((4-methoxy-2H-indazol-2-yl)methyl)benzamide



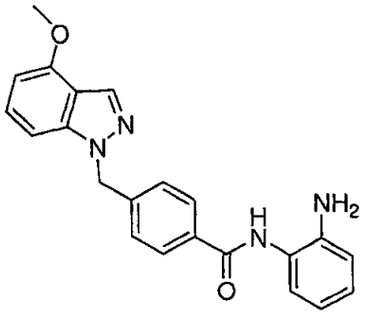
[0405] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.89 (s, 3 H), 4.89 (s, 2 H), 5.69 (s, 2 H), 6.36 - 6.46 (m, 1 H), 6.53 - 6.64 (m, 1 H), 6.76 (d, *J*=8.08 Hz, 1 H), 6.91 - 7.02 (m, 1 H), 7.11 - 7.20 (m, 3 H), 7.42 (d, *J*=7.83 Hz, 2 H), 7.94 (d, *J*=7.83 Hz, 2 H), 8.55 (s, 1 H), 9.62 (s, 1 H). ESI-MS: *m/z* 373.2 $(M + H)^+$.

Example 84: N-(2-aminophenyl)-4-((7-methoxy-1H-indazol-1-yl)methyl)benzamide



[0406] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.92 (s, 3 H), 4.87 (s, 2 H), 5.85 (s, 2 H), 6.54 - 6.61 (m, 1 H), 6.76 (d, *J*=7.83 Hz, 1 H), 6.87 (d, *J*=7.58 Hz, 1 H), 6.92 - 6.99 (m, 1 H), 7.03 - 7.10 (m, 1 H), 7.13 (d, *J*=7.83 Hz, 1 H), 7.24 (d, *J*=7.83 Hz, 2 H), 7.32 (d, *J*=8.08 Hz, 1 H), 7.88 (d, *J*=7.58 Hz, 2 H), 8.09 (s, 1 H), 9.56 (s, 1 H). ESI-MS: *m/z* 373.3 $(M + H)^+$.

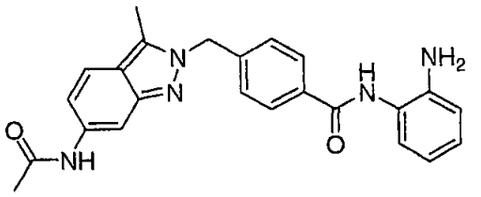
Example 85: N-(2-aminophenyl)-4-((4-methoxy-1H-indazol-1-yl)methyl)benzamide



[0407] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.93 (s, 3 H), 4.87 (s, 2 H), 5.72 (s, 2 H), 6.54 - 6.63 (m, 2 H), 6.76 (d, *J*=7.83 Hz, 1 H), 6.90 - 7.00 (m, 1 H), 7.13 (d, *J*=7.83 Hz, 1

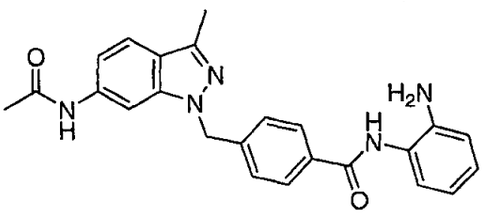
H), 7.23 - 7.33 (m, 4 H), 7.89 (d, *J*=7.83 Hz, 2 H), 8.10 (s, 1 H), 9.58 (s, 1 H). ESI-MS: *m/z* 373.3 $(M + H)^+$.

Example 86: 4-((6-acetamido-3-methyl-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide



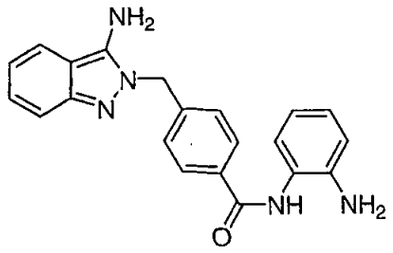
[0408] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.06 (s, 3 H), 2.53 - 2.57 (m, 2 H), 4.88 (s, 2 H), 5.66 (s, 2 H), 6.53 - 6.63 (m, 1 H), 6.76 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.93 - 7.04 (m, 2 H), 7.14 (d, *J*=7.07 Hz, 1 H), 7.27 (d, *J*=8.08 Hz, 2 H), 7.59 (d, *J*=9.09 Hz, 1 H), 7.93 (d, *J*=8.08 Hz, 2 H), 7.99 (s, 1 H), 9.62 (s, 1 H), 9.91 (s, 1 H). ESI-MS: *m/z* 414.3 $(M + H)^+$.

Example 87: 4-((6-acetamido-3-methyl-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



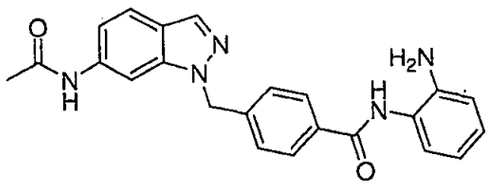
[0409] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.06 (s, 3 H), 2.44 - 2.48 (m, 3 H), 4.88 (s, 2 H), 5.56 (s, 2 H), 6.53 - 6.63 (m, 1 H), 6.73 - 6.81 (m, 1 H), 6.91 - 7.01 (m, 1 H), 7.08 - 7.19 (m, 2 H), 7.24 (d, *J*=8.08 Hz, 2 H), 7.63 (d, *J*=8.59 Hz, 1 H), 7.89 (d, *J*=8.08 Hz, 2 H), 8.01 (s, 1 H), 9.58 (s, 1 H), 10.09 (s, 1 H). ESI-MS: *m/z* 414.3 $(M + H)^+$.

Example 88: 4-((3-amino-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide



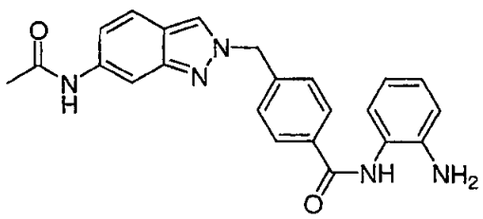
[0410] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.88 (s, 2 H), 5.46 (s, 2 H), 6.27 (s, 2 H), 6.58 (t, *J*=7.45 Hz, 1 H), 6.65 (t, *J*=7.33 Hz, 1 H), 6.76 (d, *J*=8.08 Hz, 1 H), 6.96 (t, *J*=7.58 Hz, 1 H), 7.05 (t, *J*=7.58 Hz, 1 H), 7.12 - 7.20 (m, 2 H), 7.29 (d, *J*=7.83 Hz, 2 H), 7.63 (d, *J*=8.34 Hz, 1 H), 7.91 (d, *J*=7.83 Hz, 2 H), 9.6 (s, 1H). ESI-MS: *m/z* 358.2 $(M + H)^+$.

Example 89: 4-((6-acetamido-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



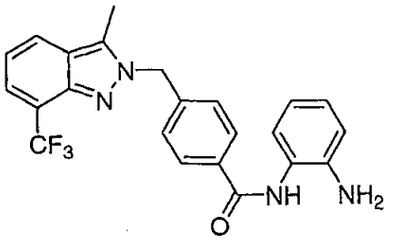
[0411] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.93 - 2.13 (m, 3 H), 4.87 (s, 2 H), 5.66 (s, 2 H), 6.53 - 6.61 (m, 1 H), 6.75 (dd, *J*=7.96, 1.39 Hz, 1 H), 6.91 - 6.98 (m, 1 H), 7.13 (dd, *J*=8.72, 1.64 Hz, 2 H), 7.24 (d, *J*=8.34 Hz, 2 H), 7.69 (d, *J*=8.59 Hz, 1 H), 7.90 (d, *J*=8.08 Hz, 2 H), 8.05 (s, 1 H), 8.08 (s, 1 H), 9.59 (s, 1 H), 10.11 (s, 1 H). ESI-MS: *m/z* 400.2 $(M + H)^+$.

Example 90: 4-((6-acetamido-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide



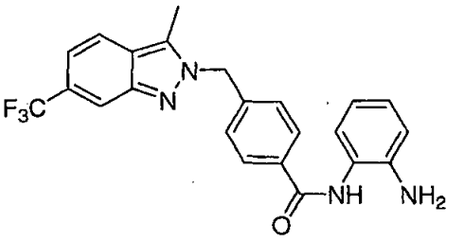
[0412] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.06 (s, 3 H), 4.88 (s, 2 H), 5.67 (s, 2 H), 6.51 - 6.65 (m, 1 H), 6.76 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.89 - 7.00 (m, 1 H), 7.06 (dd, *J*=8.84, 1.77 Hz, 1 H), 7.14 (d, *J*=7.33 Hz, 1 H), 7.40 (d, *J*=8.08 Hz, 2 H), 7.63 (d, *J*=8.34 Hz, 1 H), 7.94 (d, *J*=8.08 Hz, 2 H), 8.04 (s, 1 H), 8.42 (s, 1 H), 9.62 (s, 1 H), 9.93 (s, 1 H). ESI-MS: *m/z* 400.2 $(M + H)^+$.

Example 91: N-(2-aminophenyl)-4-((3-methyl-7-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide



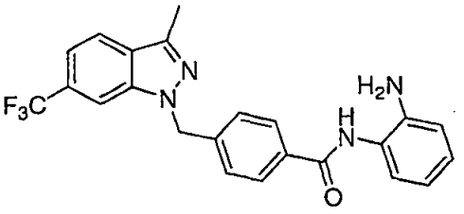
[0413] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.66 (s, 3 H), 4.89 (s, 2 H), 5.82 (s, 2 H), 6.58 (t, *J*=7.45 Hz, 1 H), 6.76 (d, *J*=7.83 Hz, 1 H), 6.96 (t, *J*=7.58 Hz, 1 H), 7.14 (ddd, *J*=7.26, 3.92, 3.73 Hz, 2 H), 7.28 (d, *J*=8.08 Hz, 2 H), 7.66 (d, *J*=6.82 Hz, 1 H), 7.94 (d, *J*=8.08 Hz, 2 H), 8.05 (d, *J*=8.34 Hz, 1 H), 9.62 (s, 1H). ESI-MS: *m/z* 425.2 $(M + H)^+$.

Example 92: N-(2-aminophenyl)-4-((3-methyl-6-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide



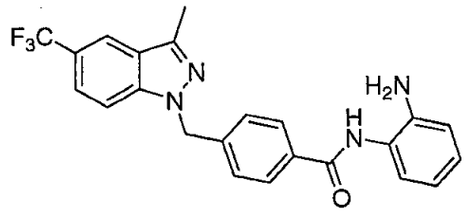
[0414] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.67 (s, 3 H), 4.88 (s, 2 H), 5.80 (s, 2 H), 6.58 (t, *J*=7.58 Hz, 1 H), 6.76 (d, *J*=7.83 Hz, 1 H), 6.96 (t, *J*=7.71 Hz, 1 H), 7.14 (d, *J*=7.83 Hz, 1 H), 7.22 (d, *J*=8.84 Hz, 1 H), 7.30 (d, *J*=8.08 Hz, 2 H), 7.92 - 8.02 (m, 4 H), 9.63 (s, 1H). ESI-MS: *m/z* 425.2 $(M + H)^+$.

Example 93: N-(2-aminophenyl)-4-((3-methyl-6-(trifluoromethyl)-1H-indazol-1-yl)methyl)benzamide



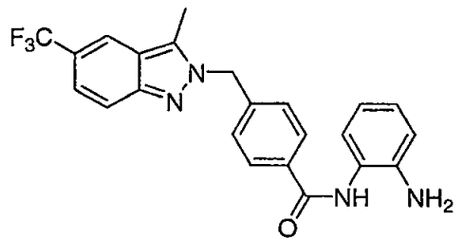
[0415] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.55 (s, 3 H), 4.87 (s, 2 H), 5.79 (s, 2 H), 6.57 (t, *J*=7.33 Hz, 1 H), 6.75 (d, *J*=8.08 Hz, 1 H), 6.95 (t, *J*=7.58 Hz, 1 H), 7.13 (d, *J*=7.58 Hz, 1 H), 7.33 (d, *J*=8.08 Hz, 2 H), 7.41 (d, *J*=8.59 Hz, 1 H), 7.90 (d, *J*=7.83 Hz, 2 H), 7.98 (d, *J*=8.34 Hz, 1 H), 8.24 (s, 1 H), 9.58 (s, 1H). ESI-MS: *m/z* 425.2 $(M + H)^+$.

Example 94: N-(2-aminophenyl)-4-((3-methyl-5-(trifluoromethyl)-1H-indazol-1-yl)methyl)benzamide



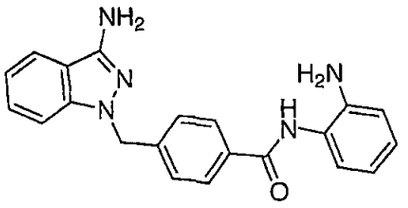
[0416] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.57 (s, 3 H), 4.87 (s, 2 H), 5.73 (s, 2 H), 6.57 (t, *J*=7.45 Hz, 1 H), 6.75 (d, *J*=7.83 Hz, 1 H), 6.95 (t, *J*=7.45 Hz, 1 H), 7.13 (d, *J*=7.58 Hz, 1 H), 7.33 (d, *J*=7.83 Hz, 2 H), 7.67 (d, *J*=8.84 Hz, 1 H), 7.90 (d, *J*=8.34 Hz, 3 H), 8.22 (s, 1 H), 9.58 (s, 1H). ESI-MS: *m/z* 425.2 $(M + H)^+$.

Example 95: N-(2-aminophenyl)-4-((3-methyl-5-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide



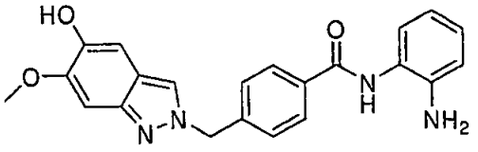
[0417] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.70 (s, 3 H), 4.88 (s, 2 H), 5.78 (s, 2 H), 6.58 (t, *J*=7.45 Hz, 1 H), 6.76 (d, *J*=8.08 Hz, 1 H), 6.93 - 6.99 (m, 1 H), 7.14 (d, *J*=7.33 Hz, 1 H), 7.31 (d, *J*=8.08 Hz, 2 H), 7.44 (d, *J*=8.84 Hz, 1 H), 7.75 (d, *J*=9.09 Hz, 1 H), 7.94 (d, *J*=8.08 Hz, 2 H), 8.25 (s, 1 H), 9.63 (s, 1H). ESI-MS: *m/z* 425.2 $(M + H)^+$.

Example 96: 4-((3-amino-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide



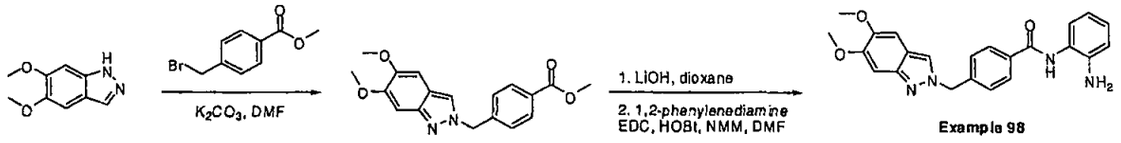
[0418] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (s, 2 H), 5.39 (s, 2 H), 5.52 (s, 2 H), 6.57 (t, *J*=7.45 Hz, 1 H), 6.75 (d, *J*=7.83 Hz, 1 H), 6.94 (q, *J*=7.75 Hz, 2 H), 7.13 (d, *J*=7.58 Hz, 1 H), 7.27 (t, *J*=8.21 Hz, 3 H), 7.44 (d, *J*=8.34 Hz, 1 H), 7.70 (d, *J*=7.83 Hz, 1 H), 7.86 (d, *J*=7.83 Hz, 2 H), 9.55 (s, 1 H). ESI-MS: *m/z* 358.4 $(M + H)^+$.

Example 97: N-(2-aminophenyl)-4-((5-hydroxy-6-methoxy-2H-indazol-2-yl)methyl)benzamide



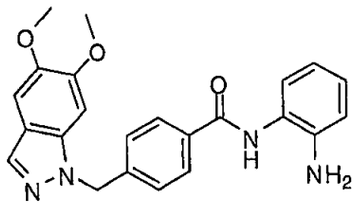
[0419] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.81 (s, 2 H) 4.89 (s, 2 H) 5.58 (s, 2 H) 6.59 (t, *J*=7.58 Hz, 1 H) 6.77 (dd, *J*=7.96, 1.39 Hz, 1 H) 6.85 (s, 1 H) 6.91 (s, 1 H) 6.96 (dd, *J*=15.16, 1.52 Hz, 1 H) 7.15 (d, *J*=7.33 Hz, 1 H) 7.36 (d, *J*=8.08 Hz, 2 H) 7.93 (d, *J*=8.08 Hz, 2 H) 8.11 (s, 1 H) 8.82 (s, 1 H) 9.62 (s, 1 H). ESI-MS: *m/z* 389.4 $(M + H)^+$.

Example 98: N-(2-aminophenyl)-4-((5,6-dimethoxy-2H-indazol-2-yl)methyl)benzamide



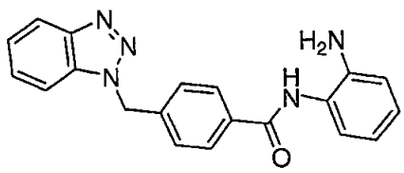
[0420] 5,6-dimethoxy-1H-indazole was prepared according to the procedure described in Dennler *et al.*, "Synthesis of indazoles using polyphosphoric acid- I" **Tetrahedron**, **22**(9): 3131-3141 (1966), which is hereby incorporated by reference in its entirety. The title compound was then prepared using a procedure analogous to that described in Scheme 1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.78 (s, 3 H) 3.83 (s, 3 H) 4.88 (br. s., 2 H) 5.69 (s, 2 H) 6.58 (t, *J*=7.45 Hz, 1 H) 6.77 (d, *J*=1.01 Hz, 1 H) 6.96 (dd, *J*=15.16, 1.26 Hz, 1 H) 7.17 (s, 1 H) 7.13 (d, *J*=7.58 Hz, 1 H) 7.27 (s, 1 H) 7.30 (d, *J*=8.34 Hz, 2 H) 7.83 - 7.93 (m, 3 H) 9.59 (s, 1 H). ESI-MS: *m/z* 403.4 $(M + H)^+$.

Example 99: N-(2-aminophenyl)-4-((5,6-dimethoxy-1H-indazol-1-yl)methyl)benzamide



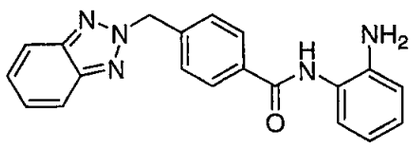
[0421] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.78 (s, 3 H) 3.83 (s, 3 H) 4.88 (br. s., 2 H) 5.69 (s, 2 H) 6.58 (s, 1 H) 6.77 (d, *J*=1.01 Hz, 1 H) 6.95 (d, *J*=7.33 Hz, 1 H) 7.17 (s, 1 H) 7.13 (d, *J*=7.58 Hz, 1 H) 7.27 (s, 1 H) 7.30 (d, *J*=8.34 Hz, 2 H) 7.82 - 7.94 (m, 3 H) 9.59 (s, 1 H). ESI-MS: *m/z* 403.4 $(M + H)^+$.

Example 100: 4-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide



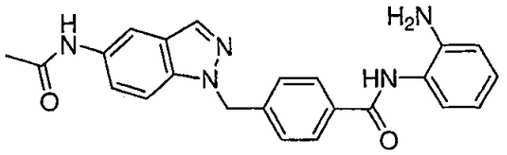
[0422] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.88 (s, 2 H), 6.08 (s, 2 H), 6.57 (t, *J*=7.58 Hz, 1 H), 6.74 - 6.78 (m, 1 H), 6.93 - 6.98 (m, 1 H), 7.13 (d, *J*=7.58 Hz, 1 H), 7.39 - 7.46 (m, 3 H), 7.55 (t, *J*=7.71 Hz, 1 H), 7.86 (d, *J*=8.34 Hz, 1 H), 7.94 (d, *J*=8.08 Hz, 2 H), 8.07 (d, *J*=8.34 Hz, 1 H), 9.60 (s, 1 H). ESI-MS: *m/z* 344.4 $(M + H)^+$.

Example 101: 4-((2*H*-benzo[*d*][1,2,3]triazol-2-yl)methyl)-*N*-(2-aminophenyl)benzamide



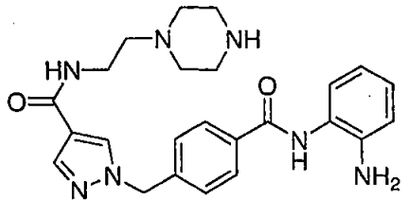
[0423] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.88 (s, 2 H), 6.07 (s, 2 H), 6.55 - 6.61 (m, 1 H), 6.77 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.93 - 6.99 (m, 1 H), 7.15 (d, *J*=7.58 Hz, 1 H), 7.43 - 7.48 (m, 2 H), 7.50 (d, *J*=8.34 Hz, 2 H), 7.91 - 7.99 (m, 4 H), 9.63 (s, 1 H). ESI-MS: *m/z* 344.4 $(M + H)^+$.

Example 102: 4-((5-acetamido-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide



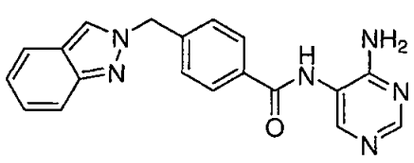
[0424] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.05 (s, 3 H), 5.70 (s, 2 H), 6.95 - 7.03 (m, 4 H), 7.06 - 7.13 (m, 1 H), 7.30 - 7.40 (m, 5 H), 7.64 (d, *J*=9.09 Hz, 1 H), 7.75 (d, *J*=8.84 Hz, 2 H), 7.86 (d, *J*=8.08 Hz, 2 H), 8.11 (d, *J*=17.68 Hz, 2 H), 9.96 (s, 1 H), 10.21 (s, 1 H). ESI-MS: *m/z* 477.3 $(M + H)^+$.

Example 103: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(piperazin-1-yl)ethyl)-1H-pyrazole-4-carboxamide



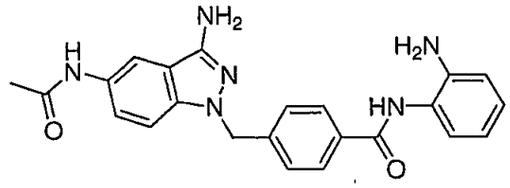
[0425] ^{1}H NMR (400 MHz, DMSO-d_6) of the *bis*-trifluoroacetic acid salt: δ ppm 3.06 (s, 2 H), 3.22 (s, 4 H), 3.30 (s, 4 H), 3.44 - 3.52 (m, 2 H), 5.46 (s, 2 H), 6.79 (t, *J*=7.33 Hz, 1 H), 6.93 (d, *J*=7.07 Hz, 1 H), 7.07 (td, *J*=7.64, 1.39 Hz, 1 H), 7.22 (d, *J*=8.59 Hz, 1 H), 7.38 (d, *J*=8.34 Hz, 2 H), 7.90 (d, *J*=0.51 Hz, 1 H), 7.97 (d, *J*=8.08 Hz, 2 H), 8.29 - 8.32 (m, 1 H), 8.32 - 8.35 (m, 1 H), 9.85 (s, 1 H). ESI-MS: *m/z* 448.4 $(M + H)^+$.

Example 104: 4-((2*H*-indazol-2-yl)methyl)-*N*-(4-aminopyrimidin-5-yl)benzamide



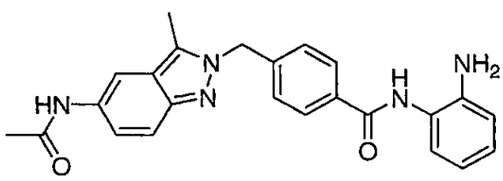
[0426] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.74 (s, 2 H), 6.82 (s, 2 H), 7.00 - 7.08 (m, 1 H), 7.23 (dd, *J*=8.72, 6.69 Hz, 1 H), 7.43 (d, *J*=8.34 Hz, 2 H), 7.59 (d, *J*=8.84 Hz, 1 H), 7.72 (d, *J*=8.34 Hz, 1 H), 7.95 (d, *J*=8.08 Hz, 2 H), 8.15 (s, 1 H), 8.26 (s, 1 H), 8.53 (s, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 345.3 $(M + H)^+$.

Example 105: 4-((5-acetamido-3-amino-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



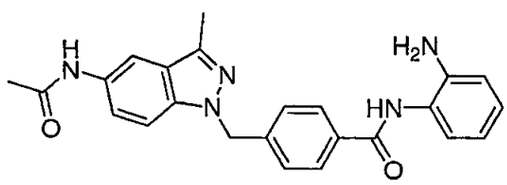
[0427] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.03 (s, 3 H), 4.86 (s, 2 H), 5.35 (s, 2 H), 5.43 (s, 2 H), 6.57 (t, *J*=7.45 Hz, 1 H), 6.75 (d, *J*=7.07 Hz, 1 H), 6.92 - 6.98 (m, 1 H), 7.13 (d, *J*=7.33 Hz, 1 H), 7.24 - 7.31 (m, 3 H), 7.35 - 7.41 (m, 1 H), 7.86 (d, *J*=7.83 Hz, 2 H), 7.96 (s, 1 H), 9.55 (s, 1 H), 9.81 (s, 1 H). ESI-MS: *m/z* 415.3 $(M + H)^+$.

Example 106: 4-((5-acetamido-3-methyl-2*H*-indazol-2-yl)methyl)-*N*-(2-aminophenyl)benzamide



[0428] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.05 (s, 3 H), 2.53 (s, 3 H), 4.88 (s, 2 H), 5.68 (s, 2 H), 6.58 (t, *J*=7.45 Hz, 1 H), 6.76 (d, *J*=7.83 Hz, 1 H), 6.93 - 6.98 (m, 1 H), 7.14 (d, *J*=7.83 Hz, 1 H), 7.20 (dd, *J*=9.22, 1.64 Hz, 1 H), 7.27 (d, *J*=8.34 Hz, 2 H), 7.49 (d, *J*=9.09 Hz, 1 H), 7.93 (d, *J*=8.08 Hz, 2 H), 8.05 (s, 1 H), 9.62 (s, 1 H), 9.85 (s, 1 H). ESI-MS: *m/z* 414.3 $(M + H)^+$.

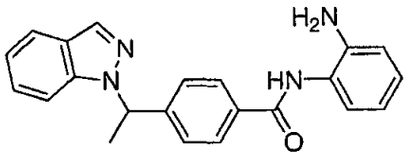
Example 107: 4-((5-acetamido-3-methyl-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide



[0429] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.04 (s, 3 H), 2.45 (s, 3 H), 4.87 (s, 2 H), 5.61 (s, 2 H), 6.54 - 6.60 (m, 1 H), 6.75 (dd, *J*=7.96, 1.39 Hz, 1 H), 6.92 - 6.98 (m, 1 H), 7.13 (d, *J*=7.33 Hz, 1 H), 7.30 (d, *J*=8.34 Hz, 2 H), 7.38 (dd, *J*=9.09, 1.77 Hz, 1 H), 7.57

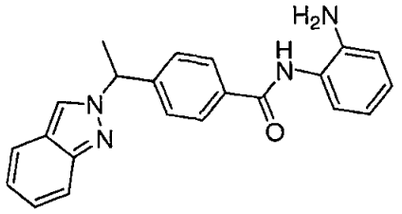
(d, *J*=8.84 Hz, 1 H), 7.88 (d, *J*=8.34 Hz, 2 H), 8.04 (d, *J*=1.26 Hz, 1 H), 9.57 (s, 1 H), 9.94 (s, 1 H). ESI-MS: *m/z* 414.3 $(M + H)^+$.

Example 108: 4-(1-(1*H*-indazol-1-yl)ethyl)-*N*-(2-aminophenyl)benzamide



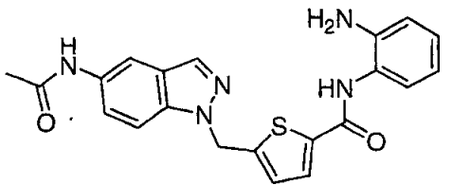
[0430] ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 1.97 (d, *J*=7.07 Hz, 3 H), 4.86 (s, 2 H), 6.16 (q, *J*=6.99 Hz, 1 H), 6.57 (t, *J*=7.58 Hz, 1 H), 6.75 (d, *J*=6.82 Hz, 1 H), 6.91 - 6.98 (m, 1 H), 7.13 (t, *J*=7.20 Hz, 2 H), 7.34 (t, *J*=7.58 Hz, 1 H), 7.39 (d, *J*=8.34 Hz, 2 H), 7.66 (d, *J*=8.34 Hz, 1 H), 7.77 (d, *J*=8.08 Hz, 1 H), 7.87 (d, *J*=8.08 Hz, 2 H), 8.17 (s, 1 H), 9.55 (s, 1 H). ESI-MS: *m/z* 357.4 $(M + H)^+$.

Example 109: 4-(1-(2*H*-indazol-2-yl)ethyl)-*N*-(2-aminophenyl)benzamide



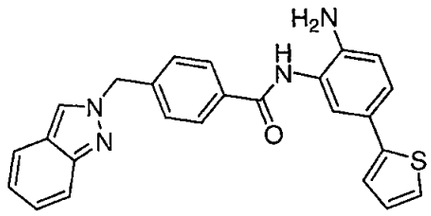
[0431] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.99 (d, *J*=7.07 Hz, 3 H), 4.88 (s, 2 H), 6.04 (q, *J*=6.99 Hz, 1 H), 6.57 (t, *J*=7.58 Hz, 1 H), 6.76 (d, *J*=8.08 Hz, 1 H), 6.91 - 6.99 (m, 1 H), 7.01 - 7.06 (m, 1 H), 7.14 (d, *J*=7.58 Hz, 1 H), 7.20 - 7.26 (m, 1 H), 7.44 (d, *J*=8.34 Hz, 2 H), 7.61 (d, *J*=8.84 Hz, 1 H), 7.71 (d, *J*=8.34 Hz, 1 H), 7.92 (d, *J*=8.34 Hz, 2 H), 8.56 (s, 1 H), 9.60 (s, 1 H). ESI-MS: *m/z* 357.4 $(M + H)^+$.

Example 110: 5-((5-acetamido-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)thiophene-2-carboxamide



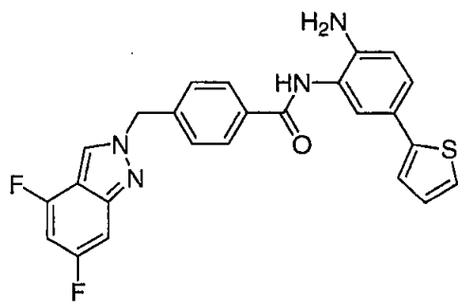
[0432] ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 2.05 (s, 3 H), 4.86 (s, 2 H), 5.85 (s, 2 H), 6.52 - 6.58 (m, 1 H), 6.74 (d, *J*=6.82 Hz, 1 H), 6.92 - 6.97 (m, 1 H), 7.02 - 7.07 (m, 1 H), 7.16 (d, *J*=3.54 Hz, 1 H), 7.44 (dd, *J*=9.09, 1.77 Hz, 1 H), 7.71 (d, *J*=9.09 Hz, 1 H), 7.78 (d, *J*=3.03 Hz, 1 H), 8.08 (s, 1 H), 8.13 (d, *J*=1.26 Hz, 1 H), 9.62 (s, 1 H), 9.97 (s, 1 H). ESI-MS: *m/z* 406.3 $(M + H)^+$.

Example 111: 4-((2*H*-indazol-2-yl)methyl)-*N*-(2-amino-5-(thiophen-2-yl)phenyl)benzamide



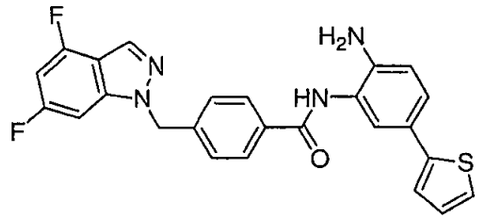
[0433] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 5.75 (s, 2 H), 6.98 - 7.09 (m, 3 H), 7.24 (ddd, *J*=8.46, 6.95, 1.26 Hz, 1 H), 7.31 - 7.35 (m, 1 H), 7.39 - 7.47 (m, 4 H), 7.54 (d, *J*=2.02 Hz, 1 H), 7.60 (dd, *J*=8.84, 1.01 Hz, 1 H), 7.73 (d, *J*=8.34 Hz, 1 H), 7.98 (d, *J*=8.34 Hz, 2 H), 8.54 (d, *J*=1.01 Hz, 1 H), 9.96 (s, 1 H). ESI-MS: *m/z* 425.5 $(M + H)^+$.

Example 112: *N*-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4,6-difluoro-2*H*-indazol-2-yl)methyl)benzamide



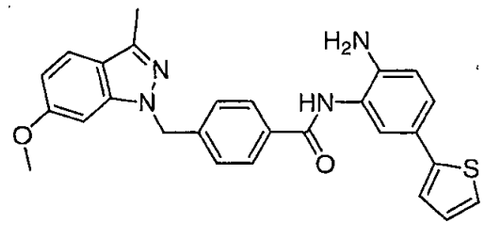
[0434] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 5.76 (s, 2 H), 6.93 (s, 1 H), 7.07 (d, *J*=8.59 Hz, 2 H), 7.30 (d, *J*=3.28 Hz, 1 H), 7.35 - 7.42 (m, 4 H), 7.50 (d, *J*=1.77 Hz, 1 H), 7.62 (d, *J*=9.35 Hz, 1 H), 7.95 (d, *J*=8.08 Hz, 2 H), 8.30 (s, 1 H), 9.86 (s, 1 H). ESI-MS: *m/z* 461.3 $(M + H)^+$.

Example 113: *N*-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4,6-difluoro-1*H*-indazol-1-yl)methyl)benzamide



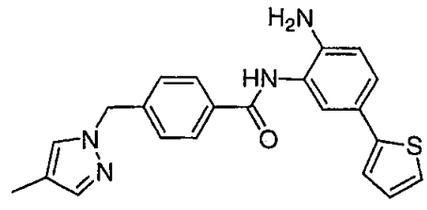
[0435] ^{1}H NMR (400 MHz, DMSO- d_6) of the trifluoroacetic acid salt: δ ppm 5.74 (s, 2 H), 6.85 - 6.97 (m, 2 H), 7.04 - 7.07 (m, 1 H), 7.24 - 7.29 (m, 2 H), 7.34 (dd, *J*=8.34, 1.77 Hz, 1 H), 7.38 (d, *J*=5.05 Hz, 1 H), 7.45 - 7.50 (m, 3 H), 7.98 (d, *J*=8.08 Hz, 2 H), 8.84 (s, 1 H), 9.81 (s, 1 H). ESI-MS: *m/z* 461.3 $(M + H)^+$.

Example 114: *N*-(2-amino-5-(thiophen-2-yl)phenyl)-4-((6-methoxy-3-methyl-1*H*-indazol-1-yl)methyl)benzamide



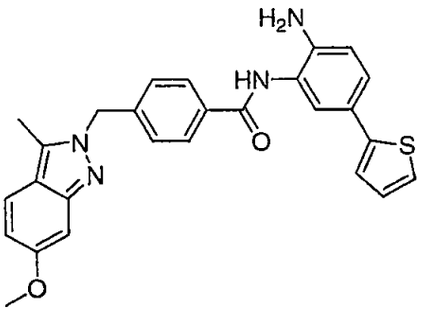
[0436] ^{1}H NMR (400 MHz, DMSO- d_6) of the trifluoroacetic acid salt: δ ppm 2.54 (s, 3 H), 3.78 (s, 3 H), 5.64 (s, 2 H), 6.65 (d, *J*=9.09 Hz, 1 H), 6.86 (s, 2 H), 7.05 (s, 1 H), 7.27 (s, 4 H), 7.37 (s, 1 H), 7.48 (s, 1 H), 7.56 (s, 1 H), 7.96 (d, *J*=7.83 Hz, 2 H), 9.78 (s, 1 H). ESI-MS: *m/z* 469.3 $(M + H)^+$.

Example 115: *N*-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-methyl-1*H*-pyrazol-1-yl)methyl)benzamide



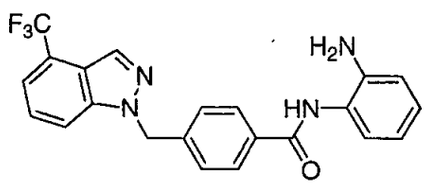
[0437] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.02 (s, 3 H), 5.15 (s, 2 H), 5.34 (s, 2 H), 6.80 (d, *J*=8.34 Hz, 1 H), 7.03 - 7.07 (m, 1 H), 7.24 (d, *J*=3.28 Hz, 1 H), 7.27 - 7.33 (m, 4 H), 7.35 (d, *J*=5.05 Hz, 1 H), 7.46 (s, 1 H), 7.60 (s, 1 H), 7.95 (d, *J*=7.83 Hz, 2 H), 9.71 (s, 1 H). ESI-MS: *m/z* 389.3(M + H)$^+$.

Example 116: *N*-(2-amino-5-(thiophen-2-yl)phenyl)-4-((6-methoxy-3-methyl-2*H*-indazol-2-yl)methyl)benzamide



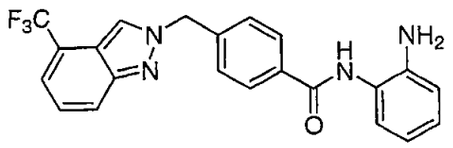
[0438] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 2.43 (s, 3 H), 3.81 (s, 3 H), 5.61 (s, 2 H), 6.74 (dd, *J*=8.84, 2.02 Hz, 1 H), 7.00 (d, *J*=8.34 Hz, 1 H), 7.08 (dd, *J*=5.05, 3.79 Hz, 1 H), 7.15 (d, *J*=2.02 Hz, 1 H), 7.35 (d, *J*=8.08 Hz, 3 H), 7.40 - 7.45 (m, 2 H), 7.52 - 7.60 (m, 2 H), 7.93 (d, *J*=8.08 Hz, 2 H), 9.94 (s, 1 H). ESI-MS: *m/z* 469.3 (M + H)$^+$.

Example 117: *N*-(2-aminophenyl)-4-((4-(trifluoromethyl)-1*H*-indazol-1-yl)methyl)benzamide



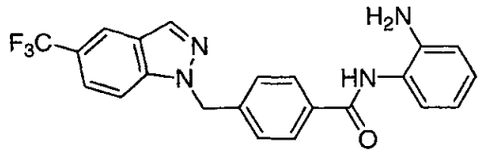
[0439] ^{1}H NMR (400 MHz, DMSO- d_6) of the trifluoroacetic acid salt: δ ppm 5.88 (s, 2 H), 6.95 (t, *J*=7.33 Hz, 1 H), 7.05 (d, *J*=7.33 Hz, 1 H), 7.11 - 7.18 (m, 1 H), 7.27 (d, *J*=7.33 Hz, 1 H), 7.39 (d, *J*=8.34 Hz, 2 H), 7.59 (s, 1 H), 7.60 (d, *J*=2.27 Hz, 1 H), 7.93 (d, *J*=8.08 Hz, 2 H), 8.10 - 8.17 (m, 1 H), 8.27 (s, 1 H), 9.97 (s, 1 H). ESI-MS: *m/z* 411.3 (M + H)$^+$.

Example 118: *N*-(2-aminophenyl)-4-((4-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide



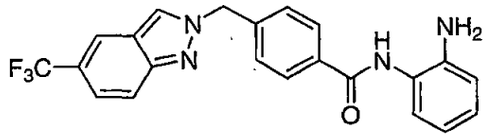
[0440] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 5.83 (s, 2 H), 7.11 (t, *J*=7.33 Hz, 1 H), 7.16 - 7.25 (m, 2 H), 7.34 (d, *J*=7.33 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.52 (d, *J*=8.08 Hz, 3 H), 7.95 (d, *J*=8.59 Hz, 1 H), 7.99 (d, *J*=8.08 Hz, 2 H), 8.80 (s, 1 H), 10.16 (s, 1 H). ESI-MS: *m/z* 411.3 $(M + H)^+$.

Example 119: *N*-(2-aminophenyl)-4-((5-(trifluoromethyl)-1*H*-indazol-1-yl)methyl)benzamide



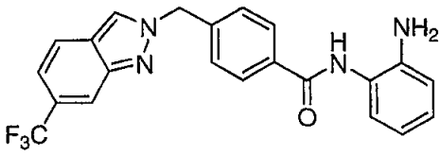
[0441] ^{1}H NMR (400 MHz, DMSO- d_6) of the trifluoroacetic acid salt: δ ppm 5.85 (s, 2 H), 6.93 (t, *J*=7.20 Hz, 1 H), 7.03 (d, *J*=7.83 Hz, 1 H), 7.13 (t, *J*=7.07 Hz, 1 H), 7.25 (d, *J*=7.33 Hz, 1 H), 7.36 (d, *J*=8.08 Hz, 2 H), 7.70 (dd, *J*=8.84, 1.52 Hz, 1 H), 7.91 - 7.99 (m, 3 H), 8.28 (s, 1 H), 8.34 (s, 1 H), 9.95 (s, 1 H). ESI-MS: *m/z* 411.3 $(M + H)^+$.

Example 120: *N*-(2-aminophenyl)-4-((5-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide



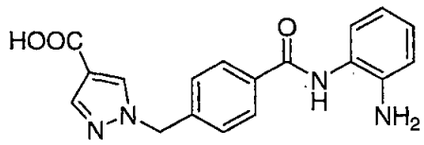
[0442] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 5.83 (s, 2 H), 6.98 (t, *J*=7.45 Hz, 1 H), 7.07 (d, *J*=7.83 Hz, 1 H), 7.16 (t, *J*=7.20 Hz, 1 H), 7.29 (d, *J*=7.58 Hz, 1 H), 7.44 - 7.50 (m, 3 H), 7.81 (d, *J*=9.09 Hz, 1 H), 7.98 (d, *J*=8.08 Hz, 2 H), 8.28 (s, 1 H), 8.80 (s, 1 H), 10.03 (s, 1 H). ESI-MS: *m/z* 411.3 $(M + H)^+$.

Example 121: *N*-(2-aminophenyl)-4-((6-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide



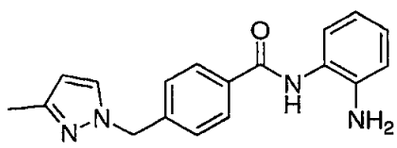
[0443] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.90 (s, 2 H), 5.82 (s, 2 H), 6.59 (t, *J*=7.45 Hz, 1 H), 6.77 (d, *J*=7.07 Hz, 1 H), 6.94 - 6.99 (m, 1 H), 7.16 (d, *J*=7.58 Hz, 1 H), 7.45 (d, *J*=8.59 Hz, 3 H), 7.97 (d, *J*=8.34 Hz, 2 H), 8.27 (s, 1 H), 8.74 (s, 1 H), 8.79 (s, 1 H), 9.65 (s, 1 H). ESI-MS: *m/z* 411.3 $(M + H)^+$.

Example 122: 1-(4-(2-aminophenylcarbamoyl)benzyl)-1H-pyrazole-4-carboxylic acid



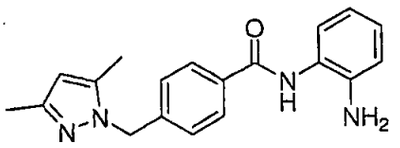
[0444] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 5.47 (s, 2 H), 6.93 - 6.99 (m, 1 H), 7.05 (d, *J*=7.33 Hz, 1 H), 7.15 (t, *J*=8.34 Hz, 1 H), 7.28 (d, *J*=7.83 Hz, 1 H), 7.41 (d, *J*=8.34 Hz, 2 H), 7.85 (s, 1 H), 7.97 (d, *J*=8.34 Hz, 2 H), 8.44 (s, 1 H), 10.01 (s, 1 H). ESI-MS: *m/z* 337.3 $(M + H)^+$.

Example 123: N-(2-aminophenyl)-4-((3-methyl-1H-pyrazol-1-yl)methyl)benzamide



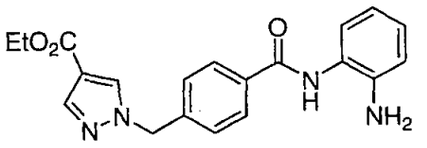
[0445] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 2.15 (s, 3 H), 5.33 (s, 2 H), 6.07 (d, *J*=2.27 Hz, 1 H), 7.11 - 7.16 (m, 1 H), 7.18 - 7.26 (m, 2 H), 7.34 (d, *J*=8.34 Hz, 2 H), 7.37 (dd, *J*=7.96, 0.88 Hz, 1 H), 7.74 (d, *J*=2.02 Hz, 1 H), 7.98 (d, *J*=8.34 Hz, 2 H), 10.18 (s, 1 H). ESI-MS: *m/z* 307.4 $(M + H)^+$.

Example 124: N-(2-aminophenyl)-4-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzamide



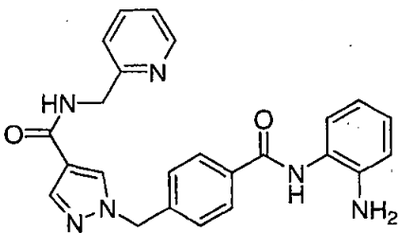
[0446] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 2.12 (s, 3 H), 2.17 (s, 3 H), 5.30 (s, 2 H), 5.90 (s, 1 H), 7.10 - 7.15 (m, 1 H), 7.16 - 7.20 (m, 1 H), 7.21 - 7.25 (m, 3 H), 7.35 (dd, *J*=7.83, 1.26 Hz, 1 H), 7.96 (d, *J*=8.34 Hz, 2 H), 10.15 (s, 1 H). ESI-MS: *m/z* 321.4 $(M + H)^+$.

Example 125: Ethyl 1-(4-(2-aminophenylcarbamoyl)benzyl)-1H-pyrazole-4-carboxylate



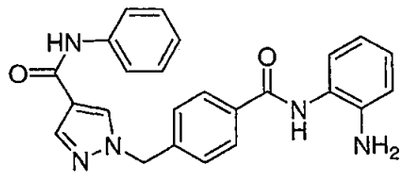
[0447] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 1.27 (t, *J*=7.07 Hz, 3 H), 4.22 (q, *J*=7.07 Hz, 2 H), 5.48 (s, 2 H), 6.99 (t, *J*=7.33 Hz, 1 H), 7.05 - 7.11 (m, 1 H), 7.14 - 7.20 (m, 1 H), 7.30 (d, *J*=7.83 Hz, 1 H), 7.41 (d, *J*=8.34 Hz, 2 H), 7.90 (s, 1 H), 7.97 (d, *J*=8.08 Hz, 2 H), 8.53 (s, 1 H), 10.04 (s, 1 H). ESI-MS: *m/z* 365.4 $(M + H)^+$.

Example 126: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide



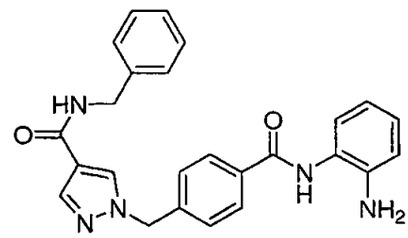
[0448] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.49 (d, *J*=6.06 Hz, 2 H), 4.90 (s, 2 H), 5.45 (s, 2 H), 6.59 (td, *J*=7.45, 1.26 Hz, 1 H), 6.77 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.97 (td, *J*=7.58, 1.52 Hz, 1 H), 7.16 (d, *J*=7.07 Hz, 1 H), 7.25 (ddd, *J*=7.58, 4.80, 1.01 Hz, 1 H), 7.30 (d, *J*=7.83 Hz, 1 H), 7.39 (d, *J*=8.08 Hz, 2 H), 7.75 (td, *J*=7.64, 1.89 Hz, 1 H), 7.94 - 7.98 (m, 3 H), 8.34 (s, 1 H), 8.50 (ddd, *J*=4.93, 1.89, 1.01 Hz, 1 H), 8.75 (t, *J*=5.94 Hz, 1 H), 9.65 (s, 1 H). ESI-MS: *m/z* 427.4 $(M + H)^+$.

Example 127: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-phenyl-1H-pyrazole-4-carboxamide



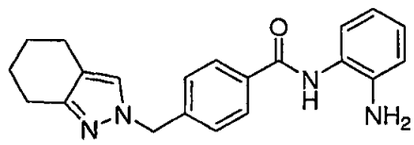
[0449] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.90 (s, 2 H), 5.49 (s, 2 H), 6.59 (td, *J*=7.52, 1.39 Hz, 1 H), 6.77 (dd, *J*=7.96, 1.39 Hz, 1 H), 6.97 (td, *J*=7.71, 1.52 Hz, 1 H), 7.04 - 7.09 (m, 1 H), 7.16 (d, *J*=7.33 Hz, 1 H), 7.30 - 7.35 (m, 2 H), 7.40 (d, *J*=8.34 Hz, 2 H), 7.70 (dt, *J*=8.65, 1.61 Hz, 2 H), 7.97 (d, *J*=8.08 Hz, 2 H), 8.09 (d, *J*=0.76 Hz, 1 H), 8.49 (s, 1 H), 9.66 (s, 1 H), 9.86 (s, 1 H). ESI-MS: *m/z* 412.4 $(M + H)^+$.

Example 128: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-benzyl-1H-pyrazole-4-carboxamide



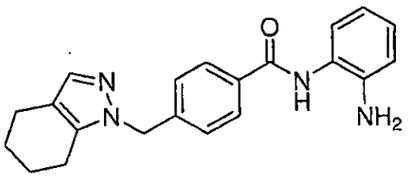
[0450] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.41 (d, *J*=6.06 Hz, 2 H), 4.90 (s, 2 H), 5.44 (s, 2 H), 6.59 (td, *J*=7.52, 1.39 Hz, 1 H), 6.77 (dd, *J*=7.96, 1.39 Hz, 1 H), 6.97 (td, *J*=7.58, 1.52 Hz, 1 H), 7.15 (d, *J*=7.07 Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.27 - 7.34 (m, 4 H), 7.38 (d, *J*=8.34 Hz, 2 H), 7.95 (s, 2 H), 7.97 (s, 1 H), 8.32 (s, 1 H), 8.65 (t, *J*=6.06 Hz, 1 H), 9.65 (s, 1 H). ESI-MS: *m/z* 426.4 $(M + H)^+$.

Example 129: N-(2-aminophenyl)-4-((4,5,6,7-tetrahydro-2H-indazol-2-yl)methyl)benzamide



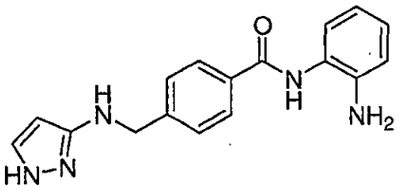
[0451] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 1.63 - 1.74 (m, 4 H), 2.45 - 2.49 (m, 4 H), 5.27 (s, 2 H), 6.90 - 6.98 (m, 1 H), 7.04 (d, *J*=8.59 Hz, 1 H), 7.14 (t, *J*=7.83 Hz, 1 H), 7.28 (d, *J*=7.58 Hz, 1 H), 7.36 (d, *J*=8.34 Hz, 2 H), 7.50 (s, 1 H), 7.94 (d, *J*=8.34 Hz, 2 H), 9.96 (s, 1 H). ESI-MS: *m/z* 347.4 $(M + H)^+$.

Example 130: N-(2-aminophenyl)-4-((4,5,6,7-tetrahydro-1H-indazol-1-yl)methyl)benzamide



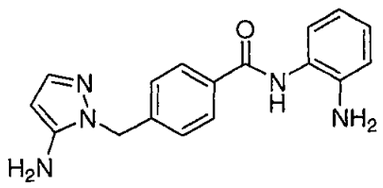
[0452] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 1.59 - 1.66 (m, 2 H), 1.68 - 1.76 (m, 2 H), 2.44 (t, *J*=5.94 Hz, 2 H), 2.47 - 2.50 (m, 2 H), 5.31 (s, 2 H), 7.04 (t, *J*=7.33 Hz, 1 H), 7.10 - 7.13 (m, 1 H), 7.16 - 7.21 (m, 1 H), 7.23 - 7.27 (m, 3 H), 7.31 (dd, *J*=7.96, 1.14 Hz, 1 H), 7.95 (d, *J*=8.34 Hz, 2 H), 10.07 (s, 1 H). ESI-MS: *m/z* 347.4 $(M + H)^+$.

Example 131: 4-((1H-pyrazol-3-ylamino)methyl)-N-(2-aminophenyl)benzamide



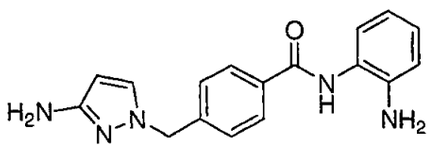
[0453] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 4.42 (s, 2 H), 5.74 (d, *J*=2.53 Hz, 1 H), 6.85 (t, *J*=7.45 Hz, 1 H), 6.96 - 7.00 (m, 1 H), 7.10 (td, *J*=7.64, 1.39 Hz, 1 H), 7.23 - 7.27 (m, 1 H), 7.48 (d, *J*=8.34 Hz, 2 H), 7.80 (d, *J*=2.78 Hz, 1 H), 7.97 (d, *J*=8.34 Hz, 2 H), 9.89 (s, 1 H). ESI-MS: *m/z* 308.4 $(M + H)^+$.

Example 132: 4-((5-amino-1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



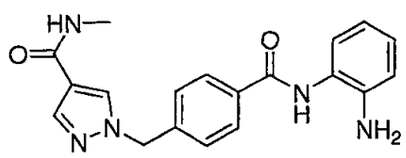
[0454] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.89 (s, 2 H), 5.19 (s, 2 H), 5.29 (s, 2 H), 5.31 (d, *J*=2.02 Hz, 1 H), 6.59 (td, *J*=7.52, 1.39 Hz, 1 H), 6.77 (dd, *J*=8.08, 1.52 Hz, 1 H), 6.96 (td, *J*=7.58, 1.52 Hz, 1 H), 7.10 (d, *J*=2.02 Hz, 1 H), 7.15 (d, *J*=6.82 Hz, 1 H), 7.22 (d, *J*=8.34 Hz, 2 H), 7.90 (d, *J*=8.08 Hz, 2 H), 9.60 (s, 1 H). ESI-MS: *m/z* 308.4 (M + H)$^+$.

Example 133: 4-((3-amino-1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)benzamide



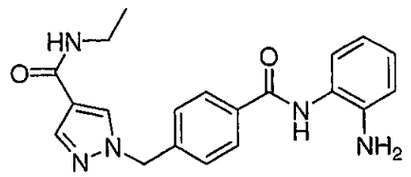
[0455] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.59 (s, 2 H), 4.89 (s, 2 H), 5.11 (s, 2 H), 5.44 (d, *J*=2.27 Hz, 1 H), 6.59 (td, *J*=7.58, 1.26 Hz, 1 H), 6.77 (dd, *J*=8.08, 1.52 Hz, 1 H), 6.96 (td, *J*=7.58, 1.52 Hz, 1 H), 7.16 (d, *J*=7.83 Hz, 1 H), 7.28 (d, *J*=8.08 Hz, 2 H), 7.48 (d, *J*=2.02 Hz, 1 H), 7.91 (d, *J*=8.08 Hz, 2 H), 9.61 (s, 1 H). ESI-MS: *m/z* 308.4 (M + H)$^+$.

Example 134: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-methyl-1H-pyrazole-4-carboxamide



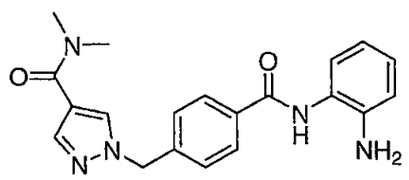
[0456] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.70 (d, *J*=4.55 Hz, 3 H), 4.89 (s, 2 H), 5.43 (s, 2 H), 6.59 (td, *J*=7.52, 1.14 Hz, 1 H), 6.77 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.94 - 6.99 (m, 1 H), 7.15 (d, *J*=7.33 Hz, 1 H), 7.35 (d, *J*=8.34 Hz, 2 H), 7.86 (s, 1 H), 7.95 (d, *J*=8.08 Hz, 2 H), 8.05 (q, *J*=4.55 Hz, 1 H), 8.25 (s, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 350.3 (M + H)$^+$.

Example 135: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-ethyl-1H-pyrazole-4-carboxamide



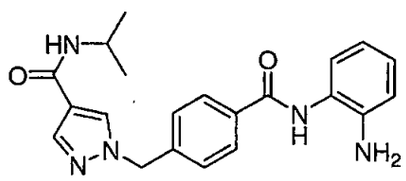
[0457] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (t, *J*=7.20 Hz, 3 H), 3.16 - 3.24 (m, 2 H), 4.89 (s, 2 H), 5.43 (s, 2 H), 6.59 (td, *J*=7.58, 1.26 Hz, 1 H), 6.77 (dd, *J*=7.96, 1.39 Hz, 1 H), 6.96 (td, *J*=7.71, 1.52 Hz, 1 H), 7.15 (d, *J*=8.34 Hz, 1 H), 7.35 (d, *J*=8.34 Hz, 2 H), 7.87 (d, *J*=0.76 Hz, 1 H), 7.95 (d, *J*=8.34 Hz, 2 H), 8.07 (t, *J*=5.43 Hz, 1 H), 8.25 (s, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 364.4 $(M + H)^+$.

Example 136: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N,N-dimethyl-1H-pyrazole-4-carboxamide



[0458] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.97 (m, 3 H), 3.14 (m, 3 H), 4.90 (s, 2 H), 5.44 (s, 2 H), 6.59 (t, *J*=7.71 Hz, 1 H), 6.77 (dd, *J*=7.83, 1.01 Hz, 1 H), 6.94 - 6.99 (m, 1 H), 7.15 (d, *J*=7.83 Hz, 1 H), 7.37 (d, *J*=8.34 Hz, 2 H), 7.77 (s, 1 H), 7.95 (d, *J*=8.34 Hz, 2 H), 8.31 (s, 1 H), 9.63 (s, 1 H). ESI-MS: *m/z* 364.3 $(M + H)^+$.

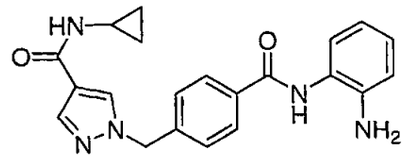
Example 137: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-isopropyl-1H-pyrazole-4-carboxamide



[0459] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.11 (d, *J*=6.82 Hz, 6 H), 4.02 (dq, *J*=13.80, 6.77 Hz, 1 H), 4.89 (s, 2 H), 5.43 (s, 2 H), 6.56 - 6.61 (m, 1 H), 6.77 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.97 (td, *J*=7.58, 1.26 Hz, 1 H), 7.15 (d, *J*=7.58 Hz, 1 H), 7.36 (d, *J*=8.08

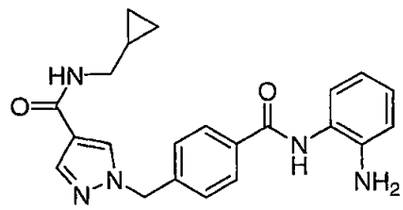
Hz, 2 H), 7.83 (d, *J*=7.83 Hz, 1 H), 7.89 (s, 1 H), 7.96 (d, *J*=8.08 Hz, 2 H), 8.26 (s, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 378.4 $(M + H)^+$.

Example 138: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-cyclopropyl-1H-pyrazole-4-carboxamide



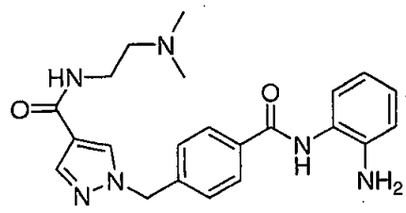
[0460] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.48 (m, 2 H), 0.65 (m, 2 H), 2.70 - 2.77 (m, *J*=7.31, 7.31, 3.92, 3.74, 3.74 Hz, 1 H), 4.90 (s, 2 H), 5.42 (s, 2 H), 6.56 - 6.62 (m, 1 H), 6.77 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.94 - 6.99 (m, 1 H), 7.15 (d, *J*=7.33 Hz, 1 H), 7.35 (d, *J*=8.08 Hz, 2 H), 7.87 (s, 1 H), 7.95 (d, *J*=8.08 Hz, 2 H), 8.08 (d, *J*=3.79 Hz, 1 H), 8.25 (s, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 376.3 $(M + H)^+$.

Example 139: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(cyclopropylmethyl)-1H-pyrazole-4-carboxamide



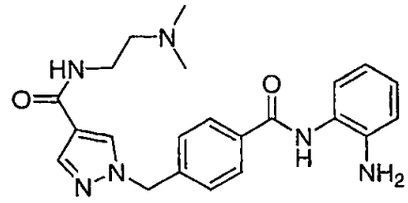
[0461] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.17 - 0.21 (m, 2 H), 0.39 - 0.44 (m, 2 H), 0.91 - 1.01 (m, 1 H), 3.07 (t, *J*=6.32 Hz, 2 H), 4.90 (s, 2 H), 5.44 (s, 2 H), 6.59 (t, *J*=7.45 Hz, 1 H), 6.77 (dd, *J*=8.08, 1.01 Hz, 1 H), 6.94 - 6.99 (m, 1 H), 7.15 (d, *J*=7.58 Hz, 1 H), 7.37 (d, *J*=8.08 Hz, 2 H), 7.90 (s, 1 H), 7.96 (d, *J*=8.08 Hz, 2 H), 8.17 (t, *J*=5.68 Hz, 1 H), 8.28 (s, 1 H), 9.65 (s, 1 H). ESI-MS: *m/z* 390.4 $(M + H)^+$.

Example 140: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(dimethylamino)ethyl)-1H-pyrazole-4-carboxamide



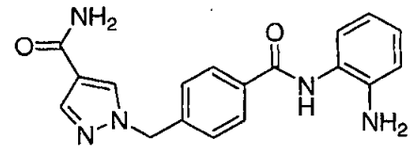
[0462] ^{1}H NMR (400 MHz, DMSO-d_6) of the *bis*-trifluoroacetic acid salt: δ ppm 2.52 - 2.55 (m, 2 H), 2.83 (d, *J*=4.80 Hz, 6 H), 3.17 - 3.23 (m, 2 H), 5.46 (s, 2 H), 6.61 - 6.68 (m, 1 H), 6.82 (d, *J*=7.33 Hz, 1 H), 6.97 - 7.03 (m, 1 H), 7.16 (d, *J*=8.59 Hz, 1 H), 7.38 (d, *J*=7.83 Hz, 2 H), 7.90 (s, 1 H), 7.96 (d, *J*=8.34 Hz, 2 H), 8.30 (s, 1 H), 8.34 (t, *J*=6.06 Hz, 1 H), 9.70 (s, 1 H). ESI-MS: *m/z* 407.4 $(M + H)^+$.

Example 141: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(dimethylamino)ethyl)-1H-pyrazole-4-carboxamide



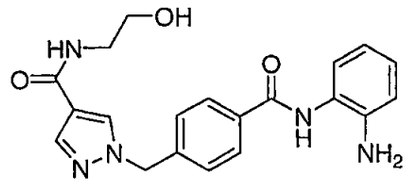
[0463] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.23 (s, 6 H), 2.47 - 2.49 (m, 2 H), 3.27 - 3.33 (m, 2 H), 4.89 (s, 2 H), 5.44 (s, 2 H), 6.59 (td, *J*=7.52, 1.39 Hz, 1 H), 6.77 (dd, *J*=8.08, 1.52 Hz, 1 H), 6.94 - 6.99 (m, 1 H), 7.15 (d, *J*=8.34 Hz, 1 H), 7.36 (d, *J*=8.34 Hz, 2 H), 7.88 (s, 1 H), 7.95 (d, *J*=8.34 Hz, 2 H), 8.04 (t, *J*=5.81 Hz, 1 H), 8.27 (s, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 407.4 $(M + H)^+$.

Example 142: 1-(4-(2-aminophenylcarbamoyl)benzyl)-1H-pyrazole-4-carboxamide



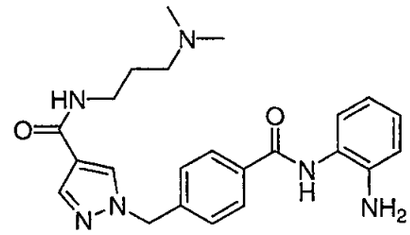
[0464] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.90 (s, 2 H), 5.43 (s, 2 H), 6.56 - 6.62 (m, 1 H), 6.77 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.94 - 6.99 (m, 1 H), 7.03 (s, 1 H), 7.15 (d, *J*=7.33 Hz, 1 H), 7.36 (d, *J*=8.08 Hz, 2 H), 7.58 (s, 1 H), 7.88 (s, 1 H), 7.96 (d, *J*=8.34 Hz, 2 H), 8.26 (s, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 336.3 $(M + H)^+$.

Example 143: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-hydroxyethyl)-1H-pyrazole-4-carboxamide



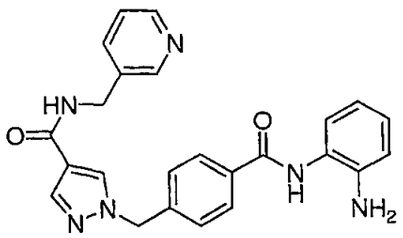
[0465] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.24 (q, *J*=5.98 Hz, 2 H), 3.45 (q, *J*=6.15 Hz, 2 H), 4.69 - 4.72 (m, 1 H), 4.89 (s, 2 H), 5.43 (s, 2 H), 6.59 (td, *J*=7.52, 1.39 Hz, 1 H), 6.77 (dd, *J*=8.08, 1.52 Hz, 1 H), 6.97 (td, *J*=7.71, 1.52 Hz, 1 H), 7.15 (d, *J*=7.58 Hz, 1 H), 7.36 (d, *J*=8.34 Hz, 2 H), 7.90 (d, *J*=0.51 Hz, 1 H), 7.95 (d, *J*=8.34 Hz, 2 H), 8.09 (t, *J*=5.68 Hz, 1 H), 8.28 (d, *J*=0.76 Hz, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 380.3 (M + H)$^+$.

Example 144: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-(dimethylamino)propyl)-1H-pyrazole-4-carboxamide



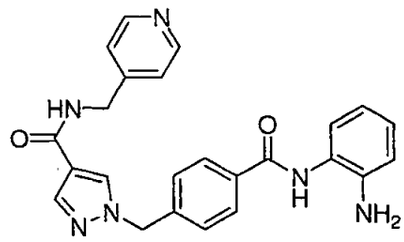
[0466] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.59 (qd, *J*=7.07, 6.82 Hz, 2 H), 2.12 (s, 6 H), 2.23 (t, *J*=7.20 Hz, 2 H), 3.16 - 3.22 (m, 2 H), 4.89 (s, 2 H), 5.43 (s, 2 H), 6.59 (td, *J*=7.52, 1.39 Hz, 1 H), 6.77 (dd, *J*=8.08, 1.52 Hz, 1 H), 6.97 (td, *J*=7.58, 1.52 Hz, 1 H), 7.15 (d, *J*=7.33 Hz, 1 H), 7.36 (d, *J*=8.08 Hz, 2 H), 7.87 (d, *J*=0.76 Hz, 1 H), 7.95 (d, *J*=8.34 Hz, 2 H), 8.10 (t, *J*=5.68 Hz, 1 H), 8.25 (d, *J*=0.51 Hz, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 421.4 (M + H)$^+$.

Example 145: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridin-3-ylmethyl)-1H-pyrazole-4-carboxamide



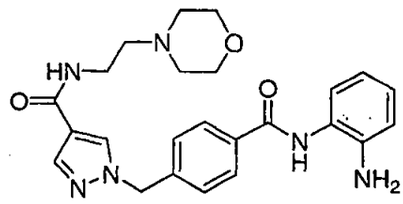
[0467] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.42 (d, *J*=5.81 Hz, 2 H), 4.89 (s, 2 H), 5.44 (s, 2 H), 6.59 (td, *J*=7.52, 1.39 Hz, 1 H), 6.77 (dd, *J*=7.96, 1.39 Hz, 1 H), 6.97 (td, *J*=7.58, 1.52 Hz, 1 H), 7.15 (d, *J*=7.33 Hz, 1 H), 7.33 - 7.36 (m, 1 H), 7.36 - 7.39 (m, 2 H), 7.69 (dt, *J*=7.83, 2.02 Hz, 1 H), 7.93 (d, *J*=0.51 Hz, 1 H), 7.95 (d, *J*=8.08 Hz, 2 H), 8.32 (d, *J*=0.51 Hz, 1 H), 8.45 (dd, *J*=4.80, 1.77 Hz, 1 H), 8.52 (d, *J*=1.52 Hz, 1 H), 8.70 (t, *J*=5.94 Hz, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 427.3 $(M + H)^+$.

Example 146: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridin-4-ylmethyl)-1H-pyrazole-4-carboxamide



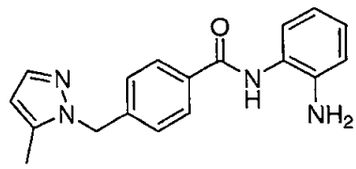
[0468] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.43 (d, *J*=6.06 Hz, 2 H), 4.90 (s, 2 H), 5.46 (s, 2 H), 6.59 (td, *J*=7.52, 1.39 Hz, 1 H), 6.77 (dd, *J*=7.96, 1.39 Hz, 1 H), 6.94 - 6.99 (m, 1 H), 7.15 (d, *J*=7.33 Hz, 1 H), 7.26 - 7.29 (m, 2 H), 7.39 (d, *J*=8.34 Hz, 2 H), 7.93 - 7.98 (m, 3 H), 8.34 (s, 1 H), 8.48 - 8.50 (m, 2 H), 8.75 (t, *J*=6.06 Hz, 1 H), 9.65 (s, 1 H). ESI-MS: *m/z* 427.3 $(M + H)^+$.

Example 147: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-morpholinoethyl)-1H-pyrazole-4-carboxamide



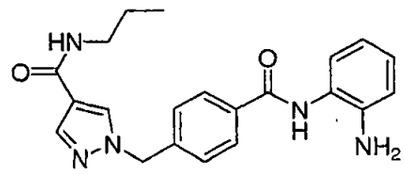
[0469] ^{1}H NMR (400 MHz, DMSO-d_6) of the *bis*-trifluoroacetic acid salt: δ ppm 3.07 - 3.19 (m, 2 H), 3.26 (t, *J*=6.19 Hz, 2 H), 3.49 - 3.59 (m, 4 H), 3.59 - 3.71 (m, 2 H), 4.00 (d, *J*=13.64 Hz, 2 H), 5.46 (s, 2 H), 6.79 (t, *J*=7.20 Hz, 1 H), 6.93 (d, *J*=7.07 Hz, 1 H), 7.05 - 7.10 (m, 1 H), 7.22 (d, *J*=7.07 Hz, 1 H), 7.39 (d, *J*=8.34 Hz, 2 H), 7.91 (d, *J*=0.51 Hz, 1 H), 7.97 (d, *J*=8.34 Hz, 2 H), 8.32 (d, *J*=0.51 Hz, 1 H), 8.42 (t, *J*=5.68 Hz, 1 H), 9.85 (s, 1 H). ESI-MS: *m/z* 449.4 $(M + H)^+$.

Example 148: N-(2-aminophenyl)-4-((5-methyl-1H-pyrazol-1-yl)methyl)benzamide



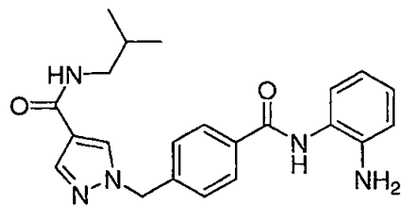
[0470] ^{1}H NMR (400 MHz, DMSO-d_6) of the trifluoroacetic acid salt: δ ppm 2.22 (s, 3 H), 5.40 (s, 2 H), 6.11 (dd, *J*=2.15, 1.14 Hz, 1 H), 7.05 (t, *J*=7.58 Hz, 1 H), 7.11 - 7.15 (m, 1 H), 7.19 (d, *J*=7.33 Hz, 1 H), 7.22 (d, *J*=8.08 Hz, 2 H), 7.32 (d, *J*=7.83 Hz, 1 H), 7.39 (d, *J*=1.77 Hz, 1 H), 7.96 (d, *J*=8.08 Hz, 2 H), 10.09 (s, 1 H). ESI-MS: *m/z* 307.3 $(M + H)^+$.

Example 149: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-propyl-1H-pyrazole-4-carboxamide



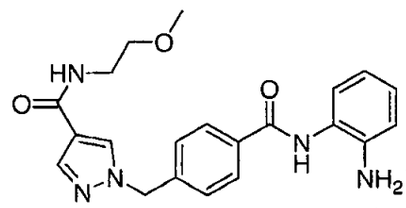
[0471] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.86 (t, *J*=7.33 Hz, 3 H), 1.43 - 1.52 (m, *J*=7.23, 7.23, 7.23, 7.23, 7.23 Hz, 2 H), 3.11 - 3.17 (m, 2 H), 4.90 (s, 2 H), 5.43 (s, 2 H), 6.59 (td, *J*=7.45, 1.26 Hz, 1 H), 6.77 (dd, *J*=7.96, 1.39 Hz, 1 H), 6.97 (td, *J*=7.71, 1.52 Hz, 1 H), 7.15 (d, *J*=7.83 Hz, 1 H), 7.36 (d, *J*=8.34 Hz, 2 H), 7.89 (d, *J*=0.51 Hz, 1 H), 7.96 (d, *J*=8.08 Hz, 2 H), 8.06 (t, *J*=5.68 Hz, 1 H), 8.26 (s, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 378.3 $(M + H)^+$.

Example 150: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-isobutyl-1H-pyrazole-4-carboxamide



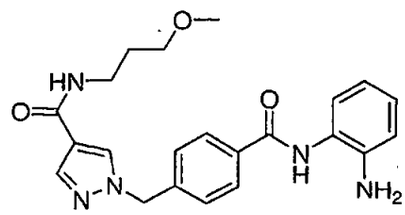
[0472] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.86 (d, J=6.57 Hz, 6 H), 1.76 (tt, J=13.52, 6.82 Hz, 1 H), 2.98 - 3.02 (m, 2 H), 4.90 (s, 2 H), 5.43 (s, 2 H), 6.59 (td, J=7.58, 1.26 Hz, 1 H), 6.77 (dd, J=8.08, 1.26 Hz, 1 H), 6.97 (td, J=7.58, 1.52 Hz, 1 H), 7.15 (d, J=7.58 Hz, 1 H), 7.37 (d, J=8.34 Hz, 2 H), 7.91 (d, J=0.51 Hz, 1 H), 7.96 (d, J=8.08 Hz, 2 H), 8.06 (t, J=5.94 Hz, 1 H), 8.27 (s, 1 H), 9.64 (s, 1 H). ESI-MS: m/z 392.4 $(M + H)^+$.

Example 151: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-methoxyethyl)-1H-pyrazole-4-carboxamide



[0473] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.25 (s, 3 H), 3.33 - 3.36 (m, 2 H), 3.38 - 3.42 (m, 2 H), 4.89 (s, 2 H), 5.43 (s, 2 H), 6.59 (td, J=7.52, 1.39 Hz, 1 H), 6.77 (dd, J=8.08, 1.26 Hz, 1 H), 6.97 (td, J=7.64, 1.39 Hz, 1 H), 7.15 (d, J=7.07 Hz, 1 H), 7.36 (d, J=8.34 Hz, 2 H), 7.90 (d, J=0.51 Hz, 1 H), 7.95 (d, J=8.08 Hz, 2 H), 8.16 (t, J=5.43 Hz, 1 H), 8.28 (d, J=0.51 Hz, 1 H), 9.64 (s, 1 H). ESI-MS: m/z 394.3 $(M + H)^+$.

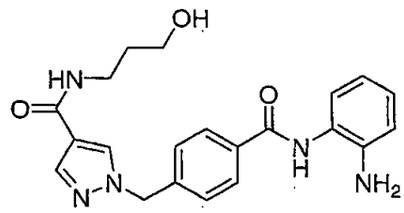
Example 152: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-methoxypropyl)-1H-pyrazole-4-carboxamide



[0474] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 - 1.73 (m, 2 H), 3.18 - 3.22 (m, 1 H), 3.22 (s, 4 H), 3.33 (t, J=3.16 Hz, 2 H), 4.89 (s, 2 H), 5.43 (s, 2 H), 6.59 (td, J=7.58,

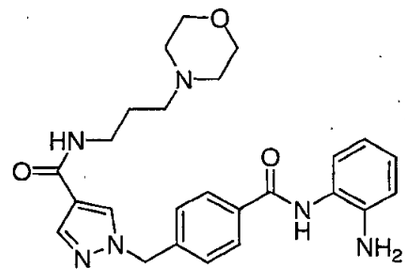
1.26 Hz, 1 H), 6.77 (dd, *J*=7.96, 1.39 Hz, 1 H), 6.97 (td, *J*=7.58, 1.52 Hz, 1 H), 7.15 (d, *J*=7.33 Hz, 1 H), 7.36 (d, *J*=8.34 Hz, 2 H), 7.88 (d, *J*=0.76 Hz, 1 H), 7.95 (d, *J*=8.08 Hz, 2 H), 8.08 (t, *J*=5.68 Hz, 1 H), 8.26 (d, *J*=0.76 Hz, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 408.4 $(M + H)^+$.

Example 153: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-hydroxypropyl)-1H-pyrazole-4-carboxamide



[0475] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.62 (qd, *J*=6.74, 6.57 Hz, 2 H), 3.23 (q, *J*=6.65 Hz, 2 H), 3.40 - 3.46 (m, 2 H), 4.46 (t, *J*=5.31 Hz, 1 H), 4.90 (s, 2 H), 5.43 (s, 2 H), 6.59 (td, *J*=7.52, 1.39 Hz, 1 H), 6.77 (dd, *J*=8.08, 1.26 Hz, 1 H), 6.97 (td, *J*=7.58, 1.52 Hz, 1 H), 7.15 (d, *J*=7.07 Hz, 1 H), 7.36 (d, *J*=8.08 Hz, 2 H), 7.89 (d, *J*=0.51 Hz, 1 H), 7.96 (d, *J*=8.08 Hz, 2 H), 8.07 (t, *J*=5.68 Hz, 1 H), 8.26 (d, *J*=0.51 Hz, 1 H), 9.64 (s, 1 H). ESI-MS: *m/z* 394.3 $(M + H)^+$.

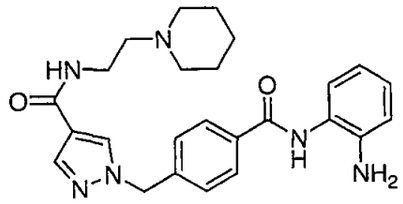
Example 154: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-morpholinopropyl)-1H-pyrazole-4-carboxamide



[0476] ^{1}H NMR (400 MHz, DMSO-d_6) of the *bis*-trifluoroacetic acid salt: δ ppm 1.83 - 1.91 (m, 2 H), 3.01 - 3.10 (m, 2 H), 3.10 - 3.17 (m, 2 H), 3.26 (q, *J*=6.32 Hz, 2 H), 3.43 (d, *J*=11.87 Hz, 2 H), 3.64 (t, *J*=11.87 Hz, 2 H), 3.97 (d, *J*=11.87 Hz, 2 H), 5.46 (s, 2 H), 6.93 (t, *J*=7.07 Hz, 1 H), 7.04 (dd, *J*=8.08, 1.26 Hz, 1 H), 7.11 - 7.17 (m, 1 H), 7.28 (d, *J*=8.84

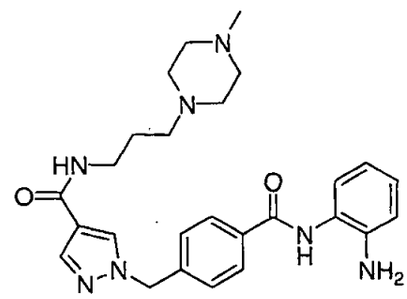
Hz, 1 H), 7.39 (d, *J*=8.34 Hz, 2 H), 7.91 (s, 1 H), 7.98 (d, *J*=8.08 Hz, 2 H), 8.29 - 8.35 (m, 2 H), 10.00 (s, 1 H). ESI-MS: *m/z* 463.4 $(M + H)^+$.

Example 155: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(piperidin-1-yl)ethyl)-1H-pyrazole-4-carboxamide



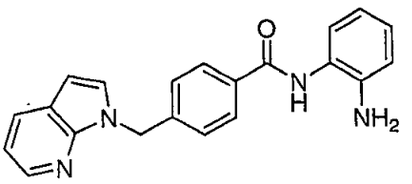
[0477] 1H NMR (400 MHz, DMSO-d_6) of the *bis*-trifluoroacetic acid salt: δ ppm 1.32 - 1.43 (m, 1 H), 1.60 - 1.71 (m, 3 H), 1.81 (d, *J*=14.40 Hz, 2 H), 2.87 - 2.97 (m, 2 H), 3.18 (d, *J*=5.31 Hz, 2 H), 3.49 - 3.59 (m, 4 H), 5.47 (s, 2 H), 6.94 (t, *J*=6.95 Hz, 1 H), 7.05 - 7.08 (m, 1 H), 7.15 (td, *J*=7.64, 1.39 Hz, 1 H), 7.30 (d, *J*=6.82 Hz, 1 H), 7.40 (d, *J*=8.34 Hz, 2 H), 7.92 (d, *J*=0.76 Hz, 1 H), 7.99 (d, *J*=8.08 Hz, 2 H), 10.02 (s, 1 H). ESI-MS: *m/z* 447.4 $(M + H)^+$.

Example 156: 1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-(4-methylpiperazin-1-yl)propyl)-1H-pyrazole-4-carboxamide



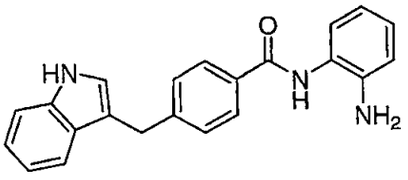
[0478] ^{1}H NMR (400 MHz, DMSO-d_6) of the *bis*-trifluoroacetic acid salt: δ ppm 1.80 - 1.88 (m, 2 H), 2.84 (s, 3 H), 3.06 - 3.13 (m, 2 H), 3.26-3.60 (m, 10 H), 5.45 (s, 2 H), 6.91 (t, *J*=6.95 Hz, 1 H), 7.03 (dd, *J*=8.08, 1.26 Hz, 1 H), 7.13 (td, *J*=7.58, 1.52 Hz, 1 H), 7.27 (d, *J*=8.84 Hz, 1 H), 7.39 (d, *J*=8.34 Hz, 2 H), 7.91 (d, *J*=0.76 Hz, 1 H), 7.98 (d, *J*=8.34 Hz, 2 H), 8.30 (d, *J*=0.76 Hz, 1 H), 9.98 (s, 1 H). ESI-MS: *m/z* 476.4 $(M + H)^+$.

Example 157: 4-((1*H*-Pyrrolo[2,3-b]pyridin-1-yl)methyl)-N-(2-aminophenyl)benzamide



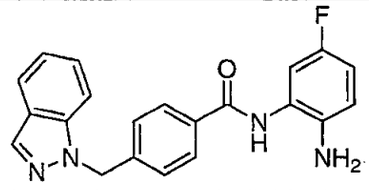
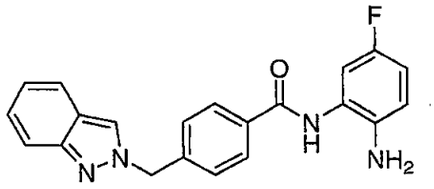
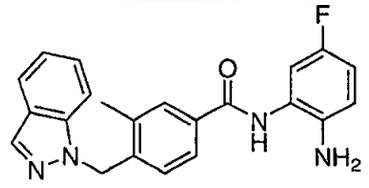
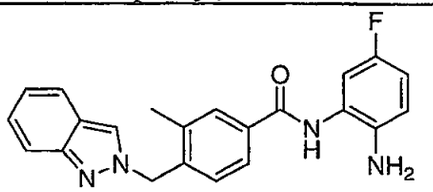
[0479] ^{1}H NMR (400 MHz, DMSO-D6) of the trifluoroacetic acid salt: δ ppm 6.03 (s, 2 H) 6.67 (s, 1 H) 6.83 (s, 1 H) 6.91 - 7.02 (m, 2 H) 7.12 (d, *J*=7.33 Hz, 1 H) 7.31 - 7.40 (m, 2 H) 7.45 (d, *J*=8.34 Hz, 1 H) 7.58 - 7.70 (m, 1 H) 7.87 - 7.99 (m, 2 H) 8.65 - 8.80 (m, 2 H) 9.76 (s, 1 H). ESI-MS: *m/z* 343.4 $(M + H)^+$.

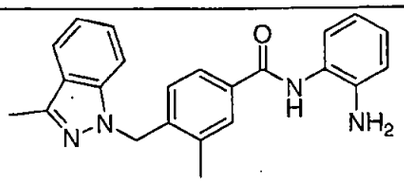
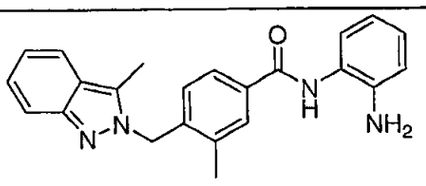
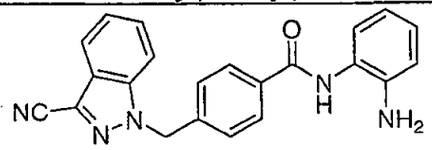
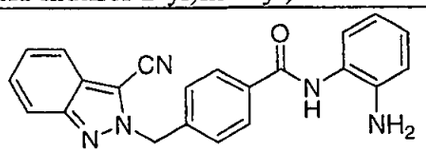
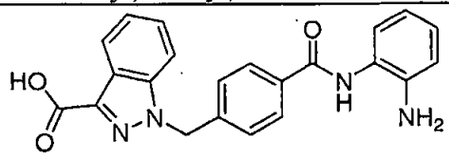
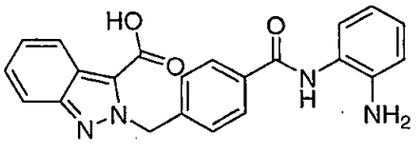
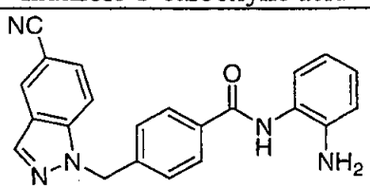
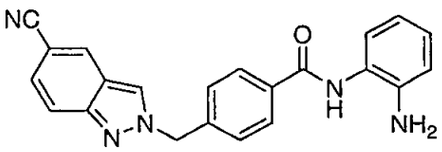
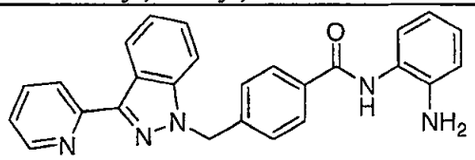
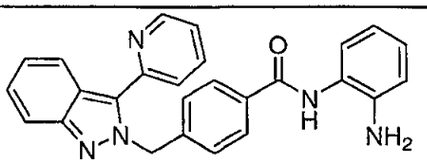
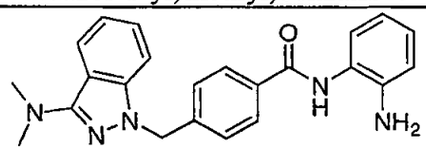
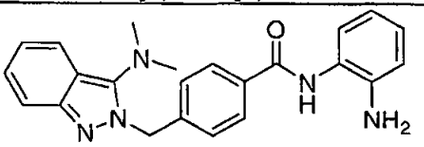
Example 158: 4-((1*H*-Indol-3-yl)methyl)-N-(2-aminophenyl)benzamide

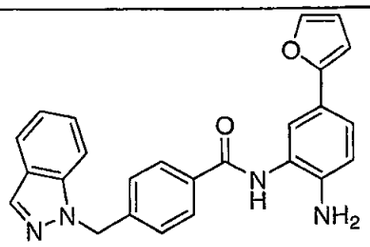
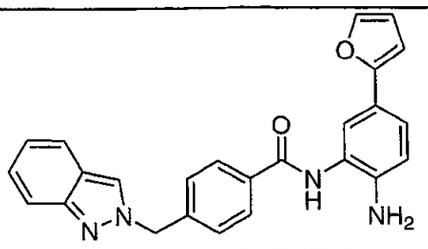
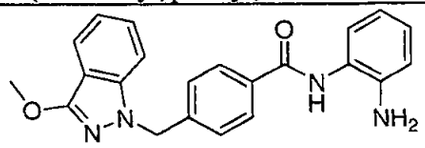
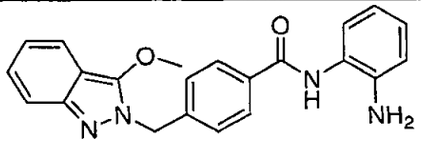
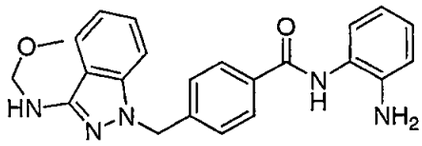
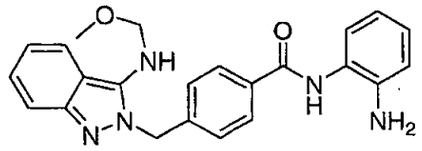
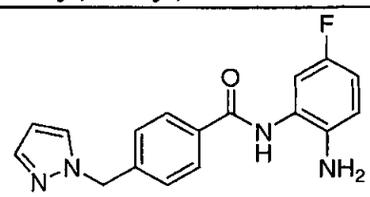
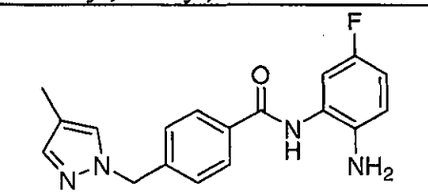
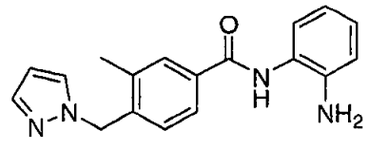
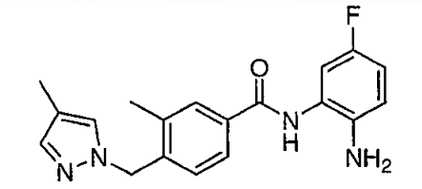
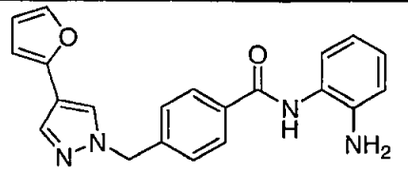
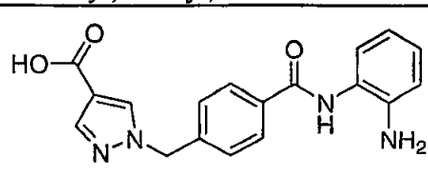


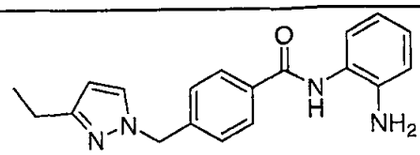
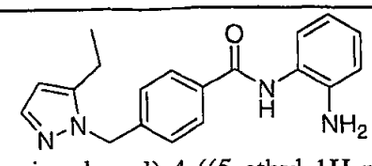
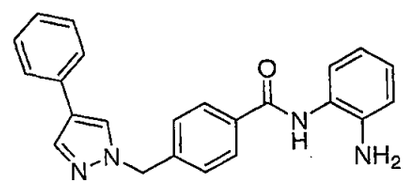
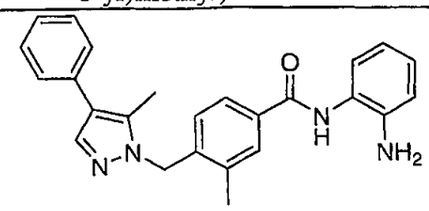
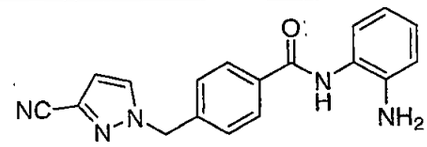
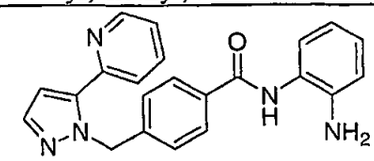
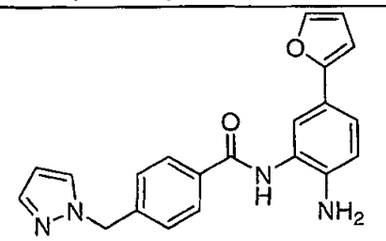
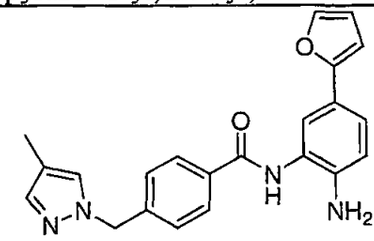
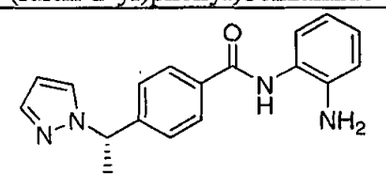
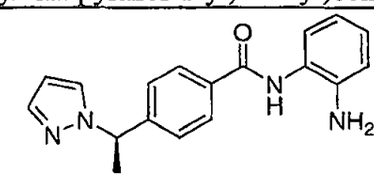
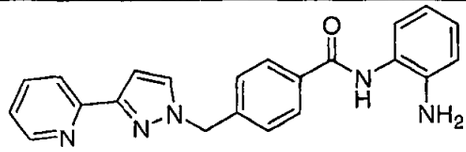
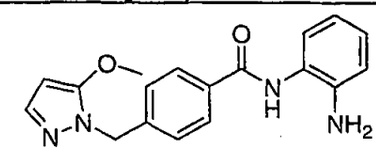
[0480] ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.10 (s, 2 H) 4.84 (s, 2 H) 6.53 - 6.60 (m, 1 H) 6.74 (d, *J*=7.83 Hz, 1 H) 6.88 - 6.97 (m, 2 H) 7.00 - 7.07 (m, 2 H) 7.11 (s, 1 H) 7.19 (d, *J*=2.27 Hz, 1 H) 7.32 (d, *J*=8.08 Hz, 1 H) 7.36 - 7.42 (m, 2 H) 7.85 (d, *J*=8.08 Hz, 2 H) 9.54 (s, 1 H) 10.87 (s, 1 H). ESI-MS: *m/z* 342.4 $(M + H)^+$.

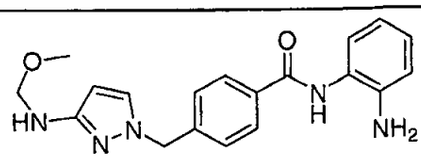
[0481] In addition to the examples described above, the following non-limiting group of compounds can be prepared utilizing the above reaction schemes, and variations thereof, with the appropriate selection of substituents:

 4-((1H-indazol-1-yl)methyl)-N-(2-amino-5-fluorophenyl)benzamide	 4-((2H-indazol-2-yl)methyl)-N-(2-amino-5-fluorophenyl)benzamide
 4-((1H-indazol-1-yl)methyl)-N-(2-amino-5-fluorophenyl)-3-methylbenzamide	 4-((2H-indazol-2-yl)methyl)-N-(2-amino-5-fluorophenyl)-3-methylbenzamide

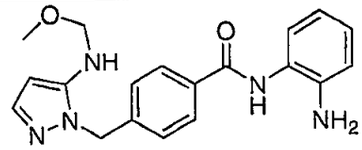
 N-(2-aminophenyl)-3-methyl-4-((3-methyl-1H-indazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-3-methyl-4-((3-methyl-2H-indazol-2-yl)methyl)benzamide
 N-(2-aminophenyl)-4-((3-cyano-1H-indazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-4-((3-cyano-2H-indazol-2-yl)methyl)benzamide
 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-indazole-3-carboxylic acid	 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2H-indazole-3-carboxylic acid
 N-(2-aminophenyl)-4-((5-cyano-1H-indazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-4-((5-cyano-2H-indazol-2-yl)methyl)benzamide
 N-(2-aminophenyl)-4-((3-(pyridin-2-yl)-1H-indazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-4-((3-(pyridin-2-yl)-2H-indazol-2-yl)methyl)benzamide
 N-(2-aminophenyl)-4-((3-(dimethylamino)-1H-indazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-4-((3-(dimethylamino)-2H-indazol-2-yl)methyl)benzamide

 4-((1H-indazol-1-yl)methyl)-N-(2-amino-5-(furan-2-yl)phenyl)benzamide	 4-((2H-indazol-2-yl)methyl)-N-(2-amino-5-(furan-2-yl)phenyl)benzamide
 N-(2-aminophenyl)-4-((3-methoxy-1H-indazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-4-((3-methoxy-2H-indazol-2-yl)methyl)benzamide
 N-(2-aminophenyl)-4-((3-(methoxymethylamino)-1H-indazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-4-((3-(methoxymethylamino)-2H-indazol-2-yl)methyl)benzamide
 4-((1H-pyrazol-1-yl)methyl)-N-(2-amino-5-fluorophenyl)benzamide	 N-(2-amino-5-fluorophenyl)-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide
 4-((1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)-3-methylbenzamide	 N-(2-amino-5-fluorophenyl)-3-methyl-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide
 N-(2-aminophenyl)-4-((4-(furan-2-yl)-1H-pyrazol-1-yl)methyl)benzamide	 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-pyrazole-4-carboxylic acid

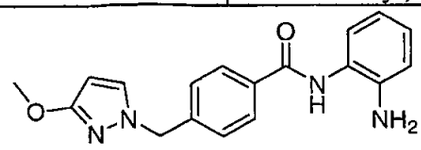
 N-(2-aminophenyl)-4-((3-ethyl-1H-pyrazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-4-((5-ethyl-1H-pyrazol-1-yl)methyl)benzamide
 N-(2-aminophenyl)-4-((4-phenyl-1H-pyrazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-3-methyl-4-((5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)benzamide
 N-(2-aminophenyl)-4-((3-cyano-1H-pyrazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-4-((5-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzamide
 4-((1H-pyrazol-1-yl)methyl)-N-(2-amino-5-(furan-2-yl)phenyl)benzamide	 N-(2-amino-5-(furan-2-yl)phenyl)-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide
 (S)-4-(1-(1H-pyrazol-1-yl)ethyl)-N-(2-aminophenyl)benzamide	 (R)-4-(1-(1H-pyrazol-1-yl)ethyl)-N-(2-aminophenyl)benzamide
 N-(2-aminophenyl)-4-((3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzamide	 N-(2-aminophenyl)-4-((5-methoxy-1H-pyrazol-1-yl)methyl)benzamide



N-(2-aminophenyl)-4-((3-(methoxymethylamino)-1H-pyrazol-1-yl)methyl)benzamide



N-(2-aminophenyl)-4-((5-(methoxymethylamino)-1H-pyrazol-1-yl)methyl)benzamide



N-(2-aminophenyl)-4-((3-methoxy-1H-pyrazol-1-yl)methyl)benzamide

Biological Testing

[0482] The activity of compounds as HDAC inhibitors may be assayed in vitro, in vivo or in a cell line. Further, compounds according to the present invention may be screened for activity against one or more HDACs. Provided below are assays for activity against HDAC1, HDAC2, HDAC6 and HDAC8.

[0483] Purified HDAC1, HDAC2, HDAC6, and HDAC8 may be obtained as follows.

[0484] For HDAC1, DNA encoding residues 1-482 of the full-length sequence of the human enzyme may be amplified by PCR and cloned into the BamHI/XbaI sites of pFastbac (Invitrogen), which incorporates a Flag tag at both the N- and C-terminus. SEQ ID NO: 1 corresponds to residues 1-482 with the N-and C-terminal Flag tag and SEQ ID NO: 2 is the DNA sequence that was used to encode SEQ ID NO: 1.

[0485] For HDAC2, DNA encoding residues 1-488 of the full-length sequence of the human enzyme may be amplified by PCR and cloned into the BamHI/SmaI sites of pFastbac (Invitrogen), which incorporates a 6-histidine tag at the C-terminus. SEQ ID NO: 3 corresponds to residues 1-488 with the C-terminal 6-histidine tag and SEQ ID NO: 4 is the DNA sequence that was used to encode SEQ ID NO: 3.

[0486] For HDAC6, DNA encoding residues 73-845 of the human enzyme may be amplified by PCR and cloned into the SmaI site of pFastbac (Invitrogen), which incorporates a 6xHistidine tag at the C-terminus. SEQ ID NO: 5 corresponds to residues 73-845 with the C-terminal 6-histidine tag and SEQ ID NO: 6 is the DNA sequence that was used to encode SEQ ID NO: 5.

[0487] For HDAC8, DNA encoding residues 1-377 corresponding to the entire sequence of the human enzyme may be amplified by PCR and cloned into the BamHI/SmaI sites of pFastbac (Invitrogen), which incorporates a 6-histidine tag at the N-terminus. SEQ ID NO: 7 corresponds to residues 1-377 with the N-terminal 6-histidine tag and SEQ ID NO: 8 is the DNA sequence that was used to encode SEQ ID NO: 7.

[0488] Recombinant baculovirus incorporating the HDAC constructs may be generated by transposition using the Bac-to-Bac system (Invitrogen). High-titer viral stocks may be generated by infection of Spodoptera frugiperda Sf9 cells; the expression of recombinant protein may be carried out by infection of Spodoptera frugiperda Sf9 or Trichoplusia ni Hi5 cells (Invitrogen) in 10L Wave Bioreactors (Wave Biotech).

[0489] Recombinant protein may be isolated from cellular extracts by passage over ProBond resin (Invitrogen), or Anti-Flag M2 Affinity Gel (Sigma) for HDAC1. Partially purified HDAC1 may then be further purified by high pressure liquid chromatography over a Mono Q column. Partially purified extracts of HDACs other than HDAC1 and HDAC6 may then be further purified by high pressure liquid chromatography over a BioSep S3000 gel filtration resin. The purity of HDAC proteins may be determined on denaturing SDS-PAGE gel. Purified HDACs may then be concentrated to a final concentration of 0.6 mg/ml for HDAC1, 10 mg/ml for HDAC2, 0.3 mg/ml for HDAC6, and 3 mg/ml for HDAC8. The proteins may be either stored at –78 °C in a buffer containing 25mM TRIS-HCl pH 7.6, 150mM NaCl, 0.1mM EDTA and 0.25 mM TCEP or at –20 °C in the presence of glycerol (final concentration of glycerol at 50%). Alternatively, HDAC6 protein can be stored at –78 °C in a buffer containing 25mM TRIS-HCl pH 7.2, 250mM NaCl, and 5% glycerol.

[0490] It should be noted that a variety of other expression systems and hosts are also suitable for the expression of HDAC, as would be readily appreciated by one of skill in the art.

[0491] The inhibitory properties of compounds relative to HDAC1, HDAC2, HDAC6 and HDAC8 may be determined using a white or black 384-well-plate format under the following reaction conditions: 25 mM Tris pH 8.0, 100 mM NaCl, 50 mM KCl, 0.1 mM EDTA, 0.01% Brij35, 0.1 mM TCEP. 50 μM tBoc-Lys(Ac)-AMC, 2% DMSO. Reaction product may be determined quantitatively by fluorescence intensity using a Fluorescence

plate reader (Molecular Devices Gemini) with an excitation wavelength at 370 nm and emission at 480 nm (for white plates) or 465 nm (for black plates).

[0492] The assay reaction may be initiated as follows: 5 µl of 150 µM tBoc-Lys(Ac)AMC was added to each well of the plate, followed by the addition of 5 µl of inhibitor (2 fold serial dilutions for 11 data points for each inhibitor) containing 6% DMSO. 5 µl of either HDAC1, HDAC2, HDAC6 or HDAC8 solution may be added to initiate the reaction (final enzyme concentrations were 2.5 nM for HDAC1, 1 nM for HDAC2, 2.5 nM for HDAC6 and 10 nM for HDAC8). The reaction mixture may then be incubated at room temperature for 60 minutes, and quenched and developed by addition of 5 µl of 10 mM phenanthroline and 4 mg/ml trypsin (final concentration of phenanthroline is 2.5 mM, and trypsin is 1 mg/ml). Fluorescence intensities of the resulting reaction mixtures may be measured after a 30 minute incubation at room temperature.

[0493] IC50 values may be calculated by non-linear curve fitting of the compound concentrations and fluorescence intensities to the standard IC50 equation. As a reference point for this assay, suberanilohydroxamic acid (SAHA) showed an IC_{50} of 63 nM for HDAC1, 69 nM for HDAC2, 108 nM for HDAC6 and 242 nM for HDAC8. IC_{50} values for selected compounds of the present invention are given in Table 4.

TABLE 4: IC_{50} of SELECTED EXEMPLIFIED COMPOUNDS AGAINST HDAC2

EXAMPLE	IC_{50}
1.	≤50 NM
2.	50-100 NM
3.	≤50 NM
4.	≤50 NM
5.	≤50 NM
6.	≤50 NM
7.	≤50 NM
8.	≤50 NM
9.	50-100 NM
10.	≤50 NM
11.	≤50 NM
12.	≤50 NM
13.	≤50 NM
14.	≤50 NM
15.	≤50 NM

EXAMPLE	IC_{50}
16.	≤50 NM
17.	≤50 NM
18.	≤50 NM
19.	100-500 NM
20.	≤50 NM
21.	≤50 NM
22.	≤50 NM
23.	≤50 NM
24.	100-500 NM
25.	100-500 NM
26.	≤50 NM
27.	≤50 NM
28.	50-100 NM
29.	50-100 NM
30.	50-100 NM
31.	≥500 NM
32.	≤50 NM
33.	≥500 NM
34.	100-500 NM
35.	50-100 NM
36.	50-100 NM
37.	50-100 NM
38.	≤50 NM
39.	≥500 NM
40.	100-500 NM
41.	50-100 NM
42.	≤50 NM
43.	≤50 NM
44.	50-100 NM
45.	50-100 NM
46.	50-100 NM
47.	50-100 NM
48.	50-100 NM
49.	≤50 NM
50.	50-100 NM
51.	50-100 NM
52.	50-100 NM
53.	50-100 NM
54.	100-500 NM
55.	50-100 NM
56.	50-100 NM
57.	50-100 NM
58.	50-100 NM
59.	≤50 NM

EXAMPLE	IC_{50}
60.	50-100 NM
61.	≤50 NM
62.	≤50 NM
63.	50-100 NM
64.	50-100 NM
65.	100-500 NM
66.	≤50 NM
67.	≤50 NM
68.	50-100 NM
69.	50-100 NM
70.	100-500 NM
71.	50-100 NM
72.	50-100 NM
73.	100-500 NM
74.	≤50 NM
75.	100-500 NM
76.	50-100 NM
77.	50-100 NM
78.	≤50 NM
79.	≤50 NM
80.	50-100 NM
81.	50-100 NM
82.	50-100 NM
83.	≤50 NM
84.	100-500 NM
85.	≤50 NM
86.	≤50 NM
87.	50-100 NM
88.	50-100 NM
89.	≤50 NM
90.	≤50 NM
91.	50-100 NM
92.	50-100 NM
93.	50-100 NM
94.	50-100 NM
95.	≤50 NM
96.	50-100 NM
97.	50-100 NM
98.	≤50 NM
99.	≤50 NM
100.	50-100 NM
101.	50-100 NM
102.	≥500 NM
103.	≤50 NM

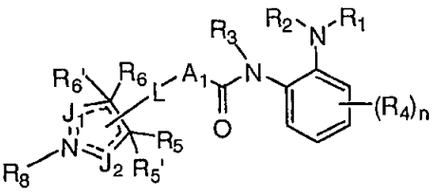
EXAMPLE	IC_{50}
104.	≥500 NM
105.	50-100 NM
106.	≤50 NM
107.	50-100 NM
108.	50-100 NM
109.	50-100 NM
110.	50-100 NM
111.	≤50 NM
112.	100-500 NM
113.	100-500 NM
114.	50-100 NM
115.	≤50 NM
116.	50-100 NM
117.	50-100 NM
118.	50-100 NM
119.	50-100 NM
120.	50-100 NM
121.	≤50 NM
122.	≥500 NM
123.	100-500 NM
124.	100-500 NM
125.	50-100 NM
126.	≤50 NM
127.	≤50 NM
128.	≤50 NM
129.	50-100 NM
130.	100-500 NM
131.	≥500 NM
132.	≥500 NM
133.	100-500 NM
134.	50-100 NM
135.	50-100 NM
136.	100-500 NM
137.	≤50 NM
138.	50-100 NM
139.	50-100 NM
140.	50-100 NM
141.	50-100 NM
142.	50-100 NM
143.	50-100 NM
144.	≤50 NM
145.	≤50 NM
146.	≤50 NM
147.	50-100 NM

EXAMPLE	IC_{50}
148.	100-500 NM
149.	≤50 NM
150.	≤50 NM
151.	50-100 NM
152.	≤50 NM
153.	≤50 NM
154.	≤50 NM
155.	≤50 NM
156.	50-100 NM
157.	100-500 NM
158.	50-100 NM

[0494] It will be apparent to those skilled in the art that various modifications and variations can be made in the compounds, compositions, kits, and methods of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

What is claimed is:

1. A compound comprising:



wherein:

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

J_1 is selected from the group consisting of $-CR_7R_7'$- and $-NR_{19}$-;

J_2 is selected from the group consisting of $-CR_{20}R_{20}'$ and $-NR_{10}$-;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl,

imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

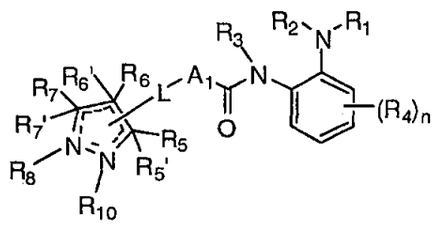
each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' may be taken together to form a substituted or unsubstituted ring, provided that R_5, R_6, R_7 and R_{20}, are each independently absent when the C to which they are bound is bound to L, and R_5', R_6', R_7' and R_{20}', are each independently absent when the C to which they are bound form part of a double bond; and

R_8, R_{10} and R_{19} are each individually selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}', R_{10} and R_{19} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}', and R_{19}, may be taken together to form a substituted or unsubstituted ring, or R_{19} and any one of R_5, R_5', R_6, R_6', R_{20}, and R_{20}', may be taken together to form a substituted or unsubstituted ring, provided that R_8, R_{10} and R_{19} are each independently absent when the N to which they are bound is bound to L, and R_8, R_{10} and R_{19} are each independently absent when the N to which they are bound form part of a double bond.

2. The compound according to claim 1 comprising



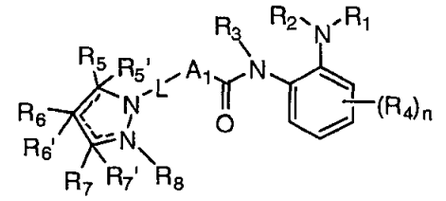
wherein:

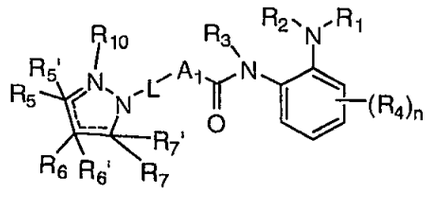
R_5, R_5', R_6, R_6', R_7 and R_7' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and

hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_5, R_6 and R_7 are each independently absent when the C to which they are bound is bound to L, and R_5', R_6' and R_7' are each independently absent when the C to which they are bound form part of a double bond; and

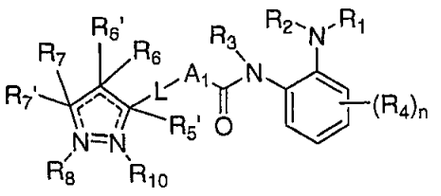
R_8 and R_{10} are each individually selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7' and R_{10} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_8 and R_{10} are each independently absent when the N to which they are bound is bound to L, and R_8 and R_{10} are each independently absent when the N to which they are bound form part of a double bond.

3. The compound according to claim 2, wherein the compound is selected from the group consisting of:





and



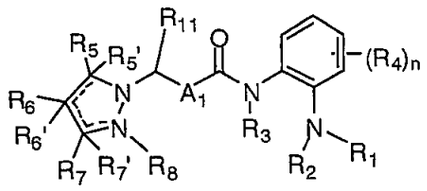
wherein:

R_5, R_5', R_6, R_6', R_7 and R_7' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_5', R_6' and R_7' are each independently absent when the C to which they are bound form part of a double bond; and

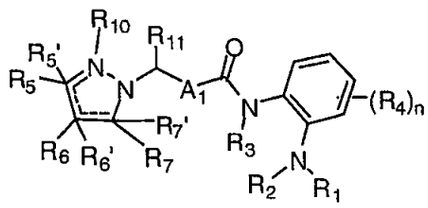
R_8 and R_{10} are each individually selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7' and R_{10} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6', R_7 and R_7' may be taken together to form a substituted or unsubstituted ring, provided that R_8 and R_{10}

are each independently absent when the N to which they are bound form part of a double bond.

4. The compound according to claim 3, wherein the compound is selected from the group consisting of:



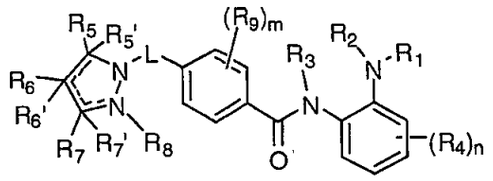
and



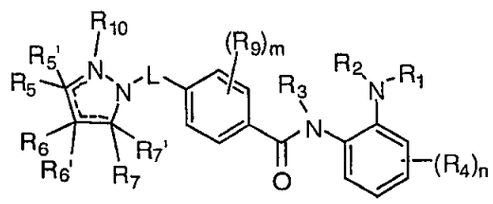
wherein:

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

5. The compound according to claim 3, wherein the compound is selected from the group consisting of:



and

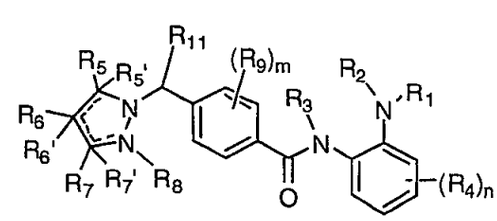


wherein:

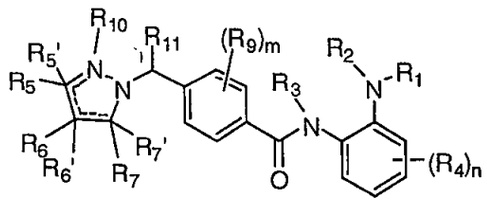
m is selected from the group consisting of 0, 1, 2, 3 and 4;

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_3, R_5, R_5', R_7, R_7', R_8 and R_{10} may be taken together to form a substituted or unsubstituted ring.

6. The compound according to claim 3, wherein the compound is selected from the group consisting of:



and



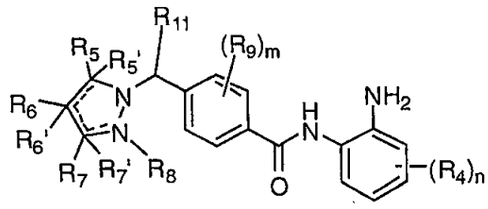
wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

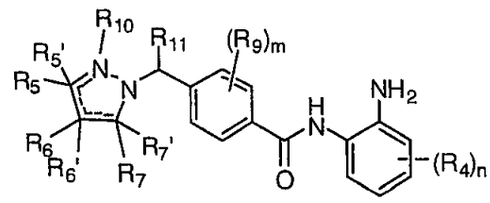
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_3, R_5, R_5', R_7, R_7', R_8 and R_{10} may be taken together to form a substituted or unsubstituted ring; and

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring.

7. The compound according to claim 3, wherein the compound is selected from the group consisting of:



and



wherein:

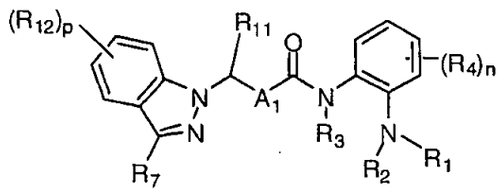
m is selected from the group consisting of 0, 1, 2, 3 and 4;

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_5, R_5', R_7, R_7', R_8 and R_{10} may be taken together to form a substituted or unsubstituted ring; and

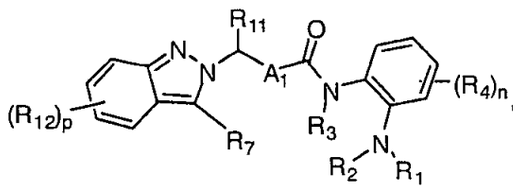
R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring.

8. The compound according to claim 3, wherein the compound is selected from the group consisting of:



and



wherein:

p is selected from the group consisting of 0, 1, 2, 3 and 4;

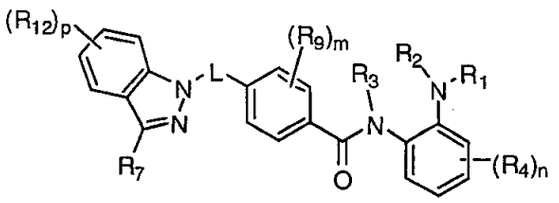
R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino,

sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_7 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

9. The compound according to claim 3, wherein the compound is selected from the group consisting of:



and

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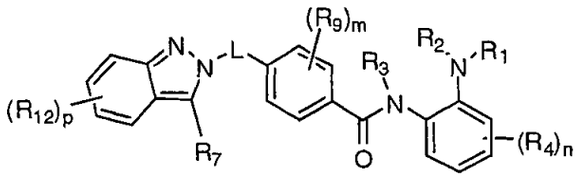


wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

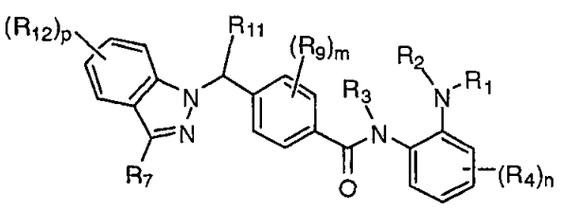
R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9, or one R_9 and R_3 may be taken together to form a substituted or unsubstituted ring; and

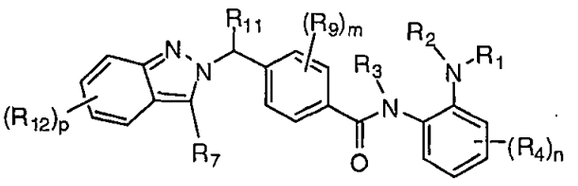
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl,

amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 may be taken together to form a substituted or unsubstituted ring.

10. The compound according to claim 3, wherein the compound is selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

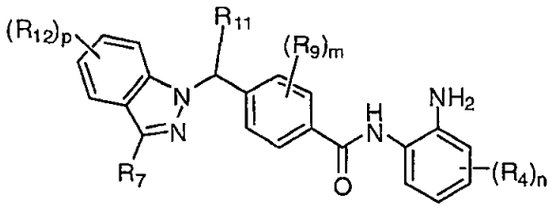
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and R_3 may be taken together to form a substituted or unsubstituted ring;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

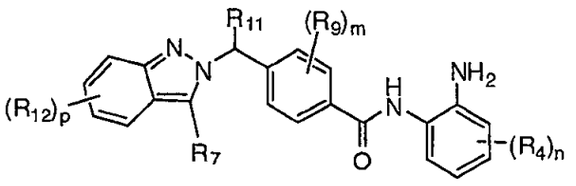
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

11. The compound according to claim 3, wherein the compound is selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

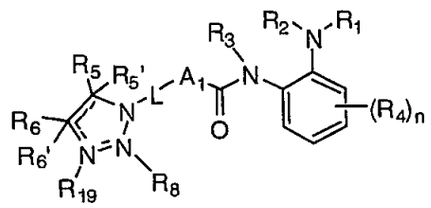
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 may be taken together to form a substituted or unsubstituted ring;

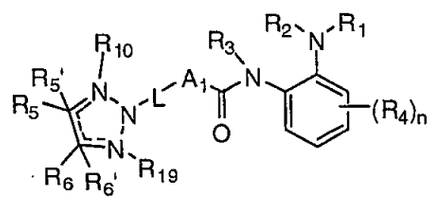
R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_7 or R_9 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and

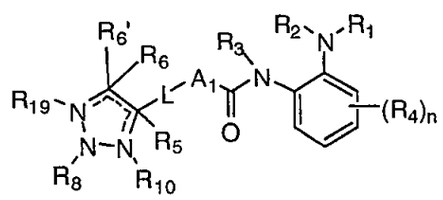
hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

12. The compound according to claim 1, wherein the compound is selected from the group consisting of:





and



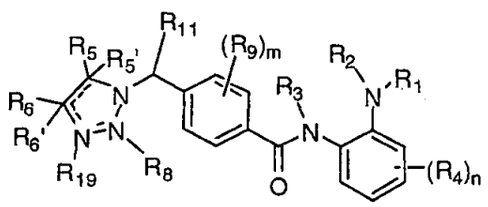
wherein:

R_5, R_5', R_6 and R_6' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6 and R_6' may be taken together to form a substituted or unsubstituted ring, provided that

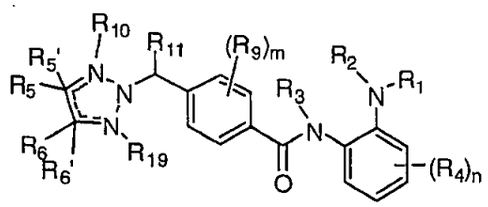
R_5' and R_6' are each independently absent when the C to which they are bound form part of a double bond; and

R_8, R_{10} and R_{19}, are each individually selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_{10} and R_{19} may be taken together to form a substituted or unsubstituted ring, or R_{10} and any one of R_5, R_5', R_6, R_6' and R_{19} may be taken together to form a substituted or unsubstituted ring, or R_{19} and any one of R_5, R_5', R_6 and R_6' may be taken together to form a substituted or unsubstituted ring, provided that R_8, R_{10} and R_{19} are each independently absent when the N to which they are bound form part of a double bond.

13. The compound according to claim 12, wherein the compound is selected from the group consisting of:



and



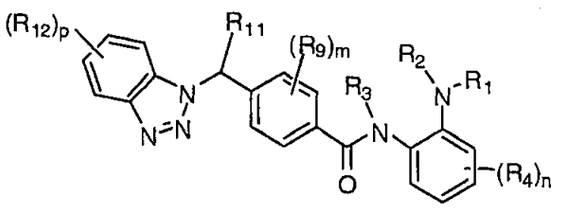
wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

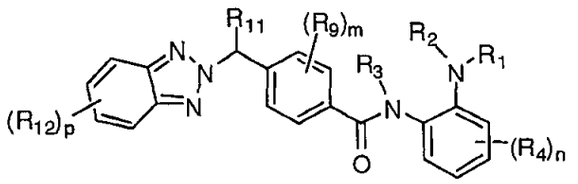
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_3, R_5, R_5', R_8, R_{10} and R_{19} may be taken together to form a substituted or unsubstituted ring; and

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring.

14. The compound according to claim 12, wherein the compound is selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

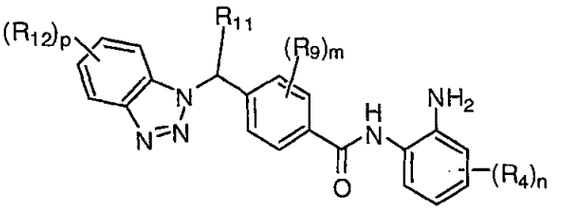
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and R_3 may be taken together to form a substituted or unsubstituted ring;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

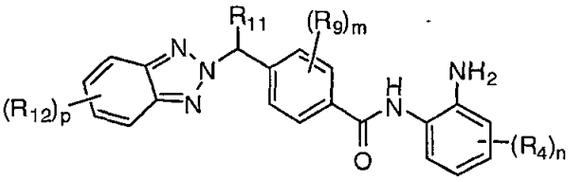
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl,

(C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_{11} may be taken together to form a substituted or unsubstituted.

15. The compound according to claim 12, wherein the compound is selected from the group consisting of:



and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

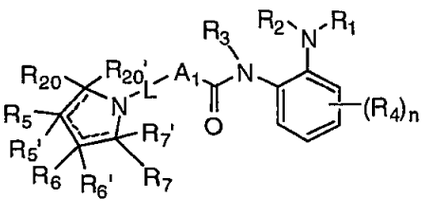
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

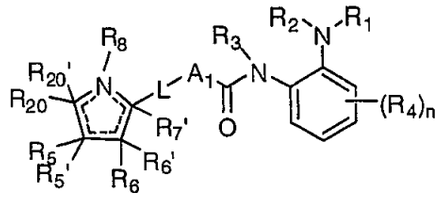
hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 may be taken together to form a substituted or unsubstituted ring;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxyl, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

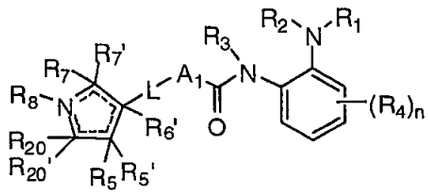
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxyl, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamide, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_{11} may be taken together to form a substituted or unsubstituted ring.

16. The compound according to claim 1, wherein the compound is selected from the group consisting of:





and



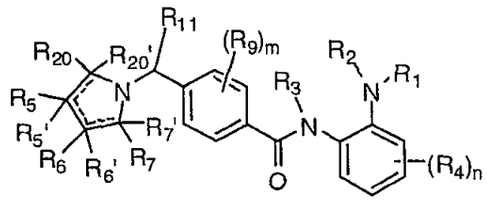
wherein:

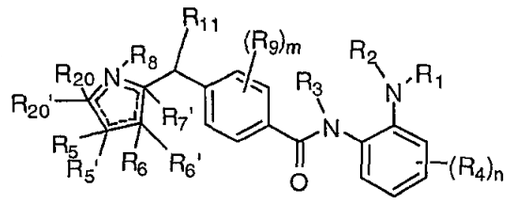
R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' may be taken together to form a substituted or unsubstituted ring, provided that R_5', R_6', R_7' and R_{20}' are each independently absent when the C to which they are bound form part of a double bond; and

R_8 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl,

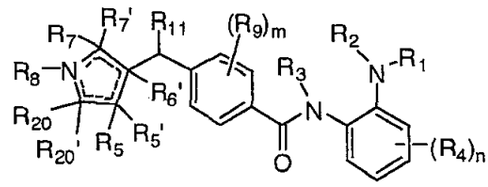
(C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 and any one of R_5, R_5', R_6, R_6', R_7, R_7', R_{20} and R_{20}' may be taken together to form a substituted or unsubstituted ring, provided that R_8 is absent when the N to which it is bound forms part of a double bond.

17. The compound according to claim 16, wherein the compound is selected from the group consisting of:





and



wherein:

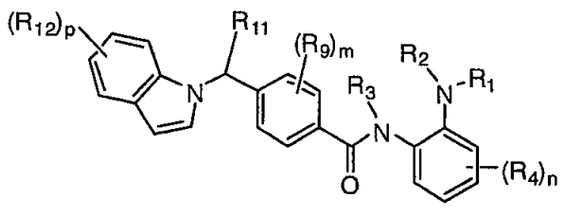
m is selected from the group consisting of 0, 1, 2, 3 and 4;

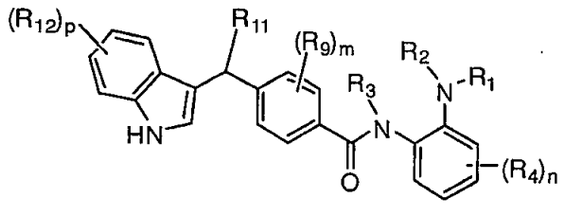
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl,

(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and any one of R_3, R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}' and R_8 may be taken together to form a substituted or unsubstituted ring; and

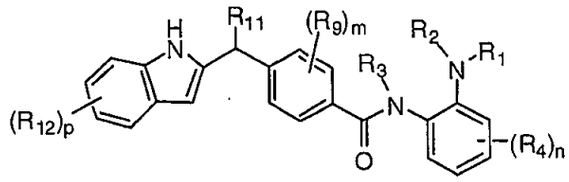
R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring.

18. The compound according to claim 16, wherein the compound is selected from the group consisting of:





and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

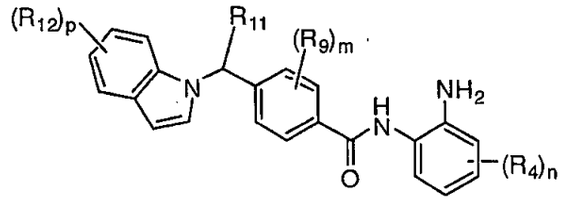
each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 or one R_9 and R_3 may be taken together to form a substituted or unsubstituted ring;

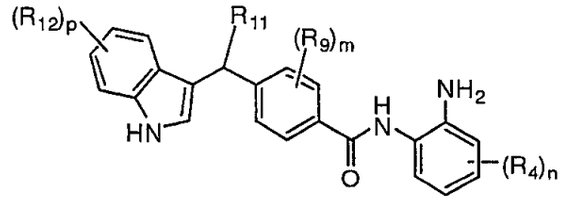
R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl,

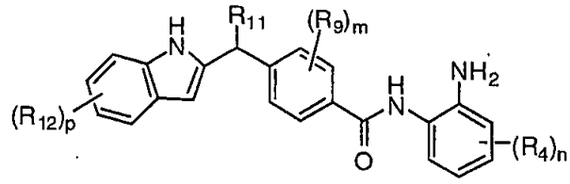
(C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_{11} may be taken together to form a substituted or unsubstituted ring.

19. The compound according to claim 16, wherein the compound is selected from the group consisting of:





and



wherein:

m is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

each R_9 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two R_9 may be taken together to form a substituted or unsubstituted ring;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{11} and R_9 may be taken together to form a substituted or unsubstituted ring; and

each R_{12} *is independently selected from the group consisting of* hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_{11} may be taken together to form a substituted or unsubstituted ring.

20. The compound according to any one of claims 1-6, 8-10, 12-14 and 16-18, wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl and imino(C_{1-3})alkyl, each substituted or unsubstituted.

21. The compound according to any one of claims 1-6, 8-10, 12-14 and 16-18, wherein R_1 is hydrogen or a substituent convertible *in vivo* to hydrogen.

22. The compound according to any one of claims 1-6, 8-10, 12-14 and 16-18, wherein R_2 is hydrogen or a substituent convertible *in vivo* to hydrogen.

23. The compound according to any one of claims 1-6, 8-10, 12-14 and 16-18, wherein R_3 is hydrogen or a substituent convertible *in vivo* to hydrogen.

24. The compound according to any one of claims 1-19, wherein R_4 is selected from the group consisting of hydrogen, halo, aryl and heteroaryl, each substituted or unsubstituted.

25. The compound according to any one of claims 1-19, wherein R_4 is selected from the group consisting of phenyl, oxazolyl, thiazolyl, morpholinyl and thiomorpholinyl, each substituted or unsubstituted.

26. The compound according to any one of claims 1-13 and 16-17, wherein R_5, R_6, R_7 and R_{20} are each independently selected from the group consisting of carbonyl, oxo, amino, (C_{1-10})alkylamino, amido, carboxamido, cyano, alkoxy, (C_{1-10})alkyl, aryl, and heteroaryl, each substituted or unsubstituted.

27. The compound according to any one of claims 1-7, 12-13 and 16-17, wherein R_5 and R_6 are taken together to form a substituted or unsubstituted ring.

28. The compound according to any one of claims 1-7, 12-13 and 16-17, wherein R_5 and R_6 are taken together to form a ring selected from the group consisting of aryl and heteroaryl, each substituted or unsubstituted.

29. The compound according to any one of claims 1-7, 12-13 and 16-17, wherein the ring formed by R_5 and R_6 is substituted with a substituent selected from the group consisting of halo, alkoxy, amino(C_{1-10})alkoxy, amino(C_{1-10})alkylamino, amino(C_{1-10})alkylsulfanyl, amido, carboxamido, halo(C_{1-10})alkyl, aryl and heteroaryl, each substituted or unsubstituted.

30. The compound according to any one of claims 1-7, 12-13 and 16-17, wherein the ring formed by R_5 and R_6 is substituted with a substituent selected from the group consisting of thiopheneyl, pyridinyl, furanyl and pyrimidinyl, each substituted or unsubstituted.

31. The compound according to any one of claims 1-7, 12-13 and 16-17, wherein the ring formed by R_5 and R_6 is substituted with $-O-CH_2CH_2-NR_{13}R_{14}$, wherein R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero (C_{8-12})bicycloaryl (C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{13} and R_{14} may be taken together to form a substituted or unsubstituted ring.

32. The compound according any one of claims 1-7, 12-13 and 16-17, wherein the ring formed by R_5 and R_6 is substituted with $-NH-CH_2CH_2-NR_{13}R_{14}$, wherein R_{13} and R_{14} are

each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero (C_{8-12})bicycloaryl (C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{13} and R_{14} may be taken together to form a substituted or unsubstituted ring.

33. The compound according to any one of claims 1-7, 12-13 and 16-17, wherein the ring formed by R_5 and R_6 is substituted with $-S-CH_2CH_2-NR_{13}R_{14}$, wherein R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero (C_{8-12})bicycloaryl (C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{13} and R_{14} may be taken together to form a substituted or unsubstituted ring.

34. The compound according to any one of claims 31-33, wherein R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, and heteroaryl, each substituted or unsubstituted.

35. The compound according to any one of claims 31-33, wherein R_{13} and R_{14} are taken together to form a ring selected from the group consisting of morpholinyl, pyrrolidinyl, piperazinyl and thiomorpholinyl, each substituted or unsubstituted.

36. The compound according to any one of claims 1-7, 12-13, and 16-17, wherein R_8, R_{10} and R_{19} are each independently selected from the group consisting of hydrogen and substituted or unsubstituted (C_{1-10})alkyl.

37. The compound according to any one of claims 1-3, 5, 9, 12 and 16 wherein L is a linker providing a 1-5 atom separation between the two ring atoms to which L is attached.

38. The compound according to any one of claims 1-3, 5, 9, 12 and 16, wherein L is a linker providing a 1-3 atom separation between the two ring atoms to which L is attached.

39. The compound according to any one of claims 1-3, 5, 9, 12 and 16, wherein L is a substituted or unsubstituted alkylene.

40. The compound according to any one of claims 1-3, 5, 9, 12 and 16, wherein L is $-CH_2-$.

41. The compound according to any one of claims 1-3, 5, 9, 12 and 16, wherein L is selected from the group consisting of $-NR_{15}-$; $-NR_{15}-CH_2-$; $-O-CH_2-$; $-S-CH_2-$; $-CH_2-NR_{15}-$; $-CH_2-O-$ and $-CH_2-S-$, wherein R_{15} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

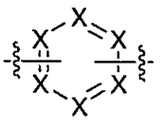
42. The compound according to any one of claims 1-4, 8, 12 and 16, wherein A_1 is selected from the group consisting of aryl and heteroaryl, each substituted or unsubstituted.

43. The compound according to any one of claims 1-4, 8, 12 and 16, wherein A_1 is a substituted or unsubstituted phenylene.

44. The compound according to any one of claims 1-4, 8, 12 and 16, wherein A_1 is a substituted or unsubstituted 1,4-phenylene.

45. The compound according to any one of claims 1-4, 8, 12 and 16, wherein A_1 is selected from the group consisting of a thiophenediyl, furandiyl, pyrrolediyl, thiazolediyl, oxazolediyl, imidazolediyl and pyridinediyl, each substituted or unsubstituted.

46. The compound according to any one of claims 1-4, 8, 12 and 16, wherein A_1 comprises:



wherein:

each X is independently selected from the group consisting of CR_{16} and N; and

each R_{16} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{16} is absent

when the C to which it is bound is further bound to L or the carbonyl adjacent to A_1.

47. The compound according to claim 11, wherein m is 0, R_{11} is hydrogen, and R_{12} is selected from the group consisting of hydroxyl, alkoxy, halo, amido, carboxamido, and (C_{1-10})alkylamido, each substituted or unsubstituted.

48. The compound according to claim 47, wherein n is 0, p is 2, and R_{12} is selected from the group consisting of hydroxyl, alkoxy, and halo.

49. The compound according to claim 48, wherein R_7 is hydrogen, and R_{12} is alkoxy.

50. A compound selected from the group consisting of:

4-((1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((2*H*-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-acetamido-1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-acetamido-2*H*-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((5-nitro-1H-indazol-1-yl)methyl)benzamide;

4-((5-benzamido-1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-amino-1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((5-nitro-2*H*-indazol-2-yl)methyl)benzamide;

4-((5-amino-2*H*-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-benzamido-2*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

2-Methoxyethyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-ylcarbamate;

Methyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-ylcarbamate;

2-Methoxyethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate;

Methyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate;

Benzyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate;

Benzyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-ylcarbamate;

N-(4-Amino-biphenyl-3-yl)-4-(5-nitro-indazol-2-ylmethyl)-benzamide;

N-(2-(4-((2-Aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-yl)morpholine-4-carboxamide;

5-((2*H*-Indazol-2-yl)methyl)-N-(2-aminophenyl)thiophene-2-carboxamide;

N-(2-Aminophenyl)-5-((5-nitro-2*H*-indazol-2-yl)methyl)thiophene-2-carboxamide;

N-(1-(4-((2-Aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-yl)morpholine-4-carboxamide;

2-Morpholinoethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate;

Pyridin-3-ylmethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate;

5-((1*H*-Indazol-1-yl)methyl)-N-(2-aminophenyl)thiophene-2-carboxamide;

4-((2*H*-Pyrazolo[3,4-b]pyridine-2-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(4-Amino-biphenyl-3-yl)-4-pyrazolo[3,4-*b*]□yridine-2-ylmethyl-benzamide;

N-(4-Amino-biphenyl-3-yl)-4-indazol-2-ylmethyl-benzamide;

N-(2-Aminophenyl)-4-((3-methyl-1*H*-indazol-1-yl)methyl)benzamide;

N-(2-Aminophenyl)-4-((3-methyl-2*H*-indazol-2-yl)methyl)benzamide;

4-((1H-indazol-3-ylamino)methyl)-N-(2-aminophenyl)benzamide;

4-((1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-(4-((2-Aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-yl)morpholine-4-carboxamide;

Methyl 3-(4-((2H-indazol-2-yl)methyl)benzamido)-4-aminobenzoate;

N-(2-aminophenyl)-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-fluoro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-fluoro-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5-fluoro-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5-fluoro-2H-indazol-2-yl)methyl)benzamide;
4-(1-(1H-indazol-1-yl)propan-2-yl)-N-(2-aminophenyl)benzamide;
4-(2-(1H-indazol-1-yl)ethyl)-N-(2-aminophenyl)benzamide;
4-(2-(2H-indazol-2-yl)ethyl)-N-(2-aminophenyl)benzamide;
N-(2-aminophenyl)-4-((4-chloro-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-chloro-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4,6-difluoro-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4,6-difluoro-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((7-fluoro-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((7-fluoro-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-fluoro-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-fluoro-2H-indazol-2-yl)methyl)benzamide;
(R)-4-(1-(2H-indazol-2-yl)ethyl)-N-(2-aminophenyl)benzamide;
(S)-4-(1-(2H-indazol-2-yl)ethyl)-N-(2-aminophenyl)benzamide;
N-(2-aminophenyl)-4-((7-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((7-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5,6-difluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5,6-difluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((6-methoxy-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((6-methoxy-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-chloro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-chloro-2H-indazol-2-yl)methyl)benzamide;

4-((3-amino-5-(trifluoromethyl)-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((3-amino-5-(trifluoromethyl)-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((3-oxo-2,3-dihydro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-oxo-1H-indazol-2(3H)-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-methoxy-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-methoxy-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-fluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-fluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-ethyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-ethyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-hydroxy-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-hydroxy-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-phenyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-phenyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-methoxy-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-methoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3,5-dimethyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3,5-dimethyl-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((7-methoxy-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-methoxy-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((7-methoxy-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-methoxy-1H-indazol-1-yl)methyl)benzamide;
4-((6-acetamido-3-methyl-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;
4-((6-acetamido-3-methyl-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;
4-((3-amino-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;
4-((6-acetamido-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;
4-((6-acetamido-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;
N-(2-aminophenyl)-4-((3-methyl-7-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-methyl-6-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-methyl-6-(trifluoromethyl)-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-methyl-5-(trifluoromethyl)-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-methyl-5-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide;
4-((3-amino-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;
N-(2-aminophenyl)-4-((5-hydroxy-6-methoxy-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5,6-dimethoxy-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5,6-dimethoxy-1H-indazol-1-yl)methyl)benzamide;
4-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;
4-((2*H*-benzo[*d*][1,2,3]triazol-2-yl)methyl)-*N*-(2-aminophenyl)benzamide;
4-((5-acetamido-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(piperazin-1-yl)ethyl)-1H-pyrazole-4-carboxamide;

4-((2*H*-indazol-2-yl)methyl)-*N*-(4-aminopyrimidin-5-yl)benzamide;

4-((5-acetamido-3-amino-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;

4-((5-acetamido-3-methyl-2*H*-indazol-2-yl)methyl)-*N*-(2-aminophenyl)benzamide;

4-((5-acetamido-3-methyl-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)benzamide;

4-(1-(1*H*-indazol-1-yl)ethyl)-*N*-(2-aminophenyl)benzamide;

4-(1-(2*H*-indazol-2-yl)ethyl)-*N*-(2-aminophenyl)benzamide;

5-((5-acetamido-1*H*-indazol-1-yl)methyl)-*N*-(2-aminophenyl)thiophene-2-carboxamide;

4-((2*H*-indazol-2-yl)methyl)-*N*-(2-amino-5-(thiophen-2-yl)phenyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4,6-difluoro-2*H*-indazol-2-yl)methyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4,6-difluoro-1*H*-indazol-1-yl)methyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((6-methoxy-3-methyl-1*H*-indazol-1-yl)methyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-methyl-1*H*-pyrazol-1-yl)methyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((6-methoxy-3-methyl-2*H*-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-(trifluoromethyl)-1*H*-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-(trifluoromethyl)-1*H*-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-1H-pyrazole-4-carboxylic acid;

N-(2-aminophenyl)-4-((3-methyl-1H-pyrazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzamide;

Ethyl 1-(4-(2-aminophenylcarbamoyl)benzyl)-1H-pyrazole-4-carboxylate;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridine-2-ylmethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-phenyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-benzyl-1H-pyrazole-4-carboxamide;

N-(2-aminophenyl)-4-((4,5,6,7-tetrahydro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4,5,6,7-tetrahydro-1H-indazol-1-yl)methyl)benzamide;

4-((1H-pyrazol-3-ylamino)methyl)-N-(2-aminophenyl)benzamide;

4-((5-amino-1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((3-amino-1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-methyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-ethyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N,N-dimethyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-isopropyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-cyclopropyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(cyclopropylmethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(dimethylamino)ethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-hydroxyethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-(dimethylamino)propyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridine-3-ylmethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridine-4-ylmethyl)-1H-pyrazole-4-carboxamide.;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-morpholinoethyl)-1H-pyrazole-4-carboxamide;

N-(2-aminophenyl)-4-((5-methyl-1H-pyrazol-1-yl)methyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-propyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-isobutyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-methoxyethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-methoxypropyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-hydroxypropyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-morpholinopropyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(piperidin-1-yl)ethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-(4-methylpiperazin-1-yl)propyl)-1H-pyrazole-4-carboxamide;

4-((1*H*-Pyrrolo[2,3-b]pyridine-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((1*H*-Indol-3-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((1H-indazol-1-yl)methyl)-N-(2-amino-5-fluorophenyl)benzamide;

4-((2H-indazol-2-yl)methyl)-N-(2-amino-5-fluorophenyl)benzamide;

4-((1H-indazol-1-yl)methyl)-N-(2-amino-5-fluorophenyl)-3-methylbenzamide;

4-((2H-indazol-2-yl)methyl)-N-(2-amino-5-fluorophenyl)-3-methylbenzamide;

N-(2-aminophenyl)-3-methyl-4-((3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-3-methyl-4-((3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-cyano-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-cyano-2H-indazol-2-yl)methyl)benzamide;

1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-indazole-3-carboxylic acid;

2-(4-((2-aminophenyl)carbamoyl)benzyl)-2H-indazole-3-carboxylic acid;

N-(2-aminophenyl)-4-((5-cyano-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-cyano-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-(pyridine-2-yl)-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-(pyridine-2-yl)-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-(dimethylamino)-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-(dimethylamino)-2H-indazol-2-yl)methyl)benzamide;

4-((1H-indazol-1-yl)methyl)-N-(2-amino-5-(furan-2-yl)phenyl)benzamide;

4-((2H-indazol-2-yl)methyl)-N-(2-amino-5-(furan-2-yl)phenyl)benzamide;

N-(2-aminophenyl)-4-((3-methoxy-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-methoxy-2H-indazol-2-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-(methoxymethylamino)-1H-indazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-(methoxymethylamino)-2H-indazol-2-yl)methyl)benzamide;
4-((1H-pyrazol-1-yl)methyl)-N-(2-amino-5-fluorophenyl)benzamide;
N-(2-amino-5-fluorophenyl)-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide;
4-((1H-pyrazol-1-yl)methyl)-N-(2-aminophenyl)-3-methylbenzamide;
N-(2-amino-5-fluorophenyl)-3-methyl-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-(furan-2-yl)-1H-pyrazol-1-yl)methyl)benzamide;
1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-pyrazole-4-carboxylic acid;
N-(2-aminophenyl)-4-((3-ethyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5-ethyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((4-phenyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-3-methyl-4-((5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-cyano-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5-(pyridine-2-yl)-1H-pyrazol-1-yl)methyl)benzamide;
4-((1H-pyrazol-1-yl)methyl)-N-(2-amino-5-(furan-2-yl)phenyl)benzamide;
N-(2-amino-5-(furan-2-yl)phenyl)-4-((4-methyl-1H-pyrazol-1-yl)methyl)benzamide;
(S)-4-(1-(1H-pyrazol-1-yl)ethyl)-N-(2-aminophenyl)benzamide;
(R)-4-(1-(1H-pyrazol-1-yl)ethyl)-N-(2-aminophenyl)benzamide;
N-(2-aminophenyl)-4-((3-(pyridine-2-yl)-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((5-methoxy-1H-pyrazol-1-yl)methyl)benzamide;
N-(2-aminophenyl)-4-((3-(methoxymethylamino)-1H-pyrazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-(methoxymethylamino)-1H-pyrazol-1-yl)methyl)benzamide; and

N-(2-aminophenyl)-4-((3-methoxy-1H-pyrazol-1-yl)methyl)benzamide.

51. A compound selected from the group consisting of:

4-((1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-acetamido-1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-acetamido-2*H*-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((5-nitro-1H-indazol-1-yl)methyl)benzamide;

4-((5-benzamido-1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((5-amino-1*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((5-nitro-2*H*-indazol-2-yl)methyl)benzamide;

4-((5-benzamido-2*H*-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

2-Methoxyethyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2H-indazol-5-ylcarbamate;

Methyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-ylcarbamate;

2-Methoxyethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate;

Methyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1H-indazol-5-ylcarbamate;

Benzyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate;

Benzyl 2-(4-((2-aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-ylcarbamate;

N-(4-Amino-biphenyl-3-yl)-4-(5-nitro-indazol-2-ylmethyl)-benzamide;

N-(2-(4-((2-Aminophenyl)carbamoyl)benzyl)-2*H*-indazol-5-yl)morpholine-4-carboxamide;

N-(2-Aminophenyl)-5-((5-nitro-2*H*-indazol-2-yl)methyl)thiophene-2-carboxamide;

N-(1-(4-((2-Aminophenyl)carbamoyl)benzyl)-1H-indazol-5-yl)morpholine-4-carboxamide;

2-Morpholinoethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate;

Pyridin-3-ylmethyl 1-(4-((2-aminophenyl)carbamoyl)benzyl)-1*H*-indazol-5-ylcarbamate;

N-(4-Amino-biphenyl-3-yl)-4-pyrazolo[3,4-*b*]pyridin-2-ylmethyl-benzamide;

N-(4-Amino-biphenyl-3-yl)-4-indazol-2-ylmethyl-benzamide;

N-(2-aminophenyl)-4-((5-fluoro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-chloro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-chloro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-fluoro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-methoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((3-chloro-2H-indazol-2-yl)methyl)benzamide;

4-((3-amino-5-(trifluoromethyl)-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((6-methoxy-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-methoxy-3-methyl-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-hydroxy-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-methoxy-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5-methoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-methoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4-methoxy-1H-indazol-1-yl)methyl)benzamide;

4-((6-acetamido-3-methyl-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((6-acetamido-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((6-acetamido-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-aminophenyl)-4-((3-methyl-5-(trifluoromethyl)-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-dimethoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-dimethoxy-1H-indazol-1-yl)methyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(piperazin-1-yl)ethyl)-1H-pyrazole-4-carboxamide;

4-((2*H*-indazol-2-yl)methyl)-*N*-(2-amino-5-(thiophen-2-yl)phenyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-methyl-1*H*-pyrazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((6-(trifluoromethyl)-2*H*-indazol-2-yl)methyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-phenyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-benzyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-isopropyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-(dimethylamino)propyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridin-3-ylmethyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(pyridin-4-ylmethyl)-1H-pyrazole-4-carboxamide.;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-propyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-isobutyl-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-methoxypropyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-hydroxypropyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(3-morpholinopropyl)-1H-pyrazole-4-carboxamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-(2-(piperidin-1-yl)ethyl)-1H-pyrazole-4-carboxamide;

52. A compound selected from the group consisting of:

N-(2-aminophenyl)-4-((4,6-difluoro-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((4,6-difluoro-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-difluoro-3-methyl-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-difluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide;

4-((3-amino-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((6-acetamido-1H-indazol-1-yl)methyl)-N-(2-aminophenyl)benzamide;

4-((6-acetamido-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4,6-difluoro-2*H*-indazol-2-yl)methyl)benzamide;

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4,6-difluoro-1*H*-indazol-1-yl)methyl)benzamide;

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-ethyl-1H-pyrazole-4-carboxamide;

N-(2-aminophenyl)-4-((5,6-dimethoxy-1H-indazol-1-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-dimethoxy-2H-indazol-2-yl)methyl)benzamide; and

N-(2-aminophenyl)-4-((5-hydroxy-6-methoxy-2H-indazol-2-yl)methyl)benzamide.

53. A compound selected from the group consisting of:

1-(4-(2-aminophenylcarbamoyl)benzyl)-N-ethyl-1H-pyrazole-4-carboxamide;

N-(2-aminophenyl)-4-((5,6-dimethoxy-2H-indazol-2-yl)methyl)benzamide;

4-((6-acetamido-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide; and

4-((3-amino-2H-indazol-2-yl)methyl)-N-(2-aminophenyl)benzamide.

54. A compound selected from the group consisting of:

N-(2-aminophenyl)-4-((5-hydroxy-6-methoxy-2H-indazol-2-yl)methyl)benzamide.

N-(2-aminophenyl)-4-((5,6-dimethoxy-2H-indazol-2-yl)methyl)benzamide;

N-(2-aminophenyl)-4-((5,6-difluoro-3-methyl-2H-indazol-2-yl)methyl)benzamide; and

N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4,6-difluoro-2*H*-indazol-2-yl)methyl)benzamide.

55. The compound according to any one of claims 1-54, wherein the compound is in the form of a pharmaceutically acceptable salt.

56. The compound according to any one of claims 1-55, wherein the compound is present in a mixture of stereoisomers.

57. The compound according to any one of claims 1-55, wherein the compound comprises a single stereoisomer.

58. A pharmaceutical composition comprising as an active ingredient a compound according to any one of claims 1-57.

59. The pharmaceutical composition according to claim 58, wherein the composition is a solid formulation adapted for oral administration.

60. The pharmaceutical composition according to claim 58, wherein the composition is a liquid formulation adapted for oral administration.

61. The pharmaceutical composition according to claim 58, wherein the composition is a tablet.

62. The pharmaceutical composition according to claim 58, wherein the composition is a liquid formulation adapted for parenteral administration.

63. A pharmaceutical composition comprising a compound according to any one of claims 1-57, wherein the composition is adapted for administration by a route selected from the group consisting of orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery, subcutaneously, intraadiposally, intraarticularly, and intrathecally.

64. A kit comprising:

a compound of any one of claims 1-57; and

instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the compound is to be administered, storage information for the compound, dosing information and instructions regarding how to administer the compound.

65. The kit of claim 64, wherein the kit comprises the compound in a multiple dose form.

66. An article of manufacture comprising:

a compound of any one of claims 1-57; and

packaging materials.

67. The article of manufacture of claim 66, wherein the packaging material comprises a container for housing the compound.

68. The article of manufacture of claim 67, wherein the container comprises a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the compound.

69. The article of manufacture of claim 66, wherein the article of manufacture comprises the compound in a multiple dose form.

70. A therapeutic method comprising:
administering a compound according to any one of claims 1-57 to a subject.

71. A method of inhibiting histone deacetylase comprising:
contacting histone deacetylase with a compound according to any one of claims 1-57.

72. A method of inhibiting histone deacetylase comprising:
causing a compound according to any one of claims 1-57 to be present in a subject in order to inhibit histone deacetylase *in vivo*.

73. A method of inhibiting histone deacetylase comprising:
administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits histone deacetylase *in vivo*, the second compound being a compound according to any one of claims 1-57.

74. A method of treating a disease state for which histone deacetylase possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising:

causing a compound according to any one of claims 1-57 to be present in a subject in a therapeutically effective amount for the disease state.

75. A method of treating a disease state for which histone deacetylase possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising:

administering a first compound to a subject that is converted *in vivo* to a second compound according to any one of claims 1-57 wherein the second compound is present in a subject in a therapeutically effective amount for the disease state.

76. A method of treating a disease state for which histone deacetylase possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising:

administering a compound according to any one of claims 1-57, wherein the compound is present in the subject in a therapeutically effective amount for the disease state.

77. The method according to any one of claims 71-76, wherein the histone deacetylase is a HDAC2.

78. The method according to any one of claims 71-76, wherein the histone deacetylase is a HDAC8.

79. A method for treating cancer comprising:

administering a composition according to any one of claims 1-57 to a mammalian species in need thereof.

80. The method of claim 79, wherein the cancer is selected from the group consisting of squamous cell carcinoma, astrocytoma, Kaposi's sarcoma, glioblastoma, non small-cell lung cancer, bladder cancer, head and neck cancer, melanoma, ovarian cancer, prostate

cancer, breast cancer, small-cell lung cancer, glioma, colorectal cancer, genitourinary cancer and gastrointestinal cancer.

81. A method for treating inflammation, inflammatory bowel disease, psoriasis, or transplant rejection, comprising administering a compound according to any one of claims 1-57 to a mammalian species in need thereof.

82. A method for treating arthritis comprising administering a compound according to any one of claims 1-57 to a mammalian species in need thereof.

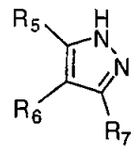
83. A method for treating degenerative diseases of the eye comprising administering a compound according to any one of claims 1-57 to a mammalian species in need thereof.

84. A method for treating multiple sclerosis, amyotrophic lateral sclerosis, thyroid neoplasm or Alzheimer's disease comprising administering a compound according to any one of claims 1-57 to a mammalian species in need thereof.

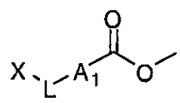
85. A method for treating hyperproliferative skin diseases or inflammatory cutaneous disorders comprising administering a compound according to any one of claims 1-57 to a mammalian species in need thereof.

86. A process comprising:

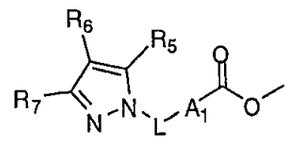
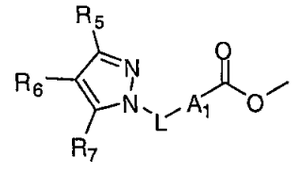
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising a formula selected from the group consisting of

 and  ,

wherein

X is a leaving group;

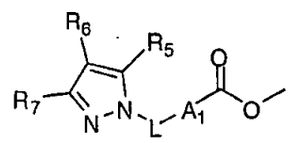
A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached; and

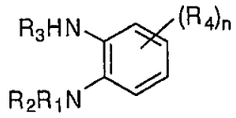
R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

87. A process comprising:

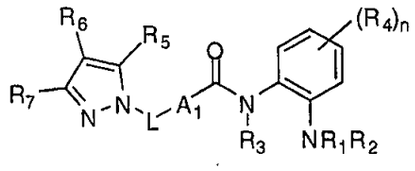
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising a formula



wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl,

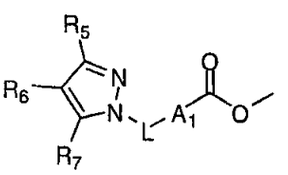
aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

88. A process comprising:

reacting a compound comprising the formula



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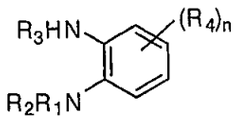
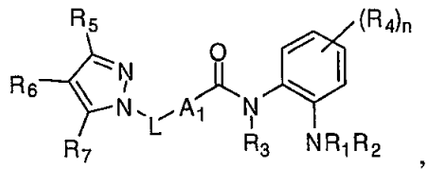
with a compound comprising the formula



under conditions that form a reaction product comprising a formula



wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl,

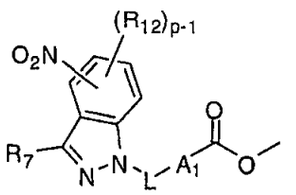
aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

89. A process comprising:

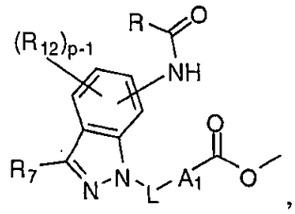
reacting a compound comprising the formula



with a compound comprising the formula

R-C(O)-X

under conditions that form a reaction product comprising a formula



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

X is a leaving group;

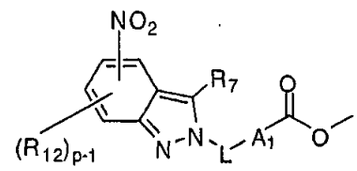
R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

90. A process comprising:

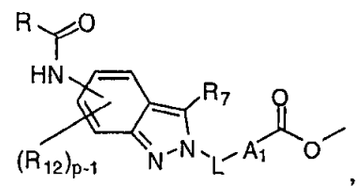
reacting a compound comprising the formula



with a compound comprising the formula

R-C(O)-X

under conditions that form a reaction product comprising a formula



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

X is a leaving group;

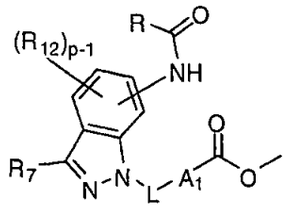
R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl,

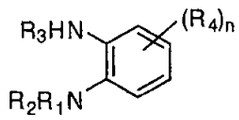
sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

91. A process comprising:

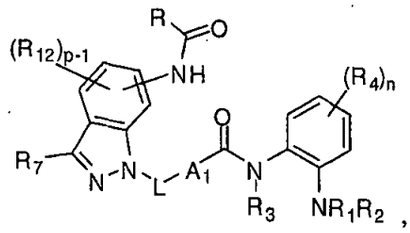
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising a formula



wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl,

(C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

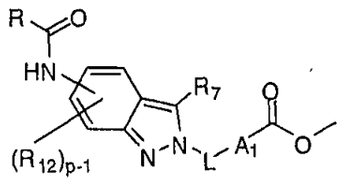
R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and

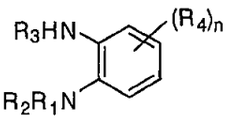
hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

92. A process comprising:

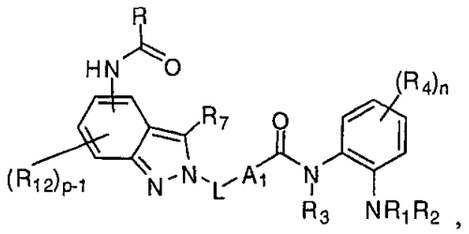
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising a formula



wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl,

thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl,

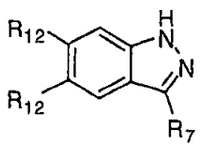
(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

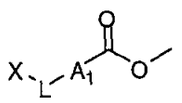
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

93. A process comprising:

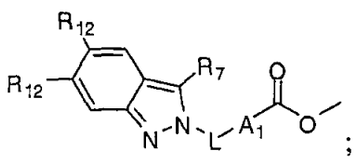
reacting a compound comprising the formula



with a compound comprising the formula

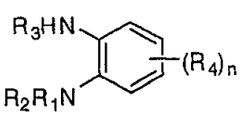


under conditions that form a first reaction product comprising a formula

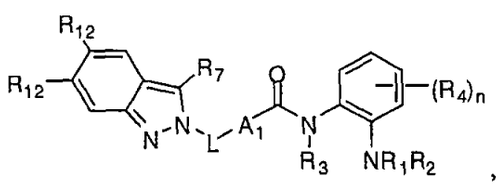


; and

reacting the first reaction product with a compound comprising the formula



under conditions that form a second reaction product comprising a formula



,

wherein

n is selected from the group consisting of 0, 1, 2, 3 and 4;

X is a leaving group;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 and R_2 may be taken together to form a substituted or unsubstituted ring;

R_3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

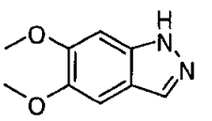
R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

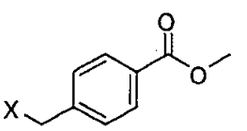
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

94. The process according to claim 93 comprising:

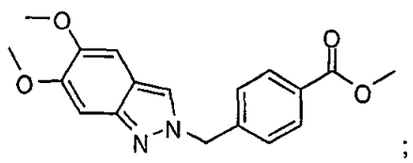
reacting a compound comprising the formula



with a compound comprising the formula

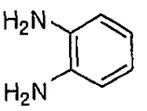


under conditions that form a first reaction product comprising a formula

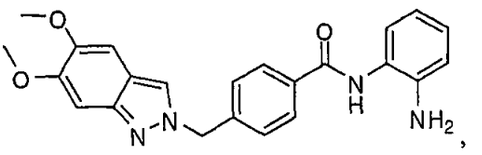


; and

reacting the first reaction product with a compound comprising the formula



under conditions that form a second reaction product comprising a formula



wherein

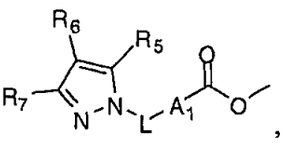
X is a leaving group.

95. The process according to any one of claims 86, 89, 90, 93 and 94 wherein X is halo.

96. The process according to claim 95 wherein X is bromo.

97. The process according to claim 95 wherein X is chloro.

98. A compound comprising:



wherein

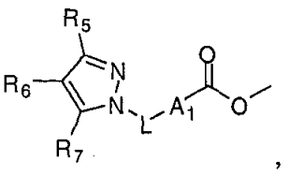
A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached; and

R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy,

carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

99. A compound comprising:



,

wherein

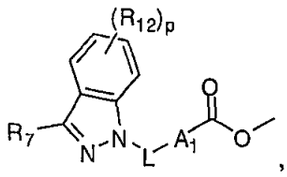
A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached; and

R_5, R_6 and R_7 are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and

hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or any two of R_5, R_6 and R_7 may be taken together to form a substituted or unsubstituted ring.

100. A compound comprising:



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

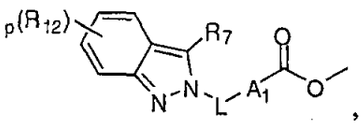
L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl,

heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

101. A compound comprising:



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

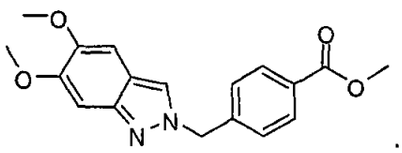
L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

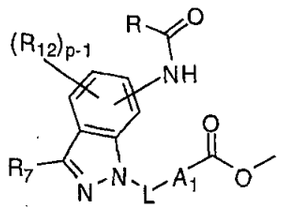
each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl,

sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

102. The compound according to claim 101 comprising:



103. A compound comprising:



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

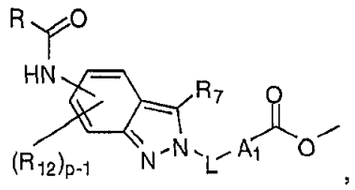
R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl,

thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

104. A compound comprising:



wherein

p is selected from the group consisting of 0, 1, 2, 3 and 4;

A_1 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

L is a linker providing a 0-6 atom separation between the two ring atoms to which L is attached;

R is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, oxo, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, amido, carboxamido, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} and R_7 or R_{11} may be taken together to form a substituted or unsubstituted ring.

FIGURE 1

Amino acid sequence for residues 1-482 of HDAC1 and a Flag tag at both the N- and C-terminus

[SEQ. I.D. No. 1]

MDYKDDDDKMAQTQGTRRKVCYYYDGDVGNYYYGQGHPMKPHRIRMTHNLLLNYGLYRKM
EIYRPHKANAEEMTKYHSDDYIKFLRSIRPDNMSEYSKQMQRFNVGEDCPVFDGLFEFCQ
LSTGGSVASAVKLNKQQTDIAVNWAGGLHHAKKSEASGFCYVNDIVLAILELLKYHQRVL
YIDIDIHHGDGVEEAFYTTDRVMTVSFHKYGEYFPGTGDLRDIGAGKGKYYAVNYPLRDG
IDDESYEAIFKPVMSKVMEMFQPSAVVLQCGSDSLSGDRLGCFNLTIKGHAKCVEFVKSF
NLPMLMLGGGGYTIRNVARCWTYETAVALDTEIPNELPYNDYFEYFGPDFKLHISPSNMT
NQNTNEYLEKIKQRLFENLRMLPHAPGVQMQAIPEDAIPEESGDEDEDDPDKRISICSSD
KRIACEEEFSDSEEEGEGGRKNSSNFKKAKRVKTEDEKEKDPEEKKEVTEEEKTKEEKPE
AKGVKEEVKLADYKDDDDK

FIGURE 2

DNA sequence used to encode residues 1-482 of HDAC1 and a Flag tag at both the N- and C-terminus

[SEQ. I.D. No. 2]

ATGGACTACAAAGACGACGACGACAAAATGGCGCAGACGCAGGGCACCCGGAGGAAAGTC
TGTTACTACTACGACGGGGATGTTGGAAATTACTATTATGGACAAGGCCACCCAATGAAG
CCTCACCGAATCCGCATGACTCATAATTTGCTGCTCAACTATGGTCTCTACCGAAAAATG
GAAATCTATCGCCCTCACAAAGCCAATGCTGAGGAGATGACCAAGTACCACAGCGATGAC
TACATTAAATTCTTGCGCTCCATCCGTCCAGATAACATGTCGGAGTACAGCAAGCAGATG
CAGAGATTCAACGTTGGTGAGGACTGTCCAGTATTCGATGGCCTGTTTGAGTTCTGTCAG
TTGTCTACTGGTGGTTCTGTGGCAAGTGCTGTGAAACTTAATAAGCAGCAGACGGACATC
GCTGTGAATTGGGCTGGGGGCCTGCACCATGCAAAGAAGTCCGAGGCATCTGGCTTCTGT
TACGTCAATGATATCGTCTTGGCCATCCTGGAACTGCTAAAGTATCACCAGAGGGTGCTG
TACATTGACATTGATATTCACCATGGTGACGGCGTGGAAGAGGCCTTCTACACCACGGAC
CGGGTCATGACTGTGTCCTTTCATAAGTATGGAGAGTACTTCCCAGGAACTGGGGACCTA
CGGGATATCGGGGCTGGCAAAGGCAAGTATTATGCTGTTAACTACCCGCTCCGAGACGGG
ATTGATGACGAGTCCTATGAGGCCATTTTCAAGCCGGTCATGTCCAAAGTAATGGAGATG
TTCCAGCCTAGTGCGGTGGTCTTACAGTGTGGCTCAGACTCCCTATCTGGGGATCGGTTA
GGTTGCTTCAATCTAACTATCAAAGGACACGCCAAGTGTGTGGAATTTGTCAAGAGCTTT
AACCTGCCTATGCTGATGCTGGGAGGCGGTGGTTACACCATTCGTAACGTTGCCCGGTGC
TGGACATATGAGACAGCTGTGGCCCTGGATACGGAGATCCCTAATGAGCTTCCATACAAT
GACTACTTTGAATACTTTGGACCAGATTTCAAGCTCCACATCAGTCCTTCCAATATGACT
AACCAGAACACGAATGAGTACCTGGAGAAGATCAAACAGCGACTGTTTGAGAACCTTAGA
ATGCTGCCGCACGCACCTGGGGTCCAAATGCAGGCGATTCCTGAGGACGCCATCCCTGAG
GAGAGTGGCGATGAGGACGAAGACGACCCTGACAAGCGCATCTCGATCTGCTCCTCTGAC
AAACGAATTGCCTGTGAGGAAGAGTTCTCCGATTCTGAAGAGGAGGGAGAGGGGGGCCGC
AAGAACTCTTCCAACTTCAAAAAAGCCAAGAGAGTCAAAACAGAGGATGAAAAAGAGAAA
GACCCAGAGGAGAAGAAAGAAGTCACCGAAGAGGAGAAAACCAAGGAGGAGAAGCCAGAA
GCCAAAGGGGTCAAGGAGGAGGTCAAGTTGGCCGACTACAAAGACGACGACGACAAATGA

FIGURE 3

Amino acid sequence for residues 1-488 of HDAC2 and a 6-histidine tag at the C-terminus

[SEQ. I.D. No. 3]

MGSMAYSQGGGKKKVCYYYDGDIGNYYYGQGHPMKPHRIRMTHNLLLNYGLYRKMEIYRP
HKATAEEMTKYHSDEYIKFLRSIRPDNMSEYSKQMQRFNVGEDCPVFDGLFEFCQLSTGG
SVAGAVKLNRQQTDMAVNWAGGLHHAKKSEASGFCYVNDIVLAILELLKYHQRVLYIDID
IHHGDGVEEAFYTTDRVMTVSFHKYGEYFPGTGDLRDIGAGKGKYYAVNFPMRDGIDDES
YGQIFKPIISKVMEMYQPSAVVLQCGADSLSGDRLGCFNLTVKGHAKCVEVVKTFNLPLL
MLGGGGYTIRNVARCWTYETAVALDCEIPNELPYNDYFEYFGPDFKLHISPSNMTNQNTP
EYMEKIKQRLFENLRMLPHAPGVQMQAIPEDAVHEDSGDEDGEDPDKRISIRASDKRIAC
DEEFSDSEDEGEGGRRNVADHKKGAKKARIEEDKKETEDKKTDVKEEDKSKDNSGEKTDT
KGTKSEQLSNPGHHHHHH

FIGURE 4

DNA used to encode residues 1-488 of HDAC2 and a 6-histidine tag at the C-terminus

[SEQ. I.D. No. 4]

ATGGGATCCATGGCGTACAGTCAAGGAGGCGGCAAAAAAAAAGTCTGCTACTACTACGAC
GGTGATATTGGAAATTATTATTATGGACAGGGTCATCCCATGAAGCCTCATAGAATCCGC
ATGACCCATAACTTGCTGTTAAATTATGGCTTATACAGAAAAATGGAAATATATAGGCCC
CATAAAGCCACTGCCGAAGAAATGACAAAATATCACAGTGATGAGTATATCAAATTTCTA
CGGTCAATAAGACCAGATAACATGTCTGAGTATAGTAAGCAGATGCAGAGATTTAATGTT
GGAGAAGATTGTCCAGTGTTTGATGGACTCTTTGAGTTTTGTCAGCTCTCAACTGGCGGT
TCAGTTGCTGGAGCTGTGAAGTTAAACCGACAACAGACTGATATGGCTGTTAATTGGGCT
GGAGGATTACATCATGCTAAGAAATCAGAAGCATCAGGATTCTGTTACGTTAATGATATT
GTGCTTGCCATCCTTGAATTACTAAAGTATCATCAGAGAGTCTTATATATTGATATAGAT
ATTCATCATGGTGATGGTGTTGAAGAAGCTTTTTATACAACAGATCGTGTAATGACGGTA
TCATTCCATAAATATGGGGAATACTTTCCTGGCACAGGAGACTTGAGGGATATTGGTGCT
GGAAAAGGCAAATACTATGCTGTCAATTTTCCAATGAGAGATGGTATAGATGATGAGTCA
TATGGGCAGATATTTAAGCCTATTATCTCAAAGGTGATGGAGATGTATCAACCTAGTGCT
GTGGTATTACAGTGTGGTGCAGACTCATTATCTGGTGATAGACTGGGTTGTTTCAATCTA
ACAGTCAAAGGTCATGCTAAATGTGTAGAAGTTGTAAAAACTTTTAACTTACCATTACTG
ATGCTTGGAGGAGGTGGCTACACAATCCGTAATGTTGCTCGATGTTGGACATATGAGACT
GCAGTTGCCCTTGATTGTGAGATTCCCAATGAGTTGCCATATAATGATTACTTTGAGTAT
TTTGGACCAGACTTCAAACTGCATATTAGTCCTTCAAACATGACAAACCAGAACACTCCA
GAATATATGGAAAAGATAAAACAGCGTTTGTTTGAAAATTTGCGCATGTTACCTCATGCA
CCTGGTGTCCAGATGCAAGCTATTCCAGAAGATGCTGTTCATGAAGACAGTGGAGATGAA
GATGGAGAAGATCCAGACAAGAGAATTTCTATTCGAGCATCAGACAAGCGGATAGCTTGT
GATGAAGAATTCTCAGATTCTGAGGATGAAGGAGAAGGAGGTCGAAGAAATGTGGCTGAT
CATAAGAAAGGAGCAAAGAAAGCTAGAATTGAAGAAGATAAGAAAGAAACAGAGGACAAA
AAAACAGACGTTAAGGAAGAAGATAAATCCAAGGACAACAGTGGTGAAAAAACAGATACC
AAAGGAACCAAATCAGAACAGCTCAGCAACCCCGGGCATCACCATCACCATCACTAA

FIGURE 5

Amino acid sequence for residues 73-845 of HDAC6 and a 6-histidine tag at the C-terminus

[SEQ. I.D. No. 5]

MPGMDLNLEAEALAGTGLVLDEQLNEFHCLWDDSFPEGPERLHAIKEQLIQEGLLDRCVS
FQARFAEKEELMLVHSLEYIDLMETTQYMNEGELRVLADTYDSVYLHPNSYSCACLASGS
VLRLVDAVLGAEIRNGMAIIRPPGHHAQHSLMDGYCMFNHVAVAARYAQQKHRIRRVLIV
DWDVHHGQGTQFTFDQDPSVLYFSIHRYEQGRFWPHLKASNWSTTGFGQGQGYTINVPWN
QVGMRDADYIAAFLHVLLPVALEFQPQLVLVAAGFDALQGDPKGEMAATPAGFAQLTHLL
MGLAGGKLILSLEGGYNLRALAEGVSASLHTLLGDPCPMLESPGAPCRSAQASVSCALEA
LEPFWEVLVRSTETVERDNMEEDNVEESEEEGPWEPPVLPILTWPVLQSRTGLVYDQNMM
NHCNLWDSHHPEVPQRILRIMCRLEELGLAGRCLTLTPRPATEAELLTCHSAEYVGHLRA
TEKMKTRELHRESSNFDSIYICPSTFACAQLATGAACRLVEAVLSGEVLNGAAVVRPPGH
HAEQDAACGFCFFNSVAVAARHAQTISGHALRILIVDWDVHHGNGTQHMFEDDPSVLYVS
LHRYDHGTFFPMGDEGASSQIGRAAGTGFTVNVAWNGPRMGDADYLAAWHRLVLPIAYEF
NPELVLVSAGFDAARGDPLGGCQVSPEGYAHLTHLLMGLASGRIILILEGGYNLTSISES
MAACTRSLLGDPPPLLTLPRPPLSGALASITETIQVHRRYWRSLRVMKVEDREGPGHHHH
HH

FIGURE 6

DNA sequence used to encode residues 73-845 of HDAC6 and a 6-histidine tag at the C-terminus

[SEQ. I.D. No. 6]

ATGCCCGGGATGGATCTGAACCTTGAGGCTGAAGCACTGGCTGGCACTGGCTTGGTGTTG
GATGAGCAGTTAAATGAATTCCATTGCCTCTGGGATGACAGCTTCCCGGAAGGCCCTGAG
CGGCTCCATGCCATCAAGGAGCAACTGATCCAGGAGGGCCTCCTAGATCGCTGCGTGTCC
TTTCAGGCCCGGTTTGCTGAAAAGGAAGAGCTGATGTTGGTTCACAGCCTAGAATATATT
GATCTGATGGAAACAACCCAGTACATGAATGAGGGAGAACTCCGTGTCCTAGCAGACACC
TACGACTCAGTTTATCTGCATCCGAACTCATACTCCTGTGCCTGCCTGGCCTCAGGCTCT
GTCCTCAGGCTGGTGGATGCGGTCCTGGGGGCTGAGATCCGGAATGGCATGGCCATCATT
AGGCCTCCTGGACATCACGCCCAGCACAGTCTTATGGATGGCTATTGCATGTTCAACCAC
GTGGCTGTGGCAGCCCGCTATGCTCAACAGAAACACCGCATCCGGAGGGTCCTTATCGTA
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CTGGCTGAAGGCGTCAGTGCTTCGCTCCACACCCTTCTGGGAGACCCTTGCCCCATGCTG
GAGTCACCTGGTGCCCCCTGCCGGAGTGCCCAGGCTTCAGTTTCCTGTGCTCTGGAAGCC
CTTGAGCCCTTCTGGGAGGTTCTTGTGAGATCAACTGAGACCGTGGAGAGGGACAACATG
GAGGAGGACAATGTAGAGGAGAGCGAGGAGGAAGGACCCTGGGAGCCCCCTGTGCTCCCA
ATCCTGACATGGCCAGTGCTACAGTCTCGCACAGGGCTGGTCTATGACCAAAATATGATG
AATCACTGCAACTTGTGGGACAGCCACCACCCTGAGGTACCCCAGCGCATCTTGCGGATC
ATGTGCCGTCTGGAGGAGCTGGGCCTTGCCGGGCGCTGCCTCACCCTGACACCGCGCCCT
GCCACAGAGGCTGAGCTGCTCACCTGTCACAGTGCTGAGTACGTGGGTCATCTCCGGGCC
ACAGAGAAAATGAAAACCCGGGAGCTGCACCGTGAGAGTTCCAACTTTGACTCCATCTAT
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GAGGCTGTGCTCTCAGGAGAGGTTCTGAATGGTGCTGCTGTGGTGCGTCCCCCAGGACAC
CACGCAGAGCAGGATGCAGCTTGCGGTTTTTGCTTTTTCAACTCTGTGGCTGTGGCTGCT
CGCCATGCCCAGACTATCAGTGGGCATGCCCTACGGATCCTGATTGTGGATTGGGATGTC
CACCACGGTAATGGAACTCAGCACATGTTTGAGGATGACCCCAGTGTGCTATATGTGTCC
CTGCACCGCTATGATCATGGCACCTTCTTCCCCATGGGGGATGAGGGTGCCAGCAGCCAG
ATCGGCCGGGCTGCGGGCACAGGCTTCACCGTCAACGTGGCATGGAACGGGCCCCGCATG
GGTGATGCTGACTACCTAGCTGCCTGGCATCGCCTGGTGCTTCCCATTGCCTACGAGTTT
AACCCAGAACTGGTGCTGGTCTCAGCTGGCTTTGATGCTGCACGGGGGGATCCGCTGGGG
GGCTGCCAGGTGTCACCTGAGGGTTATGCCCACCTCACCCACCTGCTGATGGGCCTTGCC
AGTGGCCGCATTATCCTTATCCTAGAGGGTGGCTATAACCTGACATCCATCTCAGAGTCC
ATGGCTGCCTGCACTCGCTCCCTCCTTGGAGACCCACCACCCCTGCTGACCCTGCCACGG
CCCCCACTATCAGGGGCCCTGGCCTCAATCACTGAGACCATCCAAGTCCATCGCAGATAC
TGGCGCAGCTTACGGGTCATGAAGGTAGAAGACAGAGAAGGACCCGGGCATCACCATCAC
CATCACTAA

FIGURE 7

Amino acid sequence for residues 1-377 of HDAC8 and a 6-histidine tag at the N-terminus

[SEQ. I.D. No. 7]

MHHHHHHPMEEPEEPADSGQSLVPVYIYSPEYVSMCDSLAKIPKRASMVHSLIEAYALHK
QMRIVKPKVASMEEMAAFHTDAYLQHLQKVSQEGDDDHPDSIEYGLGYDCPATEGIFDYA
AAIGGATITAAQCLIDGMCKVAINWSGGWHHAKKDEASGFCYLNDAVLGILRLRRKFERI
LYVDLDLHHGDGVEDAFSFTSKVMTVSLHKFSPGFFPGTGDVSDVGLGKGRYYSVNVPIQ
DGIQDEKYYQICESVLKEVYQAFNPKAVVLQLGADTIAGDPMCSFNMTPVGIGKCLKYIL
QWQLATLILGGGGYNLANTARCWTYLTGVILGKTLSSEIPDHEFFTAYGPDYVLEITPSC
RPDRNEPHRIQQILNYIKGNLKHVV

FIGURE 8

DNA sequence used to encode residues 1-377 of HDAC8 and a 6-histidine tag at the N-terminus

[SEQ. I.D. No. 8]

ATGCACCATCACCATCACCATCCCATGGAGGAGCCGGAGGAACCGGCGGACAGTGGGCAG
TCGCTGGTCCCGGTTTATATCTATAGTCCCGAGTATGTCAGTATGTGTGACTCCCTGGCC
AAGATCCCCAAACGGGCCAGTATGGTGCATTCTTTGATTGAAGCATATGCACTGCATAAG
CAGATGAGGATAGTTAAGCCTAAAGTGGCCTCCATGGAGGAGATGGCCGCCTTCCACACT
GATGCTTATCTGCAGCATCTCCAGAAGGTCAGCCAAGAGGGCGATGATGATCATCCGGAC
TCCATAGAATATGGGCTAGGTTATGACTGCCCAGCCACTGAAGGGATATTTGACTATGCA
GCAGCTATAGGAGGGGCTACGATCACAGCTGCCCAATGCCTGATTGACGGAATGTGCAAA
GTAGCAATTAACTGGTCTGGAGGGTGGCATCATGCAAAGAAAGATGAAGCATCTGGTTTT
TGTTATCTCAATGATGCTGTCCTGGGAATATTACGATTGCGACGGAAATTTGAGCGTATT
CTCTACGTGGATTTGGATCTGCACCATGGAGATGGTGTAGAAGACGCATTCAGTTTCACC
TCCAAAGTCATGACCGTGTCCCTGCACAAATTCTCCCCAGGATTTTTCCCAGGAACAGGT
GACGTGTCTGATGTTGGCCTAGGGAAGGGACGGTACTACAGTGTAAATGTGCCCATTCAG
GATGGCATACAAGATGAAAAATATTACCAGATCTGTGAAAGTGTACTAAAGGAAGTATAC
CAAGCCTTTAATCCCAAAGCAGTGGTCTTACAGCTGGGAGCTGACACAATAGCTGGGGAT
CCCATGTGCTCCTTTAACATGACTCCAGTGGGAATTGGCAAGTGTCTTAAGTACATCCTT
CAATGGCAGTTGGCAACACTCATTTTGGGAGGAGGAGGCTATAACCTTGCCAACACGGCT
CGATGCTGGACATACTTGACCGGGGTCATCCTAGGGAAAACACTATCCTCTGAGATCCCA
GATCATGAGTTTTTCACAGCATATGGTCCTGATTATGTGCTGGAAATCACGCCAAGCTGC
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CTGAAGCATGTGGTCTAG

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Arg Arg Lys Val Cys Tyr Tyr Tyr Asp Gly Asp Val Gly Asn Tyr Tyr
            20                  25                  30

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        35                  40                  45

Asn Leu Leu Leu Asn Tyr Gly Leu Tyr Arg Lys Met Glu Ile Tyr Arg
    50                  55                  60

Pro His Lys Ala Asn Ala Glu Glu Met Thr Lys Tyr His Ser Asp Asp
65                  70                  75                  80

Tyr Ile Lys Phe Leu Arg Ser Ile Arg Pro Asp Asn Met Ser Glu Tyr
                85                  90                  95

Ser Lys Gln Met Gln Arg Phe Asn Val Gly Glu Asp Cys Pro Val Phe
            100                 105                 110

Asp Gly Leu Phe Glu Phe Cys Gln Leu Ser Thr Gly Gly Ser Val Ala
        115                 120                 125

Ser Ala Val Lys Leu Asn Lys Gln Gln Thr Asp Ile Ala Val Asn Trp
    130                 135                 140

Ala Gly Gly Leu His His Ala Lys Lys Ser Glu Ala Ser Gly Phe Cys
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Tyr Val Asn Asp Ile Val Leu Ala Ile Leu Glu Leu Leu Lys Tyr His
165 170 175

Gln Arg Val Leu Tyr Ile Asp Ile Asp Ile His His Gly Asp Gly Val
180 185 190

Glu Glu Ala Phe Tyr Thr Thr Asp Arg Val Met Thr Val Ser Phe His
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Lys Tyr Gly Glu Tyr Phe Pro Gly Thr Gly Asp Leu Arg Asp Ile Gly
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Ala Gly Lys Gly Lys Tyr Tyr Ala Val Asn Tyr Pro Leu Arg Asp Gly
225 230 235 240

Ile Asp Asp Glu Ser Tyr Glu Ala Ile Phe Lys Pro Val Met Ser Lys
245 250 255

Val Met Glu Met Phe Gln Pro Ser Ala Val Val Leu Gln Cys Gly Ser
260 265 270

Asp Ser Leu Ser Gly Asp Arg Leu Gly Cys Phe Asn Leu Thr Ile Lys
275 280 285

Gly His Ala Lys Cys Val Glu Phe Val Lys Ser Phe Asn Leu Pro Met
290 295 300

Leu Met Leu Gly Gly Gly Gly Tyr Thr Ile Arg Asn Val Ala Arg Cys
305 310 315 320

Trp Thr Tyr Glu Thr Ala Val Ala Leu Asp Thr Glu Ile Pro Asn Glu
325 330 335

Leu Pro Tyr Asn Asp Tyr Phe Glu Tyr Phe Gly Pro Asp Phe Lys Leu
340 345 350

His Ile Ser Pro Ser Asn Met Thr Asn Gln Asn Thr Asn Glu Tyr Leu
355 360 365

Glu Lys Ile Lys Gln Arg Leu Phe Glu Asn Leu Arg Met Leu Pro His
370 375 380

Ala Pro Gly Val Gln Met Gln Ala Ile Pro Glu Asp Ala Ile Pro Glu
385 390 395 400

Glu Ser Gly Asp Glu Asp Glu Asp Asp Pro Asp Lys Arg Ile Ser Ile
405 410 415

Cys Ser Ser Asp Lys Arg Ile Ala Cys Glu Glu Glu Phe Ser Asp Ser
420 425 430

Glu Glu Glu Gly Glu Gly Gly Arg Lys Asn Ser Ser Asn Phe Lys Lys
435 440 445

Ala Lys Arg Val Lys Thr Glu Asp Glu Lys Glu Lys Asp Pro Glu Glu
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cctcaccgaa tccgcatgac tcataatttg ctgctcaact atggtctcta ccgaaaaatg 180

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aacctgccta tgctgatgct gggaggcggt ggttacacca ttcgtaacgt tgcccggtgc 960

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atgctgccgc acgcacctgg ggtccaaatg caggcgattc ctgaggacgc catccctgag 1200

gagagtggcg atgaggacga agacgaccct gacaagcgca tctcgatctg ctcctctgac 1260

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aagaactctt ccaacttcaa aaaagccaag agagtcaaaa cagaggatga aaaagagaaa 1380

gacccagagg agaagaaaga agtcaccgaa gaggagaaaa ccaaggagga gaagccagaa 1440

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Tyr Tyr Tyr Asp Gly Asp Ile Gly Asn Tyr Tyr Tyr Gly Gln Gly His
20 25 30

Pro Met Lys Pro His Arg Ile Arg Met Thr His Asn Leu Leu Leu Asn
35 40 45

Tyr Gly Leu Tyr Arg Lys Met Glu Ile Tyr Arg Pro His Lys Ala Thr
50 55 60

Ala Glu Glu Met Thr Lys Tyr His Ser Asp Glu Tyr Ile Lys Phe Leu
65 70 75 80

Arg Ser Ile Arg Pro Asp Asn Met Ser Glu Tyr Ser Lys Gln Met Gln
85 90 95

Arg Phe Asn Val Gly Glu Asp Cys Pro Val Phe Asp Gly Leu Phe Glu
100 105 110

Phe Cys Gln Leu Ser Thr Gly Gly Ser Val Ala Gly Ala Val Lys Leu
115 120 125

Asn Arg Gln Gln Thr Asp Met Ala Val Asn Trp Ala Gly Gly Leu His
130 135 140

His Ala Lys Lys Ser Glu Ala Ser Gly Phe Cys Tyr Val Asn Asp Ile
145 150 155 160

Val Leu Ala Ile Leu Glu Leu Leu Lys Tyr His Gln Arg Val Leu Tyr
165 170 175

Ile Asp Ile Asp Ile His His Gly Asp Gly Val Glu Glu Ala Phe Tyr
180 185 190

Thr Thr Asp Arg Val Met Thr Val Ser Phe His Lys Tyr Gly Glu Tyr
195 200 205

Phe Pro Gly Thr Gly Asp Leu Arg Asp Ile Gly Ala Gly Lys Gly Lys
210 215 220

Tyr Tyr Ala Val Asn Phe Pro Met Arg Asp Gly Ile Asp Asp Glu Ser
225 230 235 240

Tyr Gly Gln Ile Phe Lys Pro Ile Ile Ser Lys Val Met Glu Met Tyr
245 250 255

Gln Pro Ser Ala Val Val Leu Gln Cys Gly Ala Asp Ser Leu Ser Gly
260 265 270

Asp Arg Leu Gly Cys Phe Asn Leu Thr Val Lys Gly His Ala Lys Cys
275 280 285

Val Glu Val Val Lys Thr Phe Asn Leu Pro Leu Leu Met Leu Gly Gly
290 295 300

Gly Gly Tyr Thr Ile Arg Asn Val Ala Arg Cys Trp Thr Tyr Glu Thr
305 310 315 320

Ala Val Ala Leu Asp Cys Glu Ile Pro Asn Glu Leu Pro Tyr Asn Asp
325 330 335

Tyr Phe Glu Tyr Phe Gly Pro Asp Phe Lys Leu His Ile Ser Pro Ser
340 345 350

Asn Met Thr Asn Gln Asn Thr Pro Glu Tyr Met Glu Lys Ile Lys Gln

355 360 365

Arg Leu Phe Glu Asn Leu Arg Met Leu Pro His Ala Pro Gly Val Gln
370 375 380

Met Gln Ala Ile Pro Glu Asp Ala Val His Glu Asp Ser Gly Asp Glu
385 390 395 400

Asp Gly Glu Asp Pro Asp Lys Arg Ile Ser Ile Arg Ala Ser Asp Lys
405 410 415

Arg Ile Ala Cys Asp Glu Glu Phe Ser Asp Ser Glu Asp Glu Gly Glu
420 425 430

Gly Gly Arg Arg Asn Val Ala Asp His Lys Lys Gly Ala Lys Lys Ala
435 440 445

Arg Ile Glu Glu Asp Lys Lys Glu Thr Glu Asp Lys Lys Thr Asp Val
450 455 460

Lys Glu Glu Asp Lys Ser Lys Asp Asn Ser Gly Glu Lys Thr Asp Thr
465 470 475 480

Lys Gly Thr Lys Ser Glu Gln Leu Ser Asn Pro Gly His His His His
485 490 495

His His

<210> 4
<211> 1497
<212> DNA
<213> Artificial Sequence

<220>
<223> DNA used to encode residues 1-488 of HDAC2 and a 6-histidine tag at the C-terminus

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ggtgatattg gaaattatta ttatggacag ggtcatccca tgaagcctca tagaatccgc 120

atgacccata acttgctgtt aaattatggc ttatacagaa aaatggaaat atataggccc 180

cataaagcca ctgccgaaga aatgacaaaa tatcacagtg atgagtatat caaatttcta 240

cggtcaataa gaccagataa catgtctgag tatagtaagc agatgcagag atttaatgtt 300

ggagaagatt gtccagtgtt tgatggactc tttgagtttt gtcagctctc aactggcggt 360

tcagttgctg gagctgtgaa gttaaaccga caacagactg atatggctgt taattgggct 420

ggaggattac atcatgctaa gaaatcagaa gcatcaggat tctgttacgt taatgatatt 480

gtgcttgcca tccttgaatt actaaagtat catcagagag tcttatatat tgatatagat 540

attcatcatg gtgatggtgt tgaagaagct ttttatacaa cagatcgtgt aatgacggta 600

tcattccata aatatgggga atactttcct ggcacaggag acttgaggga tattggtgct 660

ggaaaaggca aatactatgc tgtcaatttt ccaatgagag atggtataga tgatgagtca 720

tatgggcaga tatttaagcc tattatctca aaggtgatgg agatgtatca acctagtgct 780

gtggtattac agtgtggtgc agactcatta tctggtgata gactgggttg tttcaatcta 840

acagtcaaag gtcatgctaa atgtgtagaa gttgtaaaaa cttttaactt accattactg 900

atgcttggag gaggtggcta cacaatccgt aatgttgctc gatgttggac atatgagact 960

gcagttgccc ttgattgtga gattcccaat gagttgccat ataatgatta ctttgagtat 1020

tttggaccag acttcaaact gcatattagt ccttcaaaca tgacaaacca gaacactcca 1080

gaatatatgg aaaagataaa acagcgtttg tttgaaaatt tgcgcatgtt acctcatgca 1140

cctggtgtcc agatgcaagc tattccagaa gatgctgttc atgaagacag tggagatgaa 1200

gatggagaag atccagacaa gagaatttct attcgagcat cagacaagcg gatagcttgt 1260

gatgaagaat tctcagattc tgaggatgaa ggagaaggag gtcgaagaaa tgtggctgat 1320

cataagaaag gagcaaagaa agctagaatt gaagaagata agaaagaaac agaggacaaa 1380

aaaacagacg ttaaggaaga agataaatcc aaggacaaca gtggtgaaaa aacagatacc 1440

aaaggaacca aatcagaaca gctcagcaac cccgggcatc accatcacca tcactaa 1497

<210> 5
<211> 782
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence for residues 73-845 of HDAC6 and a 6-histidine tag at the C-terminus

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1 5 10 15

Gly Leu Val Leu Asp Glu Gln Leu Asn Glu Phe His Cys Leu Trp Asp
20 25 30

Asp Ser Phe Pro Glu Gly Pro Glu Arg Leu His Ala Ile Lys Glu Gln
35 40 45

Leu Ile Gln Glu Gly Leu Leu Asp Arg Cys Val Ser Phe Gln Ala Arg
50 55 60

Phe Ala Glu Lys Glu Glu Leu Met Leu Val His Ser Leu Glu Tyr Ile
65 70 75 80

Asp Leu Met Glu Thr Thr Gln Tyr Met Asn Glu Gly Glu Leu Arg Val
85 90 95

Leu Ala Asp Thr Tyr Asp Ser Val Tyr Leu His Pro Asn Ser Tyr Ser
100 105 110

Cys Ala Cys Leu Ala Ser Gly Ser Val Leu Arg Leu Val Asp Ala Val
115 120 125

Leu Gly Ala Glu Ile Arg Asn Gly Met Ala Ile Ile Arg Pro Pro Gly
130 135 140

His His Ala Gln His Ser Leu Met Asp Gly Tyr Cys Met Phe Asn His
145 150 155 160

Val Ala Val Ala Ala Arg Tyr Ala Gln Gln Lys His Arg Ile Arg Arg
165 170 175

Val Leu Ile Val Asp Trp Asp Val His His Gly Gln Gly Thr Gln Phe
180 185 190

Thr Phe Asp Gln Asp Pro Ser Val Leu Tyr Phe Ser Ile His Arg Tyr
195 200 205

Glu Gln Gly Arg Phe Trp Pro His Leu Lys Ala Ser Asn Trp Ser Thr
210 215 220

Thr Gly Phe Gly Gln Gly Gln Gly Tyr Thr Ile Asn Val Pro Trp Asn
225 230 235 240

Gln Val Gly Met Arg Asp Ala Asp Tyr Ile Ala Ala Phe Leu His Val
245 250 255

Leu Leu Pro Val Ala Leu Glu Phe Gln Pro Gln Leu Val Leu Val Ala
260 265 270

Ala Gly Phe Asp Ala Leu Gln Gly Asp Pro Lys Gly Glu Met Ala Ala
275 280 285

Thr Pro Ala Gly Phe Ala Gln Leu Thr His Leu Leu Met Gly Leu Ala
290 295 300

Gly Gly Lys Leu Ile Leu Ser Leu Glu Gly Gly Tyr Asn Leu Arg Ala
305 310 315 320

Leu Ala Glu Gly Val Ser Ala Ser Leu His Thr Leu Leu Gly Asp Pro
325 330 335

Cys Pro Met Leu Glu Ser Pro Gly Ala Pro Cys Arg Ser Ala Gln Ala
340 345 350

Ser Val Ser Cys Ala Leu Glu Ala Leu Glu Pro Phe Trp Glu Val Leu
355 360 365

Val Arg Ser Thr Glu Thr Val Glu Arg Asp Asn Met Glu Glu Asp Asn
370 375 380

Val Glu Glu Ser Glu Glu Glu Gly Pro Trp Glu Pro Pro Val Leu Pro
385 390 395 400

Ile Leu Thr Trp Pro Val Leu Gln Ser Arg Thr Gly Leu Val Tyr Asp
405 410 415

Gln Asn Met Met Asn His Cys Asn Leu Trp Asp Ser His His Pro Glu
420 425 430

Val Pro Gln Arg Ile Leu Arg Ile Met Cys Arg Leu Glu Glu Leu Gly
435 440 445

Leu Ala Gly Arg Cys Leu Thr Leu Thr Pro Arg Pro Ala Thr Glu Ala
450 455 460

Glu Leu Leu Thr Cys His Ser Ala Glu Tyr Val Gly His Leu Arg Ala
465 470 475 480

Thr Glu Lys Met Lys Thr Arg Glu Leu His Arg Glu Ser Ser Asn Phe
485 490 495

Asp Ser Ile Tyr Ile Cys Pro Ser Thr Phe Ala Cys Ala Gln Leu Ala
500 505 510

Thr Gly Ala Ala Cys Arg Leu Val Glu Ala Val Leu Ser Gly Glu Val
515 520 525

Leu Asn Gly Ala Ala Val Val Arg Pro Pro Gly His His Ala Glu Gln
530 535 540

Asp Ala Ala Cys Gly Phe Cys Phe Phe Asn Ser Val Ala Val Ala Ala
545 550 555 560

Arg His Ala Gln Thr Ile Ser Gly His Ala Leu Arg Ile Leu Ile Val

565 570 575

Asp Trp Asp Val His His Gly Asn Gly Thr Gln His Met Phe Glu Asp
580 585 590

Asp Pro Ser Val Leu Tyr Val Ser Leu His Arg Tyr Asp His Gly Thr
595 600 605

Phe Phe Pro Met Gly Asp Glu Gly Ala Ser Ser Gln Ile Gly Arg Ala
610 615 620

Ala Gly Thr Gly Phe Thr Val Asn Val Ala Trp Asn Gly Pro Arg Met
625 630 635 640

Gly Asp Ala Asp Tyr Leu Ala Ala Trp His Arg Leu Val Leu Pro Ile
645 650 655

Ala Tyr Glu Phe Asn Pro Glu Leu Val Leu Val Ser Ala Gly Phe Asp
660 665 670

Ala Ala Arg Gly Asp Pro Leu Gly Gly Cys Gln Val Ser Pro Glu Gly
675 680 685

Tyr Ala His Leu Thr His Leu Leu Met Gly Leu Ala Ser Gly Arg Ile
690 695 700

Ile Leu Ile Leu Glu Gly Gly Tyr Asn Leu Thr Ser Ile Ser Glu Ser
705 710 715 720

Met Ala Ala Cys Thr Arg Ser Leu Leu Gly Asp Pro Pro Pro Leu Leu
725 730 735

Thr Leu Pro Arg Pro Pro Leu Ser Gly Ala Leu Ala Ser Ile Thr Glu
740 745 750

Thr Ile Gln Val His Arg Arg Tyr Trp Arg Ser Leu Arg Val Met Lys
755 760 765

Val Glu Asp Arg Glu Gly Pro Gly His His His His His His
770 775 780

<210> 6
<211> 2349
<212> DNA
<213> Artificial Sequence

<220>
<223> DNA sequence used to encode residues 73-845 of HDAC6 and a 6-histidine tag at the C-terminus

<400> 6

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cggctccatg ccatcaagga gcaactgatc caggagggcc tcctagatcg ctgcgtgtcc 180

tttcaggccc ggtttgctga aaaggaagag ctgatgttgg ttcacagcct agaatatatt 240

gatctgatgg aaacaaccca gtacatgaat gagggagaac tccgtgtcct agcagacacc 300

tacgactcag tttatctgca tccgaactca tactcctgtg cctgcctggc ctcaggctct 360

gtcctcaggc tggtggatgc ggtcctgggg gctgagatcc ggaatggcat ggccatcatt 420

aggcctcctg gacatcacgc ccagcacagt cttatggatg gctattgcat gttcaaccac 480

gtggctgtgg cagcccgcta tgctcaacag aaacaccgca tccggagggt ccttatcgta 540

gattgggatg tgcaccacgg tcaaggaaca cagttcacct tcgaccagga ccccagtgtc 600

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aactggtcca ccacaggttt cggccaaggc caaggatata ccatcaatgt gccttggaac 720

caggtgggga tgcgggatgc tgactacatt gctgctttcc tgcacgtcct gctgccagtc 780

gccctcgagt tccagcctca gctggtcctg gtggctgctg gatttgatgc cctgcaaggg 840

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gccacagagg ctgagctgct cacctgtcac agtgctgagt acgtgggtca tctccgggcc 1440

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<210> 7
<211> 385
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence for residues 1-377 of HDAC8 and a 6-histidine tag at the N-terminus

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20 25 30

Val Ser Met Cys Asp Ser Leu Ala Lys Ile Pro Lys Arg Ala Ser Met
35 40 45

Val His Ser Leu Ile Glu Ala Tyr Ala Leu His Lys Gln Met Arg Ile
50 55 60

Val Lys Pro Lys Val Ala Ser Met Glu Glu Met Ala Ala Phe His Thr
65 70 75 80

Asp Ala Tyr Leu Gln His Leu Gln Lys Val Ser Gln Glu Gly Asp Asp
85 90 95

Asp His Pro Asp Ser Ile Glu Tyr Gly Leu Gly Tyr Asp Cys Pro Ala
100 105 110

Thr Glu Gly Ile Phe Asp Tyr Ala Ala Ala Ile Gly Gly Ala Thr Ile
115 120 125

Thr Ala Ala Gln Cys Leu Ile Asp Gly Met Cys Lys Val Ala Ile Asn
130 135 140

Trp Ser Gly Gly Trp His His Ala Lys Lys Asp Glu Ala Ser Gly Phe
145 150 155 160

Cys Tyr Leu Asn Asp Ala Val Leu Gly Ile Leu Arg Leu Arg Arg Lys
165 170 175

Phe Glu Arg Ile Leu Tyr Val Asp Leu Asp Leu His His Gly Asp Gly
180 185 190

Val Glu Asp Ala Phe Ser Phe Thr Ser Lys Val Met Thr Val Ser Leu
195 200 205

His Lys Phe Ser Pro Gly Phe Phe Pro Gly Thr Gly Asp Val Ser Asp
210 215 220

Val Gly Leu Gly Lys Gly Arg Tyr Tyr Ser Val Asn Val Pro Ile Gln
225 230 235 240

Asp Gly Ile Gln Asp Glu Lys Tyr Tyr Gln Ile Cys Glu Ser Val Leu
245 250 255

Lys Glu Val Tyr Gln Ala Phe Asn Pro Lys Ala Val Val Leu Gln Leu
260 265 270

Gly Ala Asp Thr Ile Ala Gly Asp Pro Met Cys Ser Phe Asn Met Thr
275 280 285

Pro Val Gly Ile Gly Lys Cys Leu Lys Tyr Ile Leu Gln Trp Gln Leu
290 295 300

Ala Thr Leu Ile Leu Gly Gly Gly Gly Tyr Asn Leu Ala Asn Thr Ala
305 310 315 320

Arg Cys Trp Thr Tyr Leu Thr Gly Val Ile Leu Gly Lys Thr Leu Ser
325 330 335

Ser Glu Ile Pro Asp His Glu Phe Phe Thr Ala Tyr Gly Pro Asp Tyr
340 345 350

Val Leu Glu Ile Thr Pro Ser Cys Arg Pro Asp Arg Asn Glu Pro His
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Arg Ile Gln Gln Ile Leu Asn Tyr Ile Lys Gly Asn Leu Lys His Val
370 375 380

Val
385

<210> 8
<211> 1181
<212> DNA
<213> Artificial Sequence

<220>
<223> DNA sequence used to encode residues 1-377 of HDAC8 and a 6-histidine tag at the N-terminus

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<222> (1164)..(1164)
<223> n is a, c, g, or t

<220>
<221> misc_feature
<222> (1171)..(1171)
<223> n is a, c, g, or t

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aagatcccca aacgggccag tatggtgcat tctttgattg aagcatatgc actgcataag 180

cagatgagga tagttaagcc taaagtggcc tccatggagg agatggccgc cttccacact 240

gatgcttatc tgcagcatct ccagaaggtc agccaagagg gcgatgatga tcatccggac 300

tccatagaat atgggctagg ttatgactgc ccagccactg aagggatatt tgactatgca 360

gcagctatag gaggggctac gatcacagct gcccaatgcc tgattgacgg aatgtgcaaa 420

gtagcaatta actggtctgg agggtggcat catgcaaaga aagatgaagc atctggtttt 480

tgttatctca atgatgctgt cctgggaata ttacgattgc gacggaaatt tgagcgtatt 540

ctctacgtgg atttggatct gcaccatgga gatggtgtag aagacgcatt cagtttcacc 600

tccaaagtca tgaccgtgtc cctgcacaaa ttctccccag gatttttccc aggaacaggt 660

gacgtgtctg atgttggcct agggaaggga cggtactaca gtgtaaatgt gcccattcag 720

gatggcatac aagatgaaaa atattaccag atctgtgaaa gtgtactaaa ggaagtatac 780

caagccttta atcccaaagc agtggtctta cagctgggag ctgacacaat agctggggat 840

cccatgtgct cctttaacat gactccagtg ggaattggca agtgtcttaa gtacatcctt 900

caatggcagt tggcaacact cattttggga ggaggaggct ataaccttgc caacacggct 960

cgatgctgga catacttgac cggggtcatc ctagggaaaa cactatcctc tgagatccca 1020

gatcatgagt ttttcacagc atatggtcct gattatgtgc tggaaatcac gccaagctgc 1080

cggccagacc gcaatgagcc ccaccgaatc caacaaatcc tcaactacat caaagggaat 1140

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C07D 401/12 (2006.01) *C07D 405/12* (2006.01)
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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BRESSI, Jerome C.** [US/US]; 3799 Ibis Street, San Diego, California 92103 (US). **GANGLOFF, Anthony R.** [US/US]; 4969 Dick Street, San Diego, California 92115 (US). **KWOK, Lily** [US/US]; 10937 Caminito Arcada, San Diego, California 92131 (US).

(74) Agents: **WEITZ, David J.** et al.; TAKEDA SAN DIEGO, INC., 10410 Science Center Drive, San Diego, California 92121 (US).

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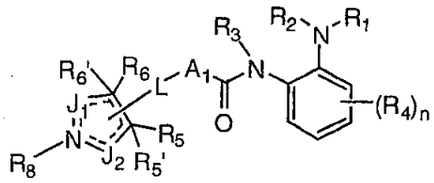
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT,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

Published:
— *with international search report*

(88) Date of publication of the international search report:
3 May 2007

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

(54) Title: HISTONE DEACETYLASE INHIBITORS



(I)

(57) Abstract: Compounds, pharmaceutical compositions, kits and methods are provided for use with HDAC that comprise a compound selected from the group consisting of: (formula) wherein the substituents are as defined herein.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/027118

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/12 C07D231/56 C07D409/06 C07D401/12 C07D471/04
C07D409/12 C07D231/14 C07D405/04 C07D401/04 C07D405/12
A61K31/416 A61P35/00

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN 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 03/024448 A (METHYLGENE INC [CA]; DELORME DANIEL [CA]; WOO SOON HYUNG [US]; VAISBUR) 27 March 2003 (2003-03-27) page 35; claim 126; compounds 22, 149, 152, 277, 286, 436, 486	1-85
X	WO 2004/035525 A (METHYLGENE INC [CA]; RAEPPEL STEPHANE [CA]; GAUDETTE FREDERIC [CA]; PA) 29 April 2004 (2004-04-29) claim 1; compounds VJ, VL, XXXA	1-85
X	US 2002/002183 A1 (ZHU BING-YAN [US] ET AL ZHU BING-YAN [US] ET AL) 3 January 2002 (2002-01-03) pages 200,201; examples 347,355	1,16,17, 20-24, 37-39, 55-70

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2006	02. 02. 2007

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NL – 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Grassi, Damian

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/027118

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/157841 A1 (FERTIG GEORG [DE] ET AL) 12 August 2004 (2004-08-12) paragraphs [0066] - [0069]; claim 13; example 9 ----	1,16,17, 20-26, 36-40, 55-85
X	WO 2004/058234 A (SCHERING AG [DE]; SCHUPPAN DETLEF [DE]; HEROLD CHRISTOPH [DE]; GANSMAY) 15 July 2004 (2004-07-15) page 38 pages 77,78 ----	1,16,17, 20-26, 36-40, 55-85

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/027118

Box 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:

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 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:

see additional sheet

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 fee, this Authority did not invite payment of any additional fee.

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.:

see annex

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,16,17,20-26,36-40,55-85(all part)

Compounds according to claim 1 in which J1 is CR7R7', J2 is CR20R20' and the residues R5, R5', R6, R6', R7, R7', R8, R20, and R20' are not taken together to form a ring.

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2. claims:
1(part),16-17(part),18,19,20-26(part), 36-40(part),55-85(part)

Compounds according to claim 1 in which J1 is CR7R7', J2 is CR20R20' and two of the residues R5, R5', R6, R6', R7, R7', R8, R20 and R20' are taken together to form a ring.

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3. claims: 1-7,20-26,36-53,55-85,87-88(all part)

Compounds according to claim 1 in which J1 is CR7R7', J2 is NR10 and the residues R5, R5', R6, R6', R7, R7', R8, and R10 are not taken together to form a ring.

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4. claims: 1-7(part),8-11,20-85(part),87-88(part),91-94,95-97(part)

Compounds according to claim 1 in which J1 is CR7R7', J2 is NR10 and the residues R5, R5', R6, R6', R7, R7', R8, and R10 are not taken together to form a ring.

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5. claims: 1(part),12-15,20-50(part),55-85(part)

Compounds according to claim 1 in which J1 is NR19 and J2 is NR10.

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6. claims: 86,89,90,95-97(part),98-104

Intermediate according to claims 98-104 or their preparation according to claims 86, 89, and 90.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/027118

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03024448 A	27-03-2003	BR 0212510 A	24-08-2004
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		JP 2006514991 T	18-05-2006

INHIBIDORES DE HISTONA DEACETILASA

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con compuestos que se pueden utilizar para inhibir histona desacetilasas (HDAC), así como con composiciones de materia y conjuntos de elementos que comprenden estos compuestos. La invención también se relaciona con métodos para inhibir HDAC y con métodos de tratamiento que emplean los compuestos acordes con la presente invención. En particular, la presente invención se relaciona con compuestos, composiciones de materia, conjuntos de elementos y métodos usados para inhibir HDAC de Clase I, tal como HDAC1, HDAC2, HDAC6 y HDAC8.

ANTECEDENTES DE LA INVENCIÓN

En las células eucariotas el ADN forma estrechos complejos con proteínas (histonas) para formar la cromatina. Las histonas son proteínas pequeñas, de carga positiva, que son ricas en aminoácidos básicos (de carga positiva a pH fisiológico), que toman contacto con los grupos fosfato (de carga negativa a pH fisiológico) del ADN. Hay cinco grandes clases de histonas: H1, H2A, H2B, H3 y H4. Las secuencias de aminoácidos de H2A, H2B, H3 y H4 muestran una notable conservación entre especies, en tanto H1 varía algo y en algunos casos es reemplazada por otra histona, por ejemplo, H5. Cuatro pares de cada uno entre H2A, H2B, H3 y H4 forman juntos un centro proteico octomérico con forma de disco, alrededor del cual se enrolla el ADN (140 base pares aproximadamente) para formar un nucleosoma. Los nucleosomas individuales están conectados por extensiones cortas de ADN ligador asociado con otra molécula de histona para formar una estructura parecida a una cadena de esferas, que a su vez se dispone como una pila helicoidal, conocida como solenoide.

La mayoría de las histonas se sintetizan durante la fase S del ciclo celular y las histonas recién sintetizadas ingresan rápidamente al núcleo para asociarse con el ADN. A los pocos minutos de su síntesis, el nuevo ADN se asocia con las histonas en estructuras nucleosómicas.

Una pequeña fracción de las histonas, más específicamente, las cadenas laterales de aminoácidos de las mismas, es modificada enzimáticamente por adición después de la traducción de grupos metilo, acetilo o fosfato, neutralización de la carga positiva de la cadena lateral o conversión de la misma en una carga

negativa. Por ejemplo, se pueden metilar grupos lisina y arginina, se pueden acetilar grupos lisina y se pueden fosforilar grupos serina. Para la lisina, se puede acetilar la cadena lateral $-(CH_2)_4-NH_2$, por ejemplo con una enzima acetiltransferasa para obtener la amida $-(CH_2)_4-NHC(=O)CH_3$. La metilación, acetilación y fosforilación de los extremos amino terminales de las histonas que se extienden desde el centro nucleosómico afecta la estructura de la cromatina y la expresión genética. Spencer y Davie 1999. *Gene* 240:1 1-12.

La acetilación y desacetilación de histonas están asociadas con eventos de transcripción que conducen a la proliferación y/o diferenciación celular. La regulación de la función de los factores de transcripción también está mediada por una acetilación. Revisiones recientes sobre la desacetilación de histonas incluyen Kouzarides *et al.*, 1999, *Curr. Opin. Genet. Dev.* 9:1, 40-48 y Pazin *et al.*, 1997, 89:3 325-328.

Desde hace un cierto tiempo que se conoce la correlación que existe entre el estado de acetilación de histonas y la transcripción de genes. Se han identificado determinadas enzimas, específicamente acetilasas (por ejemplo, histona acetiltransferasas (HAT) y desacetilasas (histona desacetilasas o HDAC), que regulan el estado de acetilación de las histonas en muchos organismos y se han relacionado con la regulación de numerosos genes, lo que confirma la relación entre la acetilación y la transcripción. En general, se cree que la acetilación de histonas se correlaciona con la activación de la transcripción, en tanto se considera que la desacetilación de las histonas está asociada con la represión de genes.

Se ha identificado un número cada vez mayor de histona desacetilasas (HDAC). Las HDAC funcionan como parte de grandes complejos multiproteicos, que están unidos al promotor y reprimen la transcripción. Hay represores de la transcripción bien caracterizados, tal como MAD, receptores nucleares e YY1 que se asocian con los complejos HDAC para ejercer su función represora.

Los estudios sobre inhibidores de HDAC han mostrado que estas enzimas cumplen un rol importante en la proliferación y diferenciación celular. Se considera que las HDAC están asociadas con diversos estados de enfermedad diferentes incluyendo, en un sentido no limitativo, enfermedades y afecciones de proliferación celular (Marks, P.A., Richon, V.M., Breslow, R. y Rifkind, R.A., *J. Natl.*

Cancer Inst. (Bethesda) 92, 1210-1215, 2000), tal como leucemia (Lin *et al.*, 1998. *Nature* 391: 811-814; Grignani *et al.*1998. *Nature* 391: 815-818; Warrell *et al.*, 1998, *J. Natl. Cancer Inst.* 90:1621-1625; Gelmetti *et al.*, 1998, *Mol. Cell Biol.* 18:7185-7191; Wang *et al.*, 1998, *PNAS* 951 0860-10865), melanomas/carcinomas de células escamosas (Gillenwater *et al.*, 1998, *Int. J. Cancer* 75217-224; Saunders *et al.*, 1999, *Cancer Res.* 59:399-404), cáncer de mama, cáncer de próstata, cáncer de vejiga (Gelmetti *et al.*, 1998, *Mol. Cell Biol.* 18:7185-7191; Wang *et al.*, 1998, *PNAS* 951 0860-10865), cáncer de pulmón, cáncer de ovario, cáncer de colon (Hassig *et al.*, 1997, *Chem. Biol.* 4:783-789; Archer *et al.*, 1998, *PNAS*, 956791-6796; Swendeman *et al.*, 1999, *Proc. Amer. Assoc. Cancer Res.* 40, Resumen Nº 3836) y enfermedades hiperproliferativas de la piel, tales como lesiones cancerosas y precancerosas de la piel, así como trastornos cutáneos inflamatorios.

Los inhibidores de la histona desacetilasa son potentes inductores del arresto del crecimiento, la diferenciación o la muerte celular apoptótica en diversas células transformadas en cultivo y en animales con tumores (*Inhibitors of histone deacethylase as new cancer drugs*, Marks, P.A., Richon, V.M., Breslow, R. y Rifkind, R.A., *Current Opinions in Oncology*, 2001, Nov. 13 (6): 477-83; *Histone deacethylases and cancer: causes and therapies,* Marks, P., Rifkind, R.A., Richon, V.M., Breslow, R., Miller, T. y Kelly, W.K., *Nat. Rev. Cancer* 2001 Dic.1 (3):194–202). Además, los inhibidores de HDAC son de utilidad en el tratamiento o la prevención de enfermedades producidas por protozoarios (Patente de EE.UU. Nº: 5.922.837) y psoriasis (Publicación PCT Nº: WO 02/26696).

Por lo tanto, a pesar de los diversos inhibidores de HDAC que se han descrito hasta la fecha, persiste la necesidad de inhibidores de HDAC nuevos y más eficaces.

RESUMEN DE LA INVENCIÓN

La presente invención se relaciona con compuestos que tienen actividad de inhibición de histona desacetilasas (HDAC). La presente invención también provee composiciones, artículos manufacturados y equipos que comprenden estos compuestos.

En una realización, se proporciona una composición farmacéutica que comprende un inhibidor de HDAC de acuerdo con la presente invención, como ingrediente

activo. Las composiciones farmacéuticas de acuerdo con la invención pueden comprender opcionalmente 0,001%-100% de uno o más inhibidores de HDAC de esta invención. Estas composiciones farmacéuticas pueden administrarse o coadministrarse empleando una variedad de rutas, incluyendo, por ejemplo, vía oral, parenteral, intraperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposomal, por inhalación, vaginal, intraocular, por administración local (por ejemplo, empleando catéteres o stents), subcutánea, intraadiposa, intraarticular o intratecal. Las composiciones también pueden administrarse o coadministrarse en formas de dosificación de liberación lenta.

La invención también se relaciona con equipos y otros artículos manufacturados para tratar estados de enfermedad asociados con una o más HDAC.

En una realización, se proporciona un equipo que comprende una composición que comprende al menos un inhibidor de HDAC de la presente invención, en combinación con instrucciones. Las instrucciones pueden indicar el estado de enfermedad para el que puede administrarse la composición, información de almacenamiento, información de dosificación y/o instrucciones acerca de cómo administrar la composición. El equipo también puede comprender materiales de envasado. El material de envasado puede comprender un recipiente para alojar la composición. El equipo también puede comprender opcionalmente componentes adicionales, tales como jeringas para administrar la composición. El equipo puede comprender la composición bajo la forma de dosis individuales o múltiples.

En otra realización, se proporciona un artículo de manufactura que comprende una composición que comprende al menos un inhibidor de HDAC de la presente invención, en combinación con materiales de envasado. El material de envasado puede comprender un recipiente para alojar la composición. El recipiente puede comprender opcionalmente una marca que indique el estado de enfermedad para el que puede administrarse la composición, información de almacenamiento, información de dosificación y/o instrucciones acerca de cómo administrar la composición. El equipo también puede comprender opcionalmente componentes opcionales, tales como jeringas para administrar la composición. El equipo puede comprender la composición bajo la forma de dosis individuales o múltiples.

También se proporcionan métodos para preparar compuestos, composiciones y equipos de acuerdo con la presente invención. Por ejemplo, se proporcionan varios esquemas de síntesis en la presente documentación, para sintetizar los compuestos de acuerdo con la presente invención. En aún otra realización, se proveen intermediarios reactivos para su uso junto con los esquemas de síntesis.

También se proporcionan métodos para usar los compuestos, las composiciones, los equipos y artículos manufacturados de acuerdo con la presente invención.

En una realización, se usan los compuestos, las composiciones, los equipos y los artículos manufacturados para inhibir una o más HDAC.

En otra realización, se usan los compuestos, las composiciones, los equipos y los artículos manufacturados para tratar una enfermedad, donde una o más HDAC posee una actividad que contribuye a la patología y/o la sintomatología del estado de enfermedad.

En otra realización, se administra un compuesto a un sujeto, donde se altera la actividad de la HDAC en el sujeto, preferiblemente se la reduce.

En otra realización, se administra una prodroga de un compuesto al sujeto, que se convierte en el compuesto in vivo, donde éste inhibe una o más HDAC.

En otra realización, se proporciona un método para inhibir una o más HDAC, que comprende poner una HDAC en contacto con un compuesto de acuerdo con la presente invención.

En otra realización, se proporciona un método para inhibir una o más HDAC, que comprende administrar un compuesto de acuerdo con la presente invención a un sujeto, con el fin de inhibir dicha HDAC *in vivo*.

En otra realización, se proporciona un método para inhibir una HDAC, que comprende administrar un primer compuesto a un sujeto, que se convierte in vivo en un segundo compuesto, donde el segundo compuesto inhibe dicho HDAC in vivo. Puede destacarse que los compuestos de la presente invención pueden ser el primer o el segundo compuesto.

En otra realización, se proporciona un método terapéutico, que comprende administrar un compuesto de acuerdo con la presente invención.

En otra realización, se proporciona un método para tratar una condición en un paciente, de la que se sabe que está mediada por una o más HDAC, o de la que se sabe que puede tratarse con inhibidores de HDAC, que comprende administrar

al paciente una cantidad eficaz para el uso terapéutico de un compuesto de acuerdo con la presente invención.

En otra realización, se proporciona un método para tratar un estado de enfermedad, donde la actividad de una o más HDAC contribuye a la patología y/o la sintomatología del estado de enfermedad, donde el método comprende: administrar un compuesto de acuerdo con la presente invención a un sujeto, en una cantidad eficaz para el uso terapéutico en el tratamiento del estado de enfermedad.

En otra realización, se proporciona un método para tratar un estado de enfermedad, donde la actividad de una o más HDAC contribuye a la patología y/o la sintomatología del estado de enfermedad, donde el método comprende: administrar un primer compuesto a un sujeto, que se convierte in vivo en un segundo compuesto, de modo que el segundo compuesto está presente en el sujeto en una cantidad eficaz para el uso terapéutico en el tratamiento del estado de enfermedad. Puede destacarse que los compuestos de la presente invención pueden ser el primer o el segundo compuesto.

En otra realización, se proporciona un método para tratar un estado de enfermedad, donde la actividad de una o más HD contribuye a la patología y/o la sintomatología del estado de enfermedad, donde el método comprende: administrar un compuesto de acuerdo con la presente invención a un sujeto, de modo que el compuesto está presente en el sujeto en una cantidad eficaz para el uso terapéutico en el tratamiento del estado de enfermedad.

En otra realización, se provee un método para usar un compuesto acorde con la presente invención con el fin de elaborar un medicamento para su uso en el tratamiento de un estado de enfermedad conocido por estar mediado por una o más HDAC o que puede ser tratado con inhibidores de HDAC.

Debe destacarse, respecto de todas las realizaciones anteriores, que la presente invención abarca todas las formas ionizadas aceptables para el uso farmacéutico (por ejemplo, sales) y los solvatos (por ejemplo, hidratos) de los compuestos, sin importar si dichas formas ionizadas y solvatos están detallados, ya que la administración de agentes farmacéuticos ionizados y solvatados es bien conocida en la técnica. También puede destacarse que, a menos que se especifique una estereoquímicas particular, la mención de un compuesto abarca todos los

estereoisómeros posibles (por ejemplo, enantiómeros o diastereómeros, dependiendo de la cantidad de centros quirales), independientemente si el compuesto está presente como un isómero individual o como una mezcla de isómeros. Además, a menos que se especifique lo contrario, la mención de un compuesto abarca todas las formas de resonancia y tautómeros posibles. Respecto de las reivindicaciones, el término "compuesto que comprende la fórmula" abarca el compuesto y todas las formas ionizadas y los solvatos aceptables para el uso farmacéutico, todos los estereoisómeros posibles, y todas las formas de resonancia y los tautómeros posibles, a menos que se detalle específicamente algo diferente en la reivindicación particular.

Además, debe destacarse que también pueden administrarse prodrogas, que son alteradas in vivo y se transforman en un compuesto de acuerdo con la presente invención. Los distintos métodos para usar los compuestos de la presente invención abarca, sin importar la especificación de la administración de la prodroga, la administración de una prodroga que se convierte in vivo en un compuesto de acuerdo con la presente invención. También debe destacarse que pueden alterarse determinados compuestos de la presente invención in vivo, antes de inhibir quinasas y, por consiguiente, pueden ser ellos mismos prodrogas de otro compuesto. Dichas prodrogas de otro compuesto pueden tener o no independientemente actividad de inhibición de quinasas.

BREVE DESCRIPCIÓN DE LAS FIGURAS

En la Figura 1 se ilustran los residuos 1-482 de HDAC1 y una marca Flag por ambos extremos N- y C-terminales (SEQ ID Nº: 1).

En la Figura 2 se ilustra la secuencia de ADN (SEQ ID Nº: 2) que se usó para codificar la SEQ ID Nº: 1.

En la Figura 3 se ilustran los residuos 1-488 de HDAC2 y una marca de 6-histidina por el extremo C-terminal (SEQ ID Nº: 3).

En la Figura 4 se ilustra la secuencia de ADN (SEQ ID Nº: 4) que se usó para codificar la SEQ ID Nº: 3.

En la Figura 5 se ilustran los residuos 73-845 de HDAC6 y una marca de 6-histidina por el extremo C-terminal (SEQ ID Nº: 5).

En la Figura 6 se ilustra la secuencia de ADN (SEQ ID Nº: 6) que se usó para codificar la SEQ ID Nº: 5.

En la Figura 7 se ilustran los residuos 1-377 de HDAC8 y una marca de 6-histidina por el extremo N-terminal (SEQ ID Nº: 7).

En la Figura 8 se ilustra la secuencia de ADN (SEQ ID Nº: 8) que se usó para codificar la SEQ ID Nº: 7.

DEFINICIONES

A menos que se especifique lo contrario, los siguientes términos, usados en la memoria descriptiva y las reivindicaciones, tienen los significados que se indican más adelante en esta Solicitud.

"Alicíclico" representa una porción que comprende una estructura de anillos no aromáticos. Las porciones alicíclicas pueden ser saturadas o parcialmente insaturadas, con uno, dos o más enlaces dobles o triples. Las porciones alicíclicas pueden comprender también opcionalmente heteroátomos, tales como nitrógeno, oxígeno y azufre. Los átomos de nitrógeno pueden estar opcionalmente cuaternerizados u oxidados, y los átomos de azufre pueden estar opcionalmente oxidados. Los ejemplos de porciones alicíclicas incluyen, sin limitaciones, porciones con anillos C_{3-8} tales como ciclopropilo, ciclohexano, ciclopentano, ciclopenteno, ciclopentadieno, ciclohexano, ciclohexeno, ciclohexadieno, cicloheptano, ciclohepteno, cicloheptadieno, ciclooctano, cicloocteno y ciclooctadieno.

"Alifático" representa una porción caracterizada por una disposición de cadenas rectas o ramificadas constituida por átomos de carbono, que puede estar saturada o parcialmente insaturada con uno, dos o más enlaces dobles o triples.

"Alcoxilo" representa una porción de oxígeno que tiene otro sustituyente alquilo. Los grupos alcoxilo de la presente invención pueden estar opcionalmente sustituidos.

"Alquilo" representa un radical alifático recto o ramificado, insaturado, que tiene una cadena de átomos de carbono, opcionalmente con átomos de oxígeno (véase "oxalquilo") o nitrógeno (véase "aminoalquilo") entre los átomos de carbono. Se usa C_X alquilo y C_{X-Y} alquilo típicamente cuando X e Y indican la cantidad de átomos de carbono en la cadena. Por ejemplo, C_{1-6} alquilo incluye los alquilos que tienen una cadena con entre 1 y 6 carbonos (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, sec-butilo, isobutilo, ter-butilo, vinilo, alilo, 1-propenilo, isopropenilo, 1-butenilo, 2-butenilo, 3-butenilo, 2-metilalilo, etinilo, 1-propinilo, 2-

propinilo y semejantes). Alquilo, junto con otro radical (por ejemplo, como arilalquilo, heteroarilalquilo) representa un radical alifático divalente, recto o ramificado, saturado o insaturado, que tiene la cantidad de átomos indicada, o cuando no se indican átomos de carbono, representa un enlace (por ejemplo, (C_{6-10})aril(C_{1-3})alquilo incluye, bencilo, fenetilo, 1-feniletilo, 3-fenilpropilo, 2-tienilmetilo, 2-piridinilmetilo y semejantes).

"Alquenilo" representa una cadena de carbono, lineal o ramificada, que contiene al menos un doble enlace carbono-carbono. Los ejemplos de alquenilo incluyen vinilo, alilo, isopropenilo, pentenilo, hexenilo, heptenilo, 1-propenilo, 2-butenilo, 2-metil-2-butenilo y semejantes.

"Alquinilo" representa una cadena de carbono, lineal o ramificada, que contiene al menos un triple enlace carbono-carbono. Los ejemplos de alquinilo incluyen etinilo, propargilo, 3-metil-1-pentinilo, 2-heptinilo y semejantes.

"Alquileno", a menos que se indique lo contrario, representa un radical alifático divalente, recto o ramificado, saturado o insaturado. Se usa C_X alquileno y C_{X-Y} alquileno típicamente cuando X e Y indican la cantidad de átomos en la cadena. Por ejemplo, C_{1-6} alquileno incluye metileno ($-CH_2-$), etileno ($-CH_2CH_2-$), trimetileno ($-CH_2CH_2CH_2-$), tetrametileno ($-CH_2CH_2CH_2CH_2-$) 2-butenileno ($-CH_2CH=CHCH_2-$), 2-metiltetrametileno ($-CH_2CH(CH_3)CH_2CH_2-$), pentametileno ($-CH_2CH_2CH_2CH_2CH_2-$) y semejantes.

"Alquenileno" representa una cadena de carbono divalente, lineal o ramificada, que tiene uno o más dobles enlaces carbono-carbono. Los ejemplos de alquenileno incluyen eten-1,2-diilo, propen-1,3-diilo, metilen-1,1-diilo y semejantes.

"Alquinileno" representa una cadena de carbono divalente, lineal o ramificada, que tiene uno o más enlaces triples carbono-carbono. Los ejemplos de alquinileno incluyen etin-1,2-diilo, propin-1,3-diilo y semejantes.

"Alquilideno" representa un radical alifático, recto o ramificado, saturado o insaturado, conectado con la molécula progenitora a través de un enlace doble. Se usa C_X alquilideno y C_{X-Y} alquilideno típicamente cuando X e Y indican la cantidad de átomos en la cadena. Por ejemplo, C_{1-6} alquilideno incluye metileno ($=CH_2$), etilideno ($=CHCH_3$), isopropilideno ($=C(CH_3)_2$), propilideno ($=CHCH_2CH_3$), alilideno ($=CH-CH=CH_2$) y semejantes).

"Amida" representa el radical $-NR_aC(O)R_b$ donde el punto de unión a la molécula tiene lugar por el nitrógeno y R_a y R_b son sustituyentes adicionales unidos al nitrógeno y al carbono del carbonilo, respectivamente.

"Amino" representa una porción de nitrógeno que tiene otros dos sustituyentes, donde, por ejemplo, se una un átomo de hidrógeno o carbono al nitrógeno. Por ejemplo, los grupos amino representativos incluyen $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC_{1-10}$-alquilo, $-N(C_{1-10}$-alquil$)_2$, -NH-arilo, -NH-heteroarilo, $-N(\text{arilo})_2$, $-N(\text{heteroarilo})_2$ y semejantes. Opcionalmente, los dos sustituyentes junto con el nitrógeno también pueden formar un anillo. A menos que se indique lo contrario, los compuestos de la invención que contienen porciones amino pueden incluir los derivados protegidos. Los grupos protectores apropiados para las porciones amino incluyen acetilo, *ter*-butoxicarbonilo, benciloxicarbonilo y semejantes.

"Aminoalquilo" representa un alquilo, como se definió previamente, que presenta uno o más átomos de nitrógeno sustituidos o no sustituidos (–N–) entre los átomos de carbono del alquilo. Por ejemplo, un (C_{2-6}) aminoalquilo representa una cadena que comprende entre 2 y 6 carbonos, y uno o más átomos de nitrógeno localizados entre los átomos de carbono.

Un "animal" incluye seres humanos, mamíferos no humanos (por ejemplo, perros, gatos, conejos, vacas, caballos, ovejas, cabras, cerdos, venados y semejantes) y no mamíferos (por ejemplo, aves y semejantes).

"Aromático" representa una porción donde los átomos constituyentes componen un sistema de anillos no saturado, todos los átomos en el sistema de anillos presentan hibridización sp^2 y la cantidad total de electrones pi es igual a 4n+2. Un anillo aromático puede ser tal que los átomos del anillo son solamente átomos de carbono, o pueden incluir átomos de carbono y distintos de carbono (véase heteroarilo).

"Arilo" representa un sistema de anillos monocíclicos o policíclicos, donde cada anillo es aromático o, cuando está fusionado con uno o más anillos, forma un sistema de anillos aromáticos. Si uno o más átomos del anillo es distinto de carbono (por ejemplo, N, S), el arilo es un heteroarilo. Se usa C_X arilo y C_{X-Y} arilo típicamente cuando X e Y indican la cantidad de átomos en el anillo.

"Bicicloalquilo" representa un sistema de anillos bicíclicos o policíclicos con puentes, saturados o parcialmente insaturados.

"Bicicloarilo" representa un sistema de anillos bicíclicos, donde los anillos están conectados por un enlace simple o están fusionados, y al menos uno de los anillos en el sistema es aromático. Se usa C_X bicicloarilo y C_{X-Y} bicicloarilo típicamente cuando X e Y indican la cantidad de átomos de carbono en el sistema de anillos bicíclicos, unidos directamente al anillo.

"Anillo de puente", como se lo usa en la presente documentación, hace referencia a un anillo que está unido a otro anillo para formar un compuesto que tiene una estructura bicíclica, donde los dos átomos del anillo comunes para ambos anillos no están unidos entre sí. Los ejemplos no exclusivos de compuestos comunes que tienen un anillo de puente incluyen borneol, norbornano, 7-oxabiciclo[2,2,1]heptano y semejantes. Uno o ambos anillos del sistema bicíclico también pueden comprender heteroátomos.

"Carbamilo" representa el radical $-OC(O)NR_aR_b$, donde R_a y R_b son cada uno independientemente otros dos sustituyentes, donde hay un átomo de hidrógeno o carbono unido al nitrógeno.

"Carbociclo" representa un anillo que consiste en átomos de carbono.

"Derivado de cetona carbocíclica" representa un derivado carbocíclico, donde el anillo contiene una porción -CO–.

"Carbonilo" representa el radical -CO-. Debe destacarse que el radical carbonilo puede estar adicionalmente sustituido con una variedad de sustituyentes para formar distintos grupos carbonilo, incluyendo ácidos, haluros de ácidos, aldehídos, amidas, ésteres y cetonas.

"Carboxamida" representa un radical $-C(O)NR_aR_b$ donde el punto de unión a la molécula es por el carbono del carbonilo y R_a y R_b son cada uno, independientemente entre sí, dos sustituyentes adicionales sobre el nitrógeno.

"Carboxilo" representa el radical $–CO_2-$. Debe destacarse que los compuestos de la invención que contienen porciones carboxilo pueden incluir derivados protegidos de éste, es decir, formas donde se reemplaza el oxígeno por un grupo protector. Los grupos protectores para las porciones carboxilo incluyen bencilo, *ter*-butilo y semejantes.

"Ciano" representa el radical -CN.

"Cicloalquilo" representa un sistema de anillos fusionados monocíclicos, bicíclicos o policíclicos con puentes, saturados o parcialmente insaturados. Se usa C_X

cicloalquilo y C_{X-Y} cicloalquilo típicamente cuando X e Y indican la cantidad de átomos de carbono en el sistema de anillos. Por ejemplo, C_{3-10} cicloalquilo incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclohexenilo, 2,5-ciclohexadienilo, biciclo[2,2,2]octilo, adamantan-1-ilo, decahidronaftilo, oxociclohexilo, dioxociclohexilo, tiociclohexilo, 2-oxobiciclo[2,2,1]hept-1-ilo y semejantes.

"Cicloalquileno" representa un sistema de anillos divalentes, monocíclicos o policíclicos, saturados o parcialmente insaturados. Se usa C_X cicloalquileno y C_{X-Y} cicloalquileno típicamente cuando X e Y indican la cantidad de átomos de carbono en el sistema de anillos.

"Enfermedad" incluye específicamente cualquier condición no saludable en un animal o parte del mismo, e incluye una condición no saludable que pueda ser causada o provocada por una terapia médica o veterinaria aplicada a dicho animal, es decir, los "efectos colaterales" de dicha terapia.

"Anillo fusionado", como se lo usa en la presente documentación, hace referencia a un anillo que está unido a otro anillo de un compuesto que tiene una estructura bicíclica, donde los átomos del anillo comunes a ambos anillos están unidos directamente entre sí. Los ejemplos no exclusivos de anillos fusionados comunes incluyen decalina, naftaleno, antraceno, fenantreno, indol, furano, benzofurano, quinolina y semejantes. Los compuestos que tienen sistemas de anillos fusionados pueden estar saturados, parcialmente saturados, pueden ser carbocíclicos, heterocíclicos, aromáticos, heteroaromáticos y semejantes.

"Halo" representa fluoro, cloro, bromo o iodo.

"Alquilo sustituido con halo", como grupo aislado o como parte de un grupo mayor, representa "alquilo" sustituido por uno o más átomos de "halo", como se definen dichos términos en esta Solicitud. Los alquilos sustituidos con halo incluyen haloalquilo, dihaloalquilo, trihaloalquilo, perhaloalquilo y semejantes (por ejemplo, (C_{1-3})alquilo sustituido con halo incluye clorometilo, diclorometilo, difluorometilo, trifluorometilo, 2,2,2-trifluoroetilo, perfluoroetilo, 2,2,2-trifluoro-1,1-dicloroetilo y semejantes).

"Heteroátomo" hace referencia a un átomo que no es un átomo de carbono. Los ejemplos particulares de heteroátomos incluyen, sin limitaciones, nitrógeno, oxígeno y azufre.

"Porción de heteroátomos" incluye una porción, donde el átomo unido a esta porción no es un átomo de carbono. Los ejemplos de porciones de heteroátomos incluyen -N=, -NR_c-, -$N^+(O^-)$=, -O-, -S- o -$S(O)_2$-, donde R_c es otro sustituyente.

"Heterobicicloalquilo" representa un bicicloalquilo, como se lo define en esta Solicitud, donde uno o más de los átomos en el anillo es un heteroátomo. Por ejemplo hetero(C_{9-12})bicicloalquilo, como se lo usa en esta solicitud, incluye, sin limitaciones, 3-aza-biciclo[4,1,0]hept-3-ilo, 2-aza-biciclo[3,1,0]hex-2-ilo, 3-aza-biciclo[3,1,0]hex-3-ilo y semejantes.

"Heterocicloalquileno" representa un cicloalquileno, como se lo define en esta Solicitud, donde se reemplaza uno o más de los átomos de carbono miembros del anillo por un heteroátomo.

"Heteroarilo" representa un grupo cíclico aromático que tiene cinco o seis átomos en el anillo, donde al menos un átomo en el anillo es un heteroátomo, y los átomos restantes en el anillo son de carbono. Los átomos de nitrógeno pueden estar opcionalmente cuaternizados, y los átomos de azufre pueden estar opcionalmente oxidados. Los grupos heteroarilo de esta invención incluyen, sin limitaciones, aquellos derivados de furano, imidazol, isotiazol, isoxazol, oxadiazol, oxazol, 1,2,3-oxadiazol, pirazina, pirazol, piridazina, piridina, pirimidina, pirrolina, tiazol, 1,3,4–tiadiazol, triazol y tetrazol. "Heteroarilo" también incluyen, sin limitaciones, anillos bicíclicos o tricíclicos, donde el anillo de heteroarilo está fusionado a uno o dos anillos seleccionados independientemente del grupo que consiste en un anillo de arilo, un anillo de cicloalquilo, un anillo de cicloalquenilo y otro anillo monocíclico de heteroarilo o heterocicloalquilo. Estos heteroarilos bicíclicos o tricíclicos incluyen, sin limitaciones, aquellos derivados de benzo[b]furano, benzo[b]tiofeno, benzimidazol, imidazo[4,5-c]piridina, quinazolina, tieno[2,3-c]piridina, tieno[3,2-b]piridina, tieno[2,3-b]piridina, indolizina, imidazo[1,2a]piridina, quinolina, isoquinolina, ftalazina, quinoxalina, naftiridina, quinolizina, indol, isoindol, indazol, indolina, benzoxazol, benzopirazol, benzotiazol, imidazo[1,5-a]piridina, pirazolo[1,5-a]piridina, imidazo[1,2-a]pirimidina, imidazo[1,2-c]pirimidina, imidazo[1,5-a]pirimidina, imidazo[1,5-c]pirimidina, pirrolo[2,3-b]piridina, pirrolo[2,3-c]piridina, pirrolo[3,2-c]piridina, pirrolo[3,2-b]piridina, pirrolo[2,3-d]pirimidina, pirrolo[3,2-d]pirimidina, pirrolo[2,3-b]pirazina, pirazolo[1,5-a]piridina, pirrolo[1,2-b]piridazina, pirrolo[1,2-c]pirimidina, pirrolo[1,2-a]pirimidina, pirrolo[1,2-a]pirazina,

triazo[1,5-a]piridina, pteridina, purina, carbazol, acridina, fenazina, fenotiazeno, fenoxazina, 1,2-dihidropirrolo[3,2,1-*hi*]indol, indolizina, pirido[1,2-a]indol y 2(1H)-piridinona. Los anillos de heteroarilo bicíclicos o tricíclicos pueden estar unidos a la molécula progenitora a través del grupo heteroarilo en sí, o el grupo arilo, cicloalquilo, cicloalquenilo o heterocicloalquilo al que está unido. Los grupos heteroarilo de esta invención pueden estar sustituidos o no sustituidos.

"Heterobicicloarilo" representa un bicicloarilo, como se lo define en esta Solicitud, donde uno o más de los átomos en el anillo es un heteroátomo. Por ejemplo, hetero(C_{4-12})bicicloarilo, como se lo usa en esta solicitud, incluye, sin limitaciones, 2-amino-4–oxo-3,4–dihidropteridin-6-ilo, tetrahidroisoquinolinilo y semejantes.

"Heterocicloalquilo" representa un cicloalquilo, como se lo define en esta Solicitud, donde uno o más de los átomos que forma el anillo es un heteroátomo, seleccionado independientemente entre N, O o S. Los ejemplos no exclusivos de heterocicloalquilo incluyen piperidilo, 4–morfolilo, 4–piperazinilo, pirrolidinilo, perhidropirrolizinilo, 1,4–diazaperhidroepinilo, 1,3-dioxanillo, 1,4–dioxanillo y semejantes.

"Hidroxilo" representa el radical -OH.

"IC_{50}" representa la concentración molar de un inhibidor que produce un 50% de inhibición de la enzima de interés.

"Derivado de iminocetona" representa un derivado que comprende la porción -C(NR)-, donde R comprende un átomo de hidrógeno o carbono unido al nitrógeno.

"Isómeros" representan cualquier par de compuestos que tienen una fórmula molecular idéntica, pero que difieren en la naturaleza o la secuencia de unión de sus átomos, o en la disposición de sus átomos en el espacio. Los isómeros que difieren en la disposición de sus átomos en el espacio se denominan "estereoisómeros". Los estereoisómeros que no son imágenes especulares uno del otro se denominan "diastereómeros", y los estereoisómeros que son imágenes especulares no superponibles se denominan "enantiómeros" o algunas veces "isómeros ópticos". Un átomo de carbono unido a cuatro sustituyentes no idénticos se denomina un "centro quiral". Un compuesto con un centro quiral tiene dos formas enantioméricas de quiralidad opuesta. Una mezcla de dos formas enantioméricas se denomina "mezcla racémica". Un compuesto que tiene más de un centro quiral tiene 2^{n-1} pares enantioméricos, donde n es la cantidad de centros

quirales. Los compuestos con más de un centro quiral pueden existir como un diastereómero individual o como una mezcla de diastereómeros, denominada "mezcla diastereomérica". Cuando hay un centro quiral presente, un estereoisómero puede caracterizarse por la configuración absoluta de dicho centro quiral. La configuración absoluta hace referencia a la disposición en el espacio de los sustituyentes unidos al centro quiral. Los enantiómeros se caracterizan por la configuración absoluta de sus centros quirales, y se describen de acuerdo con las reglas de secuenciación *R* y *S* de Cahn, Ingold y Prelog. Las convenciones de nomenclatura éstereoquímica, los métodos para determinar la estereoquímica y separar estereoisómeros son bien conocidos en la técnica (por ejemplo, véase "Advanced Organic Chemistry", 4ª edición, Marzo, Jerry, John Wiley & Sons, Nueva York, 1992).

Un "grupo saliente" representa un grupo que puede ser desplazado por otro grupo, tal como por ataque nucleofílico, durante una reacción química. Los grupos salientes son bien conocidos en la técnica e incluyen, por ejemplo, haluros y OSO_2R' donde R' es, por ejemplo, alquilo, haloalquilo o arilo opcionalmente sustituido con halo, alquilo, alcoxi, amino y semejantes. Los ejemplos no limitativos de grupos salientes incluyen cloro, bromo, iodo, mesilato, tosilato y otros grupos similares.

"Nitro" representa el radical $-NO_2$.

"Oxo" representa el radical =O.

"Oxalquilo" representa un alquilo, como se definió previamente, donde hay uno o más átomos de oxígeno (-O-) localizados entre los átomos de carbono del alquilo. Por ejemplo, un (C_{2-6})oxalquilo hace referencia a una cadena que comprende entre 2 y 6 carbonos, y uno o más átomos de carbono localizados entre los átomos de carbono.

"Oxoalquilo" hace referencia a un alquilo sustituido con un grupo carbonilo. El grupo carbonilo puede ser un aldehído, una cetona, un éster, una amida, un ácido o un cloruro de ácido.

"Aceptable para el uso farmacéutico" representa que el compuesto es útil para preparar una composición farmacéutica que es generalmente segura, no tóxica o indeseable de otro modo, e incluye aquellos compuestos que son aceptables para uso veterinario, así como para uso farmacéutico en seres humanos.

"Sales aceptables para el uso farmacéutico" representa sales de los compuestos de la presente invención que son aceptables para el uso farmacéutico, como se definió previamente, y que poseen la actividad farmacológica deseada. Dichas sales incluyen las sales de adición ácida formadas con ácidos inorgánicos, tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y semejantes; o con ácidos orgánicos, tales como ácido acético, ácido propiónico, ácido hexanoico, ácido heptanoico, ácido ciclopentanpropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido malónico, ácido succínico, ácido málico, ácido maleico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido *o*-(4–hidroxibenzoil)benzoico, ácido cinámico, ácido mandélico, ácido metansulfónico, ácido etansulfónico, ácido 1,2-etandisulfónico, ácido 2-hidroxietansulfónico, ácido bencensulfónico, ácido *p*-clorobencensulfónico, ácido 2-naftalensulfónico, ácido *p*-toluensulfónico, ácido canforsulfónico, ácido 4–metilbiciclo[2,2,2]oct-2-en-1-carboxílico, ácido glucoheptónico, ácido 4,4'-metilenebis(3-hidroxi-2-en-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido butilacético terciario, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico y semejantes.

Las sales aceptables para el uso farmacéutico también incluyen las sales de adición básica, que pueden formarse cuando los protones presentes son capaces de reaccionar con bases inorgánicas u orgánicas. Las bases inorgánicas aceptables incluyen hidróxido de sodio, carbonato de sodio, hidróxido de potasio, hidróxido de aluminio e hidróxido de calcio. Las bases orgánicas aceptables incluyen etanolamina, dietanolamina, trietanolamina, trimetamina, *N*-metilglucamina y semejantes.

"Prodroga" representa un compuesto que puede convertirse metabólicamente *in vivo* en un inhibidor de acuerdo con la presente invención. La prodroga misma puede también presentar actividad de inhibición de HDAC, o no. Por ejemplo, puede administrarse un inhibidor que comprende un grupo hidroxilo como un éster, que se convierte por hidrólisis *in vivo* en el compuesto de hidroxilo. Los ésteres apropiados que pueden convertirse *in vivo* en compuestos de hidroxilo incluyen acetatos, citratos, lactatos, tartratos, malonatos, oxalatos, salicilatos, propionatos, succinatos, fumaratos, maleatos, metilen-bis-b-hidroxinaftoatos,

gentisatos, isetionatos, di-*p*-toluoiltartratos, metansulfonatos, etansulfonatos, bencensulfonatos, p-toluensulfonatos, ciclohexilsulfamatos, quinatos, ésteres de aminoácidos y semejantes. De forma similar, puede administrarse un inhibidor que comprende un grupo amino como una amida, que se convierte por hidrólisis *in vivo* en el compuesto de amina.

Los "derivados protegidos" representan derivados de inhibidores, donde el o los sitios reactivos están bloqueados por grupos protectores. Los derivados protegidos son útiles para preparar los inhibidores, o pueden actuar ellos mismos como inhibidores. Puede hallarse una lista exhaustiva de grupos protectores apropiados en T.W. Greene, *Protecting Grupos en Organic Síntesis*, 3ª edición, John Wiley & Sons, Inc. 1999.

Un "anillo" significa un sistema carbocíclico o heterocíclico.

"Sustituido o no sustituido" significa que una porción dada puede comprender solamente sustituyentes hidrógeno en todas las valencias disponibles (no sustituido), o puede comprender además uno o más sustituyentes distintos de hidrógeno en las valencias disponibles (sustituido), los cuales no están especificados por el nombre de la porción dada. Por ejemplo, el isopropilo es un ejemplo de una porción de etileno sustituida por $-CH_3$. En general, un sustituyente distinto de hidrógeno puede ser cualquier sustituyente unido a un átomo de la porción dada especificada como sustituida. Los ejemplos de sustituyentes incluyen, sin limitaciones, porciones de aldehído, alicíclicas, alifáticas, de (C_{1-10})alquilo, alquileno, alquilideno, amida, amino, aminoalquilo, aromáticas, de arilo, bicicloalquilo, bicicloarilo, carbamilo, carbociclilo, carboxilo, con grupos carbonilo, cicloalquilo, cicloalquileno, éster, halo, heterobicicloalquilo, heterocicloalquileno, heteroarilo, heterobicicloarilo, heterocicloalquilo, oxo, hidroxilo, iminocetona, cetona, nitro, oxaalquilo y oxoalquilo, cada una de las cuales puede estar también opcionalmente sustituida o no sustituida.

"Sulfinilo" representa el radical –SO-. Debe destacarse que el radical sulfinilo puede estar adicionalmente sustituido con una variedad de sustituyentes para formar distintos grupos sulfinilo, incluyendo ácidos sulfínicos, sulfinamidas, ésteres de sulfinilo y sulfóxidos.

"Sulfonilo" representa el radical $-SO_2-$. Debe destacarse que el radical sulfonilo puede estar adicionalmente sustituido con una variedad de sustituyentes para

formar distintos grupos sulfonilo, incluyendo ácidos sulfónicos, sulfonamidas, ésteres de sulfonato y sulfonas.

"Cantidad eficaz para el uso terapéutico" representa la cantidad que, cuando se administra a un animal para tratar una enfermedad, es suficiente para efectuar dicho tratamiento de la enfermedad.

"Tiocarbonilo" representa el radical -CS-. Debe destacarse que el radical tiocarbonilo puede estar adicionalmente sustituido con una variedad de sustituyentes para formar distintos grupos tiocarbonilo, incluyendo tioácidos, tioamidas, tioésteres y tiocetonas.

"Tratamiento" o "tratar" representa cualquier administración de un compuesto de la presente invención, e incluye:

(1) prevenir la aparición de la enfermedad en un animal que puede estar predispuesto, pero que aún no experimenta o presenta la patología o la sintomatología de la enfermedad,

(2) inhibir la enfermedad en un animal que experimenta o presenta la patología o la sintomatología de la enfermedad (es decir, detener el desarrollo posterior de la patología y/o la sintomatología), o

(3) mejorar la enfermedad en el animal que está presentando la patología o la sintomatología de la enfermedad (es decir, invertir la patología y/o la sintomatología).

Debe destacarse, respecto de todas las definiciones proporcionadas en la presente documentación, que éstas deben interpretarse como abiertas, en el sentido de que pueden incluirse otros sustituyentes más allá de aquellos especificados. Por consiguiente, un C_1 alquilo indica que existe un átomo de carbono, pero no indica cuáles son los sustituyentes en dicho átomo de carbono. De este modo, un C_1 alquilo comprende metilo (es decir, $-CH_3$), así como $-CR_aR_bR_c$, donde R_a, R_b y R_c pueden ser cada uno hidrógeno, o cualquier otro sustituyente, donde el átomo unido al carbono es un heteroátomo o ciano. Por ende, CF_3, CH_2OH y CH_2CN, por ejemplo, son todos C_1 alquilos.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención se relaciona con compuestos, composiciones, equipos y artículos manufacturados que pueden usarse para inhibir histona desacetilasas

(HDAC) y, en particular, HDAC de Clase I tales como HDAC1, HDAC2, HDAC6 y HDAC8.

Hasta la fecha se han identificado al menos diecisiete genes humanos que codifican HDAC comprobadas o putativas, algunos de los cuales se describen en Johnstone, R. W., "Histone-Deacethylase Inhibitors: Novel Drugs for the Treatment of Cancer", *Nature Reviews*, Volumen I, págs. 287-299, (2002) y Publicaciones PCT Nº: 00/10583, 01/18045, 01/42437 y 02/08273.

Las HDAC se han agrupado en tres clases distintas basado en su tamaño relativo y homología de secuencia. Las diferentes HDAC (*Homo sapiens*), clases, secuencias y referencias a HDAC que describen las diferentes HDAC se proveen en las Tablas 1-3.

TABLA 1: HDAC de CLASE I

HDAC	**GenBank, Nº Acceso**	**Referencia**
1	NP_004955	Histone deacetylase: a regulator of transcription, Wolffe, A. P., *Science* 272 (5260), 371-372 (1996)
2	NP_001518	Isolation and mapping of a human gene (RPD3L1) that is homologous to RPD3, a transcription factor in *Saccharomyces cerevisiae*; Furukawa, Y., Kawakami, T., Sudo, K., Inazawa, J., Matsumine, A., Akiyama, T. y Nakamura, Y., *Cytogenet. Cell Genet.* 73 (1-2), 130-133 (1996)
3	NP_003874	Isolation and characterization of cDNAs corresponding to an additional member of the human histone deacetylase gene family, Yang, W. M., Yao, Y. L., Sun, J. M., Davie, J. R. and Seto, E., *J. Biol. Chem.* 272 (44), 28001-28007 (1997)
8	NP_060956	Buggy, J. J., Sideris, M. L., Mak, P., Lorimer, D. D., McIntosh, B. and Clark, J. M. *Biochem. J.* 350 Pt 1, 199-205 (2000)

HDAC	GenBank, Nº Acceso	Referencia
11	NP_079103	Cloning and Functional Characterization of HDAC11, a Novel Member of the Human Histone Deacetylase Family, Gao, L., Cueto, M. A., Asselbergs, F. and Atadja, P., *J. Biol. Chem.* 277 (28), 25748-25755 (2002)

TABLA 2: HDAC de CLASE II

HDAC	GenBank Nº Acceso	Referencia
4	NP_006028	Transcriptional control. Sinful repression, Wolffe, A. P., *Nature* 387 (6628), 16-17 (1997)
5	NP_631944	Prediction of the coding sequences of unidentified human genes. IX. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro, Nagase, T., Ishikawa, K., Miyajima, N., Tanaka, A., Kotani, H., Nomura, N. and Ohara, O., *DNA Res.* 5 (1), 31-39 (1998)
6	NP_006035	Transcriptional control. Sinful repression, Wolffe,A.P., Nature 387 (6628), 16-17 (1997)
7	NP_057680	Isolation of a novel histone deacetylase reveals that class I and class II deacetylases promote SMRT-mediated repression, Kao, H. Y., Downes, M., Ordentlich, P. and Evans, R. M., *Genes Dev.* 14 (1), 55-66 (2000)
9	NP_478056	MEF-2 function is modified by a novel co-repressor, MITR, Sparrow, D. B., Miska, E. A., Langley, E., Reynaud-Deonauth, S., Kotecha, S., Towers, N., Spohr, G., Kouzarides, T. and Mohun, T. J., *EMBO J.* 18 (18), 5085-5098 (1999)

HDAC	GenBank Nº Acceso	Referencia
10	NP_114408	Isolation and characterization of mammalian HDAC10, a novel histone deacetylase, Kao, H. Y., Lee, C. H., Komarov, A., Han, C. C. and Evans, R. M., *J. Biol. Chem.* 277 (1), 187-193 (2002)

TABLA 3: HDAC de CLASE III

HDAC	GenBank Nº Acceso	Referencia
Sirtuin 1	NP_036370	Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity; Frye, R. A.; *Biochem. Biophys. Res. Commun.* 260 (1), 273-279 (1999)
Sirtuin 2	NP_085096 / NP_036369	A 'double adaptor' method for improved shotgun library construction; Andersson, B., Wentland, M. A., Ricafrente, J. Y., Liu, W. and Gibbs, R. A.; *Anal. Biochem.* 236 (1), 107-113 (1996)
Sirtuin 3	NP_036371	Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity; Frye, R. A.; *Biochem. Biophys. Res. Commun.* 260 (1), 273-279 (1999)

HDAC	GenBank Nº Acceso	Referencia
Sirtuin 4	NP_036372	Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity; Frye, R. A.; *Biochem. Biophys. Res. Commun.* 260 (1), 273-279 (1999)
Sirtuin 5	NP_112534 / NP_036373	Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity; Frye, R. A.; *Biochem. Biophys. Res. Commun.* 260 (1), 273-279 (1999)
Sirtuin 6	NP_057623	Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins; Frye, R. A.; *Biochem. Biophys. Res. Commun.* 273 (2), 793-798 (2000)
Sirtuin 7	NP_057622	Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins; Frye, R. A.; *Biochem. Biophys. Res. Commun.* 273 (2), 793-798 (2000)

Son de particular interés las HDAC de Clase I. Todas las HDAC de Clase I parecen ser sensibles a una inhibición con tricostatina A (TSA). De particular interés son HDAC2 y HDAC8, que son proteínas cuyas estructuras cristalinas fueron determinadas por los solicitantes y usadas para desarrollar la presente invención.

HDAC2 es una proteína de 488 residuos, de 55 kDa, localizada en el núcleo de una gran variedad de tejidos, así como en diversas líneas de células tumorales humanas. La forma de la HDAC2 de longitud completa de tipo salvaje se describe en GenBank, Nº Acceso NM 001527, Furukawa, Y. et al., *Cryogenet. Cell Genet.*, 73(1-2), 130-133 (1996). Es probable que el Zn^{2+} sea nativo para la proteína y necesario para la actividad de HDAC2.

HDAC8 es una proteína de 42 kDa, de 377 residuos, localizada en el núcleo de una amplia variedad de tejidos, así como en diversas líneas de células tumorales humanas. La forma de HDAC8 de longitud completa de tipo salvaje se describe en GenBank, Nº Acceso NP 060956; Buggy, J. J. et al., *Biochem. J.*, 350 (Pt 1), 199-205 (2000). Es probable que el Zn^{2+} sea nativo para la proteína y necesario para la actividad de HDAC8.

Cabe destacar que los compuestos de la presente invención también pueden presentar actividad inhibidora para otros miembros de la familia de HDAC y por lo tanto se pueden usar en los estados de enfermedad asociados con estos otros miembros de la familia.

Estructura cristalina de la histona desacetilasa

Syrrx, Inc. (actualmente Takeda San Diego, Inc.) en San Diego, California, resolvió la estructura cristalina para HDAC2. Se encontró que HDAC2 adoptaba una estructura α/β abierta que consistía de 8 láminas β paralelas centrales localizadas a modo de sándwich entre 12 hélices α. La hendidura de unión del ligando se encuentra prácticamente en el plano de la lámina β central y se forma primariamente por bucles que salen de los extremos carboxilo terminales de las cadenas β que comprenden la lámina. Los residuos que forman las regiones de los bucles que se extienden entre la cadena β 1 y la hélice α 1 y entre la hélice α 4 y la hélice α 5, proveen interacciones de superficie claves con los ligandos unidos. Los residuos que forman regiones de bucles que se extienden entre la cadena β 3 y la hélice α 6 y entre la cadena β 4 y la hélice α 7 y entre la cadena β 8 y la hélice α 10 cumplen funciones importantes en la definición de la forma del bolsillo de unión del ligando y están relacionadas con numerosas interacciones clave con los ligandos unidos.

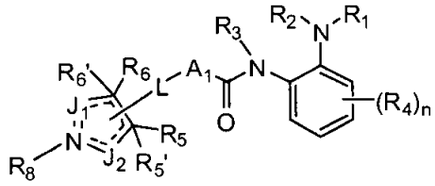
Se encontró que HDAC8 tenía una sola estructura de dominio que pertenecía a la clase de pliegues α/β abiertas. La estructura consiste de una lámina β central paralela de 8 cadenas que se ubican a modo de sándwich entre capas de hélices α. Las hendiduras de unión al ligando se encuentran casi en el plano de la lámina β central y están formadas primariamente por bucles que salen de los extremos carboxilo terminales de las cadenas β que comprenden la lámina. Hay dos extensiones estructurales grandes, que se encuentran más allá del centro del motivo α/β, fuera de la segunda y la última cadena β de la lámina β central. Los

residuos contenidos en la extensión fuera de la segunda cadena β forman una "tapa" globular sobre el centro de la proteína, cumplen un rol importante en la definición de la forma del bolsillo de unión del ligando y están relacionados con muchas de las interacciones clave con los ligandos unidos.

El conocimiento de las estructuras cristalinas se usó para diseñar los inhibidores de HDAC provistos en la presente.

Inhibitors de HDAC

En una realización, los inhibidores de HDAC de la presente invención comprenden:



en donde:

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillo a los cuales L está unido;

J_1 se selecciona del grupo formado por $-CR_7R_7'$- y $-NR_{19}$-;

J_2 se selecciona del grupo formado por $-CR_{20}R_{20}'$ y $-NR_{10}$-;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se toman juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

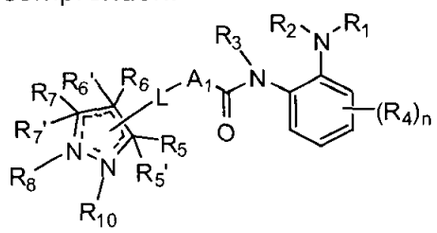
cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_5, R_5', R_6, R_6', R_7, y R_7', R_{20} y R_{20}' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo,

hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5, R_6, R_7 y R_{20}, cada uno en forma independiente están ausentes cuando el C al cual están unidos está unido a L, y R_5', R_6', R_7' y R_{20}', cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

R_8, R_{10} y R_{19} se selecciona cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}', R_{10} y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}' y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{19} y cualquiera de R_5, R_5', R_6, R_6', R_{20} y R_{20}', se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8, R_{10} y R_{19} cada uno en forma independiente están ausentes cuando el N al cual están unidos está unido a L, y R_8, R_{10} y R_{19} cada uno en forma independiente están ausentes cuando el N al cual están unidos forma parte de un doble enlace.

En otra realización, los inhibidores de HDAC de la presente invención comprenden:



en donde:

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

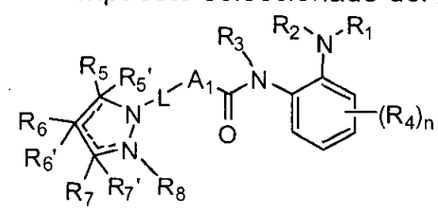
cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

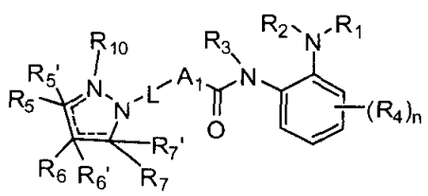
R_5, R_5', R_6, R_6', R_7 y R_7' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5, R_6 y R_7 cada uno en forma independiente están ausentes cuando el C al cual están unidos está unido a L, y R_5', R_6' y R_7'

cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

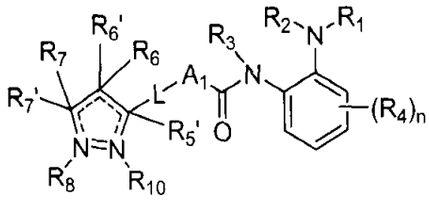
R_8 y R_{10} se selecciona cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7' y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 y R_{10} cada uno en forma independiente están ausentes cuando el N al cual están unidos está unido a L, y R_8 y R_{10} están ausentes cuando el N al cual están unidos forma parte de un doble enlace.

En otra realización, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:





y



en donde:

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo,

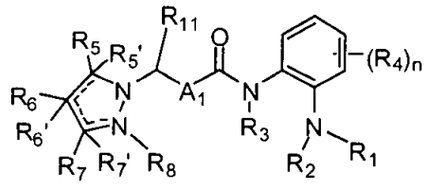
hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

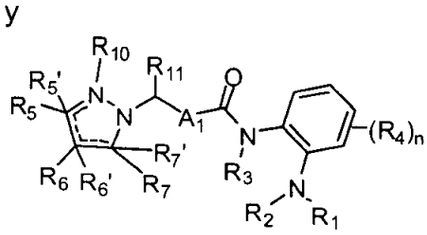
R_5, R_5', R_6, R_6', R_7 y R_7' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5', R_6' y R_7' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

R_8 y R_{10} se selecciona cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7' y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 y R_{10} cada uno en forma independiente están ausentes cuando el N al cual están unidos forma parte de un doble enlace.

En aún otra realización, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



y



en donde:

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

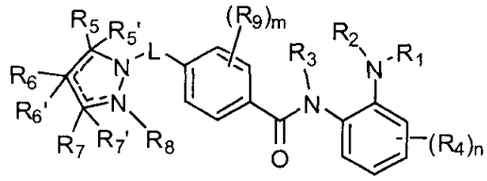
R_5, R_5', R_6, R_6', R_7 y R_7' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5', R_6' y R_7' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace;

R_8 y R_{10} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno

sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7' y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 y R_{10} cada uno en forma independiente están ausentes cuando el N al cual están unidos forma parte de un doble enlace; y

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido.

En aún otra realización adicional, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



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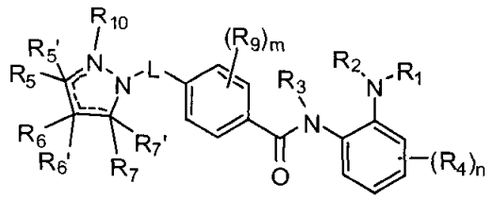


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

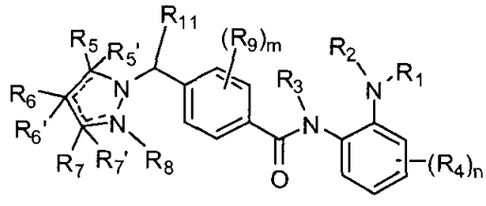
R_5, R_5', R_6, R_6', R_7 y R_7' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5', R_6' y R_7' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace;

R_8 y R_{10} se seleccionan en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno

sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7'y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 y R_{10} están ausentes cuando el N al cual están unidos forma parte de un doble enlace; y

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_3, R_5, R_5', R_7, R_7', R_8 y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En otra realización, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



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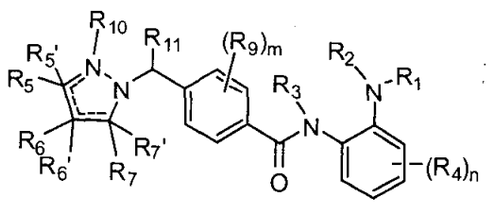


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo,

hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_5, R_5', R_6, R_6', R_7 y R_7' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5', R_6' y R_7' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace;

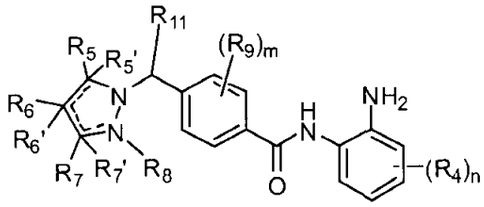
R_8 y R_{10} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7' y

R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 o R_{10} cada uno en forma independiente están ausentes cuando el N al cual está unido forma parte de un doble enlace;

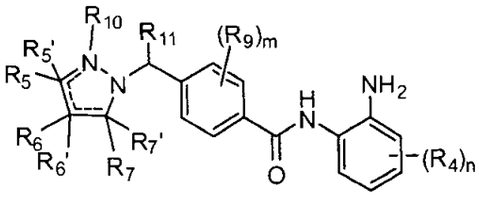
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_3, R_5, R_5', R_7, R_7', R_8 y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



y



en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_5, R_5', R_6, R_6', R_7 y R_7' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino

(C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5', R_6' y R_7' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace;

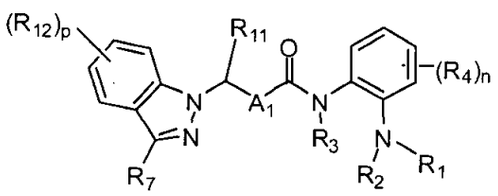
R_8 y R_{10} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7' y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 está ausente cuando el N al cual está unido forma parte de un doble enlace;

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino

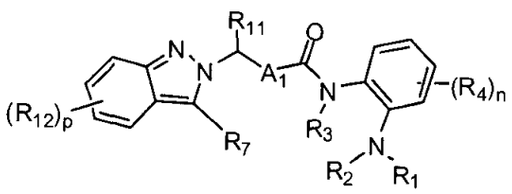
(C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_5, R_5', R_7, R_7', R_8 y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



y



en donde:

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino,

(C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

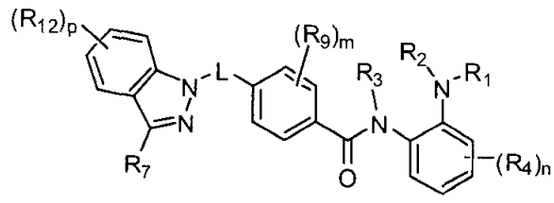
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno

sustituido o no sustituido, o R_{11} y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En otra realización, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



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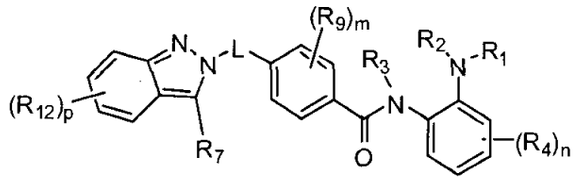


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillo a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo,

hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

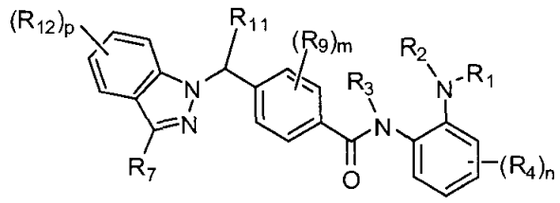
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y R_3 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo,

sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización adicional, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



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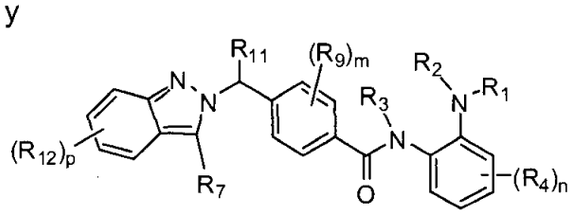


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

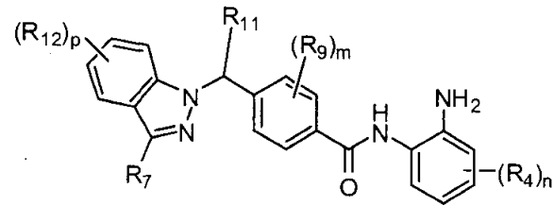
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y R_3 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi,

carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



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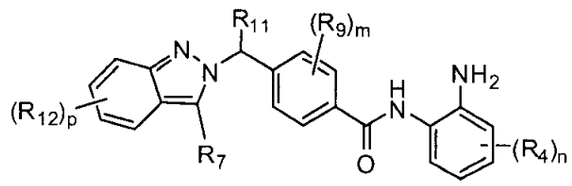


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo,

halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_7 o R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

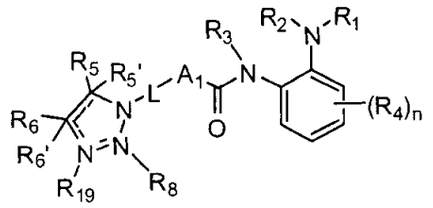
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

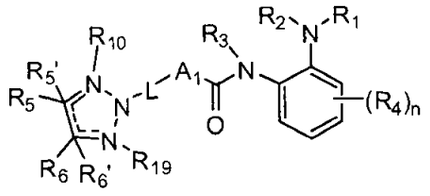
En una variación de cada una de las realizaciones precedentes, m es 0, R_{11} es hidrógeno, y R_{12} se selecciona del grupo formado por hidroxi, alcoxi, halo, amido, carboxamido, y (C_{1-10})alquilamido, cada uno sustituido o no sustituido.

En aún otra variación, *n* es 0, *p* es 2, y R_{12} se selecciona del grupo formado por hidroxi, alcoxi, y halo.

En aún otra variación, R_7 es hidrógeno, y R_{12} es alcoxi.

En aún otra realización adicional, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:





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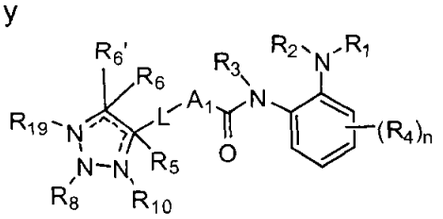


en donde:

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos de anillo a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

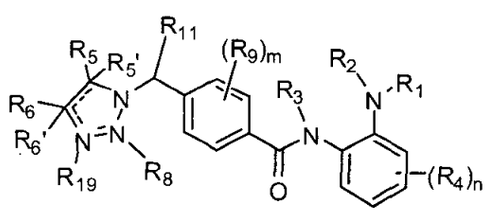
R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_5, R_5', R_6 y R_6' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, y R_6' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5' y R_6' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

R_8, R_{10} y R_{19}, se selecciona cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_{10} y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6' y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{19} y cualquiera de R_5, R_5', R_6 y R_6' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8, R_{10} y R_{19} cada uno en forma independiente están ausentes cuando el N al cual están unidos forma parte de un doble enlace.

En aún otra realización adicional, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



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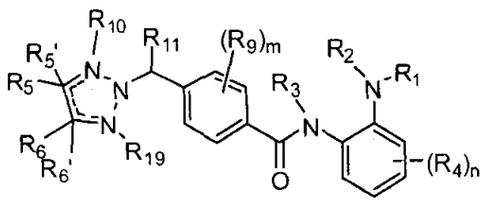


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino,

sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_5, R_5', R_6 y R_6' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6 y R_6' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5' y R_6' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace;

R_8, R_{10} y R_{19} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

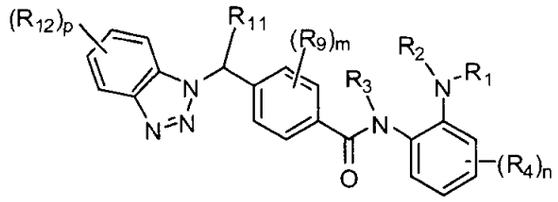
heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_{10} y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6' y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{19} y cualquiera de R_5, R_5', R_6 y R_6' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8, R_{10} y R_{19} cada uno en forma independiente están ausentes cuando el N al cual están unidos forma parte de un doble enlace.

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_3, R_5, R_5', R_8, R_{10} y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

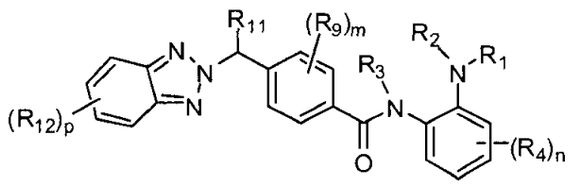
R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización adicional, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



y



en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

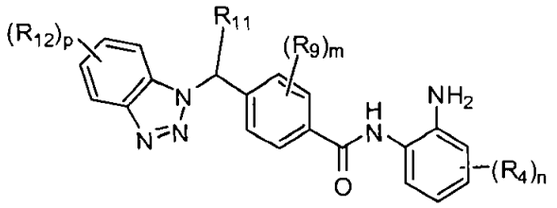
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno

sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y R_3 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En *aún otra realización adicional*, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:



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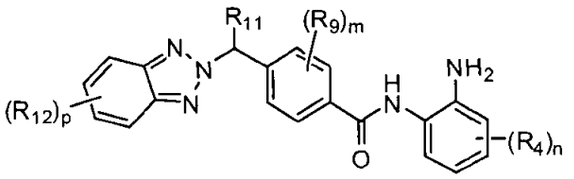


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

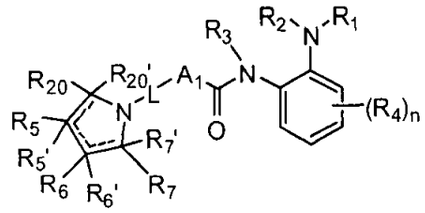
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

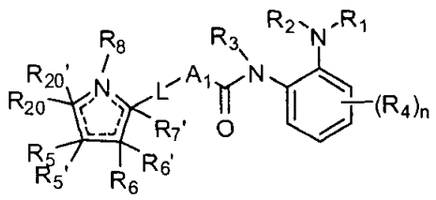
arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

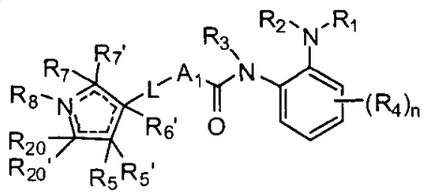
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamida, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización adicional, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:





y



en donde:

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

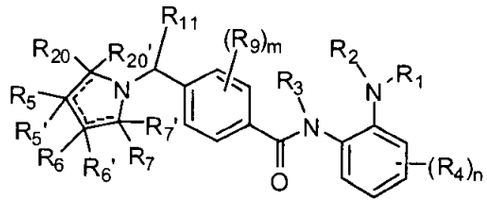
R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

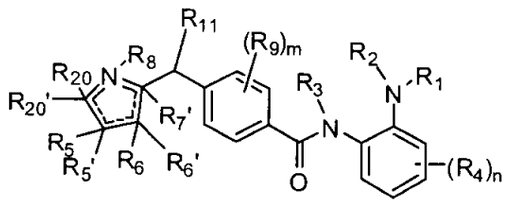
R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5', R_6', R_7' y R_{20}', cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

R_8 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 está ausente cuando el N al cual está unido forma parte de un doble enlace.

En aún otra realización adicional, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:





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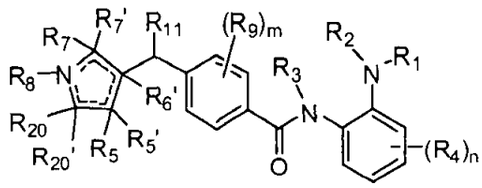


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino,

sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5', R_6', R_7' y R_{20}', cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

R_8 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo,

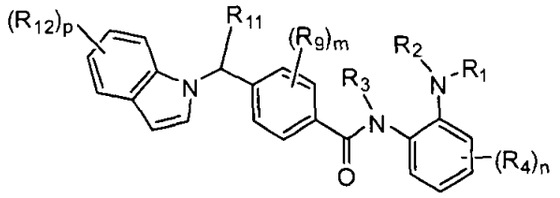
hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 está ausente cuando el N al cual está unido forma parte de un doble enlace;

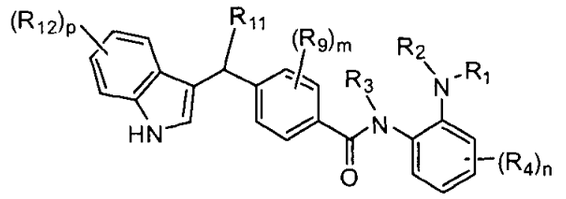
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_3, R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}' y R_8 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno

sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización adicional, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:





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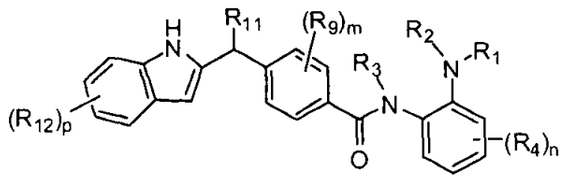


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno

sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

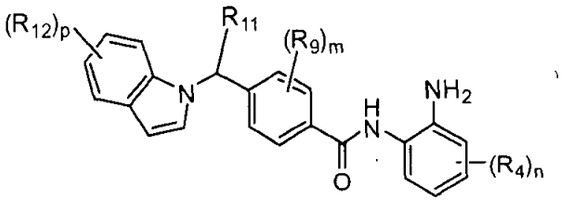
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo,

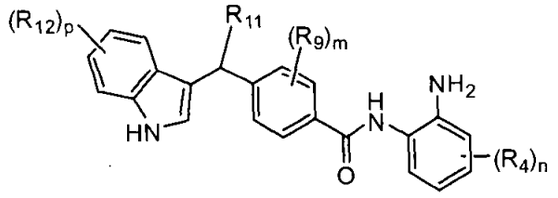
hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y R_3 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización adicional, los inhibidores de HDAC de la presente invención comprenden un compuesto seleccionado del grupo formado por:





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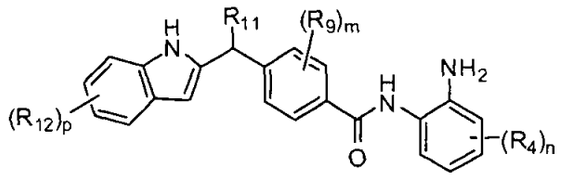


en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino

(C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno

sustituido o no sustituido, o R_{12} y R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En una variación de cada una de las realizaciones precedentes, R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquil y imino(C_{1-3})alquilo, cada uno sustituido o no sustituido.

En otra variación de cada una de las realizaciones y variaciones precedentes, R_1 es hidrógeno o un sustituyente convertible in vivo en hidrógeno. En aún otra variación de cada una de las realizaciones y variaciones precedentes, R_2 es hidrógeno o un sustituyente convertible in vivo en hidrógeno. En aún otra variación de cada una de las realizaciones y variaciones precedentes, R_3 es hidrógeno o un sustituyente convertible in vivo en hidrógeno.

En otra variación de cada una de las realizaciones y variaciones precedentes, R_4 se selecciona del grupo formado por hidrógeno, halo, arilo y heteroarilo, cada uno sustituido o no sustituido. En aún otra variación de cada una de las realizaciones y variaciones precedentes, R_4 se selecciona del grupo formado por fenilo, oxazolilo, tiazolilo, morfolinilo y tiomorfolinilo, cada uno sustituido o no sustituido.

En otra variación de cada una de las realizaciones y variaciones precedentes, R_5, R_6, R_7 y R_{20} se seleccionan en forma independiente del grupo formado por carbonilo, oxo, amino, (C_{1-10})alquilamino, amido, carboxamido, ciano, alcoxi, (C_{1-10})alquilo, arilo, y heteroarilo, cada uno sustituido o no sustituido.

En otra variación de cada una de las realizaciones y variaciones precedentes, R_5 y R_6 se toman juntos para formar un anillo sustituido o no sustituido. En una variación, el anillo es un arilo o heteroarilo, cada uno sustituido o no sustituido. En otra variación, el anillo está sustituido con un sustituyente seleccionado del grupo formado por halo, alcoxi, amino(C_{1-10})alcoxi, amino(C_{1-10})alquilamino, amino(C_{1-10})alquilsulfanilo, halo(C_{1-10})alquilo, arilo y heteroarilo, cada uno sustituido o no sustituido. En aún otra variación, el anillo está sustituido con un sustituyente

seleccionado del grupo formado por tiofenilo, piridinilo, furanilo y pirimidinilo, cada uno sustituido o no sustituido.

En aún otra variación, el anillo está sustituido con $-O-CH_2CH_2-NR_{13}R_{14}$. En otra variación, el anillo está sustituido con $-NH-CH_2CH_2-NR_{13}R_{14}$. En aún otra variación, el anillo está sustituido con $-S-CH_2CH_2-NR_{13}R_{14}$. En cada una de estas variaciones, R_{13} y R_{14} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero (C_{8-12})bicicloarilo (C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{13} y R_{14} se pueden tomar juntos para formar un anillo sustituido o no sustituido. En otras realizaciones, R_{13} y R_{14} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, y heteroarilo, cada uno sustituido o no sustituido. En aún otras realizaciones, R_{13} y R_{14} se toman juntos para formar un anillo seleccionado del grupo formado por morfolinilo, pirrolidinilo, piperazinilo y tiomorfolinilo, cada uno sustituido o no sustituido.

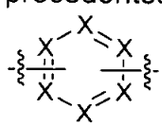
En otra variación de cada una de las realizaciones y variaciones precedentes, R_8, R_{10} y R_{19} se seleccionan del grupo formado por hidrógeno y (C_{1-10})alquilo sustituido o no sustituido.

En aún otra variación de cada una de las realizaciones y variaciones precedentes, L es un ligador que provee una separación de 1-5 átomos entre los dos átomos del anillos a los cuales L está unido. En aún otra variación de cada una de las realizaciones y variaciones precedentes, L es un ligador que provee una separación de 1-3 átomos entre los dos átomos del anillos a los cuales L está unido. En otra variación de cada una de las realizaciones y variaciones precedentes, L es un alquileno sustituido o no

sustituido. En aún otra variación de cada una de las realizaciones y variaciones precedentes, en donde L es $-CH_2-$. En otra variación de cada una de las realizaciones y variaciones precedentes, L se selecciona del grupo formado por $-NR_{15}-$; $-NR_{15}-CH_2-$; $-O-CH_2-$; $-S-CH_2-$; $-CH_2-NR_{15}-$; $-CH_2-O-$ y $-CH_2-S-$, en donde R_{15} se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido.

En aún otra variación de cada una de las realizaciones y variaciones precedentes, A_1 se selecciona del grupo formado por arilo y heteroarilo, cada uno sustituido o no sustituido. En aún otra variación de cada una de las realizaciones y variaciones precedentes, A_1 es un fenileno sustituido o no sustituido. En otra variación de cada una de las realizaciones y variaciones precedentes, A_1 es 1,4–fenileno sustituido o no sustituido. En otra variación de cada una de las realizaciones y variaciones precedentes, A_1 se selecciona del grupo formado por a tiofendiilo, furandiilo, pirroldiilo, tiazoldiilo, oxazoldiilo, imidazoldiilo y piridindiilo, cada uno sustituido o no sustituido.

En otra variación de cada una de las realizaciones y variaciones precedentes, A_1 comprende:



en donde:

cada X se selecciona en forma independiente del grupo formado por CR_{16} y N; y

cada R_{16} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{16} está ausente cuando el C al cual está unido también está unido a L o al carbonilo adyacente a A_1.

Ejemplos específicos de compuestos de acuerdo con la presente invención incluyen, pero sin carácter limitativo:

4–((1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((5-nitro-1H-indazol-1-il)metil)benzamida;

4–((5-benzamido-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((5-amino-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((5-nitro-2H-indazol-2-il)metil)benzamida;

4–((5-amino-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((5-benzamido-2H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

2-(4–((2-aminofenil)carbamoil)bencil)-2H-indazol-5-ilcarbamato de 2-Metoxietilo ;

2-(4–((2-aminofenil)carbamoil)bencil)-2H-indazol-5-ilcarbamato de Metilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1H-indazol-5-ilcarbamato de 2-Metoxietilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1H-indazol-5-ilcarbamato de Metilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1H-indazol-5-ilcarbamato de Bencilo ;

2-(4–((2-aminofenil)carbamoil)bencil)-2H-indazol-5-ilcarbamato de Bencilo ;

N-(4–Amino-bifenil-3-il)-4–(5-nitro-indazol-2-ilmetil)-benzamida;

N-(2-(4–((2-Aminofenil)carbamoil)bencil)-2H-indazol-5-il)morfolin-4–carboxamida;

5-((2H-Indazol-2-il)metil)–N–(2-aminofenil)tiofen-2-carboxamida;

N-(2-Aminofenil)-5-((5-nitro-2H-indazol-2-il)metil)tiofen-2-carboxamida;

N-(1-(4–((2-Aminofenil)carbamoil)bencil)-1H-indazol-5-il)morfolin-4–carboxamida;

1-(4–((2-aminofenil)carbamoil)bencil)-1H-indazol-5-ilcarbamato de 2-Morfolinoetilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1H-indazol-5-ilcarbamato de Piridin-3-ilmetilo;

5-((1H-Indazol-1-il)metil)–N–(2-aminofenil)tiofen-2-carboxamida;

4–((2H-Pirazolo[3,4–b]piridin-2-il)metil)–N–(2-aminofenil)benzamida;

N-(4–Amino-bifenil-3-il)-4–pirazolo[3,4–b]piridin-2-ilmetil-benzamida;

N-(4–Amino-bifenil-3-il)-4–indazol-2-ilmetil-benzamida;

N-(2-Aminofenil)-4–((3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-Aminofenil)-4–((3-metil-2H-indazol-2-il)metil)benzamida;

4–((1H-indazol-3-ilamino)metil)–N–(2-aminofenil)benzamida;

4–((1H-pirazol-1-il)metil)–N–(2-aminofenil)benzamida;

N-(2-(4–((2-Aminofenil)carbamoil)bencil)-2H-indazol-5-il)morfolin-4–carboxamida;

3-(4–((2H-indazol-2-il)metil)benzamido)-4–aminobenzoato de metilo ;

N-(2-aminofenil)-4–((4–metil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-fluoro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-fluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-fluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-fluoro-2H-indazol-2-il)metil)benzamida;

4–(1-(1H-indazol-1-il)propan-2-il)–N–(2-aminofenil)benzamida;

4–(2-(1H-indazol-1-il)etil)–N–(2-aminofenil)benzamida;

4–(2-(2H-indazol-2-il)etil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((4–chloro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–chloro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4,6-difluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4,6-difluoro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((7-fluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((7-fluoro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fluoro-2H-indazol-2-il)metil)benzamida;

(R)-4–(1-(2H-indazol-2-il)etil)–N–(2-aminofenil)benzamida;

(S)-4–(1-(2H-indazol-2-il)etil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((7-fluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((7-fluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-difluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-difluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-chloro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-chloro-2H-indazol-2-il)metil)benzamida;

4–((3-amino-5-(trifluorometil)-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((3-amino-5-(trifluorometil)-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((3-oxo-2,3-dihidro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-oxo-1H-indazol-2(3H)-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-fluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-fluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5-fluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-fluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-etil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-etil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-hidroxi-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-hidroxi-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-fenil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-fenil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5-metoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3,5-dimetil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3,5-dimetil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((7-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((7-metoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–metoxi-1H-indazol-1-il)metil)benzamida;

4–((6-acetamido-3-metil-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-3-metil-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((3-amino-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((3-metil-7-(trifluorometil)-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metil-6-(trifluorometil)-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metil-6-(trifluorometil)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metil-5-(trifluorometil)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metil-5-(trifluorometil)-2H-indazol-2-il)metil)benzamida;

4–((3-amino-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((5-hidroxi-6-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-dimetoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-dimetoxi-1H-indazol-1-il)metil)benzamida;

4–((1*H*-benzo[*d*][1,2,3]triazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((2*H*-benzo[*d*][1,2,3]triazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(piperazin-1-il)etil)-1H-pirazol-4–carboxamida;

4–((2*H*-indazol-2-il)metil)–N–(4–aminopirimidin-5-il)benzamida;

4–((5-acetamido-3-amino-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-3-metil-2*H*-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-3-metil-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–(1-(1*H*-indazol-1-il)etil)–N–(2-aminofenil)benzamida;

4–(1-(2*H*-indazol-2-il)etil)–N–(2-aminofenil)benzamida;

5-((5-acetamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)tiofen-2-carboxamida;

4–((2*H*-indazol-2-il)metil)–N–(2-amino-5-(tiofen-2-il)fenil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4,6-difluoro-2*H*-indazol-2-il)metil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4,6-difluoro-1*H*-indazol-1-il)metil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((6-metoxi-3-metil-1*H*-indazol-1-il)metil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4–metil-1*H*-pirazol-1-il)metil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((6-metoxi-3-metil-2*H*-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–(trifluorometil)-1*H*-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–(trifluorometil)-2*H*-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5-(trifluorometil)-1*H*-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-(trifluorometil)-2*H*-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-(trifluorometil)-2*H*-indazol-2-il)metil)benzamida;

ácido1-(4–(2-aminofenilcarbamoil)bencil)-1H-pirazol-4–carboxílico ;

N-(2-aminofenil)-4–((3-metil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3,5-dimetil-1H-pirazol-1-il)metil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)-1H-pirazol-4–carboxilato de etilo ;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-2-ilmetil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–fenil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–bencil-1H-pirazol-4–carboxamida;

N-(2-aminofenil)-4–((4,5,6,7-tetrahidro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4,5,6,7-tetrahidro-1H-indazol-1-il)metil)benzamida;

4–((1H-pirazol-3-ilamino)metil)–N–(2-aminofenil)benzamida;

4–((5-amino-1H-pirazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((3-amino-1H-pirazol-1-il)metil)–N–(2-aminofenil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–metil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–etil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)-N,N-dimetil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–isopropil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–ciclopropil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(ciclopropilmetil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(dimetilamino)etil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-hidroxietil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-(dimetilamino)propil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-3-ilmetil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-4–ilmetil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-morfolinoetil)-1H-pirazol-4–carboxamida;

N-(2-aminofenil)-4–((5-metil-1H-pirazol-1-il)metil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–propil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–isobutil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-metoxietil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-metoxipropil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-hidroxipropil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-morfolinopropil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(piperidin-1-il)etil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-(4–metilpiperazin-1-il)propil)-1H-pirazol-4–carboxamida;

4–((1*H*-Pirrolo[2,3-b]piridin-1-il)metil)–N–(2-aminofenil)benzamida;

4–((1*H*-Indol-3-il)metil)–N–(2-aminofenil)benzamida;

4–((1H-indazol-1-il)metil)–N–(2-amino-5-fluorofenil)benzamida;

4–((2H-indazol-2-il)metil)–N–(2-amino-5-fluorofenil)benzamida;

4–((1H-indazol-1-il)metil)–N–(2-amino-5-fluorofenil)-3-metilbenzamida;

4–((2H-indazol-2-il)metil)–N–(2-amino-5-fluorofenil)-3-metilbenzamida;

N-(2-aminofenil)-3-metil-4–((3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-3-metil-4–((3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-ciano-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-ciano-2H-indazol-2-il)metil)benzamida;

ácido1-(4–((2-aminofenil)carbamoil)bencil)-1H-indazol-3-carboxílico ;

ácido2-(4–((2-aminofenil)carbamoil)bencil)-2H-indazol-3-carboxílico ;

N-(2-aminofenil)-4–((5-ciano-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-ciano-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(piridin-2-il)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(piridin-2-il)-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(dimetilamino)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(dimetilamino)-2H-indazol-2-il)metil)benzamida;

4–((1H-indazol-1-il)metil)–N–(2-amino-5-(furan-2-il)fenil)benzamida;

4–((2H-indazol-2-il)metil)–N–(2-amino-5-(furan-2-il)fenil)benzamida;

N-(2-aminofenil)-4–((3-metoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(metoximetilamino)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(metoximetilamino)-2H-indazol-2-il)metil)benzamida;

4–((1H-pirazol-1-il)metil)–N–(2-amino-5-fluorofenil)benzamida;

N-(2-amino-5-fluorofenil)-4–((4–metil-1H-pirazol-1-il)metil)benzamida;

4–((1H-pirazol-1-il)metil)–N–(2-aminofenil)-3-metilbenzamida;

N-(2-amino-5-fluorofenil)-3-metil-4–((4–metil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–(furan-2-il)-1H-pirazol-1-il)metil)benzamida;

ácido1-(4–((2-aminofenil)carbamoil)bencil)-1H-pirazol-4–carboxílico;

N-(2-aminofenil)-4–((3-etil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-etil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fenil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-3-metil-4–((5-metil-4–fenil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-ciano-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-(piridin-2-il)-1H-pirazol-1-il)metil)benzamida;

4–((1H-pirazol-1-il)metil)–N–(2-amino-5-(furan-2-il)fenil)benzamida;

N-(2-amino-5-(furan-2-il)fenil)-4–((4–metil-1H-pirazol-1-il)metil)benzamida;

(S)-4–(1-(1H-pirazol-1-il)etil)–N–(2-aminofenil)benzamida;

(R)-4–(1-(1H-pirazol-1-il)etil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((3-(piridin-2-il)-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-metoxi-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(metoximetilamino)-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-(metoximetilamino)-1H-pirazol-1-il)metil)benzamida;

y

N-(2-aminofenil)-4–((3-metoxi-1H-pirazol-1-il)metil)benzamida.

Se hace notar que los compuestos de la presente invención pueden tener la forma de una sal aceptable para uso farmacéutico, éster biohidrolizable, amida hidrolizable, carbamato biohidrolizable, solvato, hidrato o prodroga del mismo. Por ejemplo, el compuesto opcionalmente comprende un sustituyente que es convertible in vivo en un sustituyente diferente tal como un hidrógeno.

Se hace notar además que el compuesto puede estar presente en una mezcla de estereoisómeros (incluyendo tautómeros), o el compuesto pueden comprender un solo esteroisómero.

La presente invención provee además una composición farmacéutica que comprende como ingrediente activo un compuesto de acuerdo con cualquiera de las realizaciones y variaciones precedentes. En una variación específica la composición es una formulación específica adaptada para la administración oral. En otra variación específica, la composición es una formulación líquida adaptada para la administración oral. En aún otra variación específica, la composición es una tableta. En aún otra variación específica, la composición es una formulación líquida adaptada para administración parenteral.

En otro de sus aspectos, se provee una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las realizaciones y variaciones precedentes, en donde la composición está adaptada para una administración a través de una ruta seleccionada del grupo que consiste en vía oral, parenteral, intraperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposomal, por inhalación, vaginal, intraocular, por administración local (por ejemplo, por catéter o stent), subcutánea, intraadipósica, intraarticular e intratecal.

En aún otro de sus aspectos, se provee conjunto de elementos *(kit)* que comprende un compuesto de cualquiera de las realizaciones y variaciones precedentes; e instrucciones que comprenden una o más formas de información seleccionadas del grupo formado por indicar un estado de enfermedad para el cual la composición se puede administrar, información

de almacenamiento de la composición, información de dosificación e instrucciones relativas a la forma de administración de la composición. En una variación específica el conjunto de elementos comprende el compuesto en una forma de dosificación múltiple.

En aún otros aspectos, se provee un artículo manufacturado que comprende un compuesto de cualquiera de las realizaciones y variaciones precedentes; y materiales de envase. En una variación, el material de envase comprende un recipiente para albergar el compuesto. En una variación específica el recipiente comprende una etiqueta que indica uno o más del siguiente grupo: un estado de enfermedad para el cual el compuesto se puede administrar, información de almacenamiento, información de dosificación y/o instrucciones sobre la manera de administrar el compuesto. En otra variación, el artículo manufacturado comprende el compuesto en una forma de dosificación múltiple.

En otro de sus aspectos, se provee un método terapéutico que comprende administrar un compuesto de cualquiera de las realizaciones y variaciones precedentes a un sujeto.

En otro de sus aspectos, se provee un método de inhibir HDAC que comprende poner en contacto HDAC con un compuesto de cualquiera de las realizaciones y variaciones precedentes.

En aún otro de sus aspectos, se provee un método de inhibir HDAC que comprende causar que un compuesto de cualquiera de las realizaciones y variaciones precedentes se encuentre presente en un sujeto con el fin de inhibir HDAC in vivo.

En otro de sus aspectos, se provee un método de inhibir HDAC que comprende administrar a un sujeto un primer compuesto que se convierte in vivo en un segundo compuesto en donde el segundo compuesto inhibe HDAC in vivo, siendo el segundo compuesto un compuesto de acuerdo con cualquiera de las realizaciones y variaciones precedentes.

En otro de sus aspectos, se provee un método de tratar un estado de enfermedad para el cual HDAC posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, donde el método comprende causar que un compuesto de cualquiera de las realizaciones y

variaciones precedentes se encuentre presente en un sujeto en una cantidad eficaz para uso terapéutico del estado de enfermedad.

En aún otro de sus aspectos, se provee un método de tratar un estado de enfermedad para el cual HDAC posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, donde el método comprende administrar un compuesto de cualquiera de las realizaciones y variaciones precedentes a un sujeto, en donde el compuesto está presente en el sujeto en una cantidad eficaz para uso terapéutico del estado de enfermedad.

En otro de sus aspectos, se provee un método de tratar un estado de enfermedad para el cual HDAC posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, donde el método comprende administrar a un sujeto un primer compuesto que se convierte in vivo en un segundo compuesto en donde el segundo compuesto inhibe HDAC in vivo, siendo el segundo compuesto un compuesto de acuerdo con cualquiera de las realizaciones y variaciones precedentes.

En aún otra realización adicional, la presente invención se relaciona con un método para tratar cáncer que comprende administrar un compuesto de acuerdo con cualquiera de las realizaciones y variaciones precedentes a un mamífero que lo necesita. En una variación, el cáncer se selecciona del grupo formado por carcinoma de células escamosas, astrocitoma, sarcoma de Kaposi, glioblastoma, cáncer de pulmón de células no pequeñas, cáncer de vejiga, cáncer de cabeza y cuello, melanoma, cáncer de ovario, cáncer de próstata, cáncer de mama, cáncer de pulmón de células pequeñas, glioma, cáncer colorrectal, cáncer genitourinario y cáncer gastrointestinal.

En otra realización, la presente invención se relaciona con un método para tratar inflamación, síndrome del intestino irritable, psoriasis, o rechazo de transplantes que comprende administrar un compuesto de acuerdo con cualquiera de las realizaciones y variaciones precedentes a un mamífero que lo necesita.

En otra realización, la presente invención se relaciona con un método para tratar la artritis que comprende administrar un compuesto de acuerdo con

cualquiera de las realizaciones y variaciones precedentes a un mamífero que lo necesita.

En aún otra realización, la presente invención se relaciona con un método para tratar enfermedades oftálmicas degenerativas que comprende administrar un compuesto de acuerdo con cualquiera de las realizaciones y variaciones precedentes a un mamífero que lo necesita.

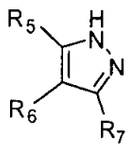
En aún otra realización adicional, la presente invención se relaciona con un método para tratar esclerosis múltiple, esclerosis amiotrófica lateral, neoplasma de tiroides o Mal de Alzheimer que comprende administrar un compuesto de acuerdo con cualquiera de las realizaciones y variaciones precedentes a un mamífero que lo necesita.

En otra realización, la presente invención se relaciona con un método para tratar enfermedades hiperproliferativas de la piel o trastornos cutáneos inflamatorios que comprende administrar un compuesto de acuerdo con cualquiera de las realizaciones y variaciones precedentes a un mamífero que lo necesita.

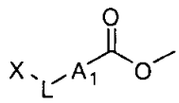
En cada una de las realizaciones y variaciones precedentes, la histona deacetilasa es opcionalmente una histona deacetilasa de Clase I. En variaciones específicas de cada una de las realizaciones y variaciones precedentes, la histona deacetilasa es HDAC2 y/o HDAC8.

En aún otro de sus aspectos, la presente invención se relaciona con métodos para elaborar los inhibidores de HDAC de la presente invención, así como intermediarios útiles para la preparación de tales inhibidores de HDAC. En una realización, los procesos comprenden:

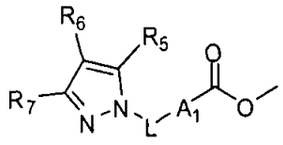
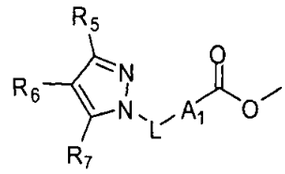
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula seleccionada del grupo formado por

 y  ,

en donde

X es un grupo saliente;

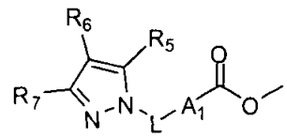
A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido; y

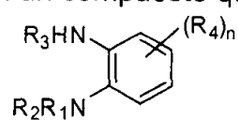
R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En otra realización, los procesos comprenden:

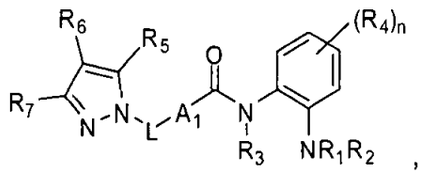
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

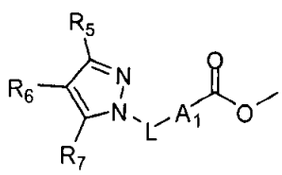
arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

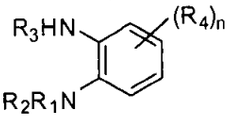
R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización adicional, los procesos comprenden:

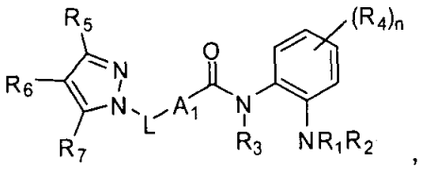
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino

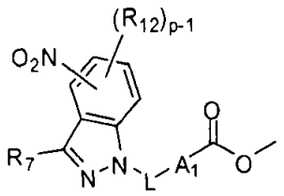
(C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización, los procesos comprenden:

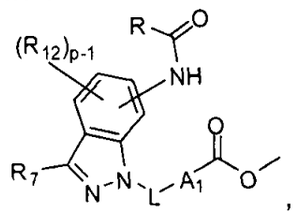
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula

R-C(O)-X

bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

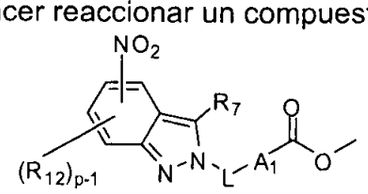
X es un grupo saliente;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En otra realización, los procesos comprenden:

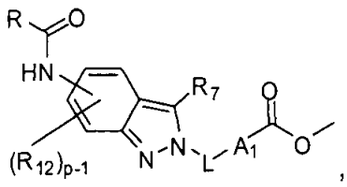
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula

R-C(O)-X

bajo condiciones que forman un producto de reacción que comprende una fórmula



,

en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

X es un grupo saliente;

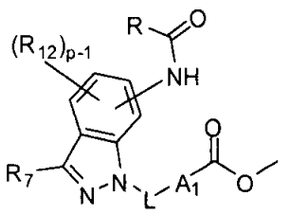
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo,

hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

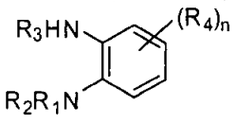
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización, los procesos comprenden:

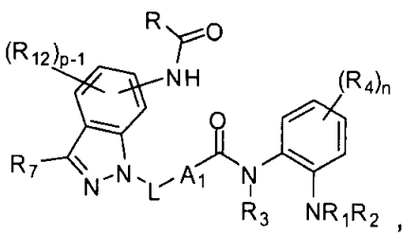
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

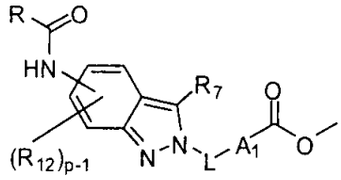
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

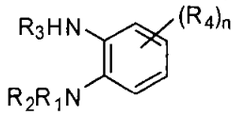
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización, los procesos comprenden:

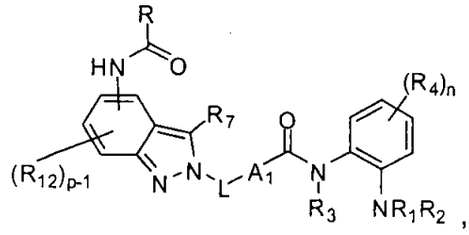
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo,

tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоaril(C_{1-5})alquilo, hetero(C_{8-12})biciclоaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})biciclоalquilo, hetero(C_{3-12})biciclоalquilo, arilo, heteroarilo, (C_{9-12})biciclоarilo y hetero(C_{4-12})biciclоarilo, cada uno sustituido o no sustituido;

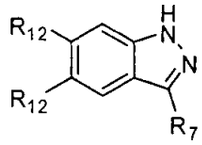
cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоaril(C_{1-5})alquilo, hetero(C_{8-12})biciclоaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})biciclоalquilo, hetero(C_{3-12})biciclоalquilo, arilo, heteroarilo, (C_{9-12})biciclоarilo y hetero(C_{4-12})biciclоarilo, cada uno sustituido o no sustituido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоaril(C_{1-5})alquilo, hetero(C_{8-12})biciclоaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})biciclоalquilo, hetero(C_{3-12})biciclоalquilo, arilo, heteroarilo, (C_{9-12})biciclоarilo y hetero(C_{4-12})biciclоarilo, cada uno sustituido o no sustituido; y

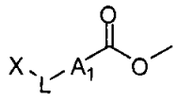
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En otra realización, los procesos comprenden:

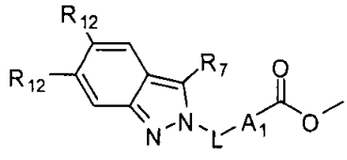
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula

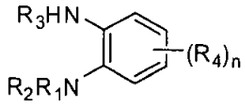


bajo condiciones que forman un primer producto de reacción que comprende una fórmula

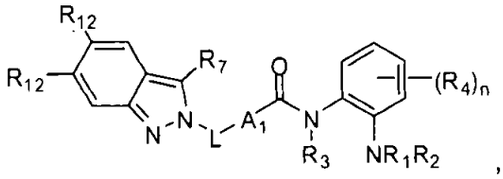


; y

hacer reaccionar el primer producto de reacción con un compuesto que comprende la fórmula



bajo condiciones que forman un segundo producto de reacción que comprende una fórmula



en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

X es un grupo saliente;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo,

hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

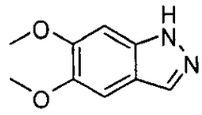
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo,

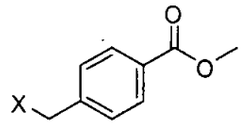
(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En otra realización, los procesos comprenden:

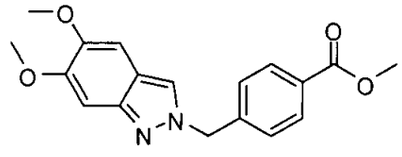
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula

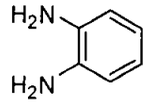


bajo condiciones que forman un primer producto de reacción que comprende una fórmula

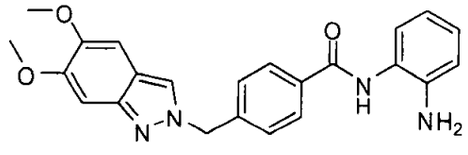


; y

hacer reaccionar el primer producto de reacción con un compuesto que comprende la fórmula



bajo condiciones que forman un segundo producto de reacción que comprende una fórmula

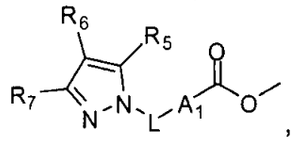


en donde

X es un grupo saliente.

En una variación de las realizaciones precedentes , X es halo. En una variación específica X es bromo. En otra variación específica, X es cloro.

En aún otro de sus aspectos, la presente invención se relaciona con compuestos útiles en la preparación de los inhibidores de HDAC de la presente invención. En una realización, los compuestos comprenden:



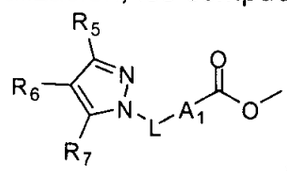
en donde

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido; y

R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En otra realización, los compuestos comprenden:



en donde

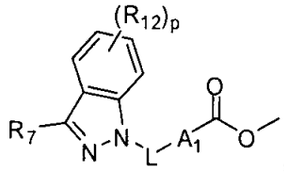
A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido; y

R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización adicional, los compuestos comprenden:



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

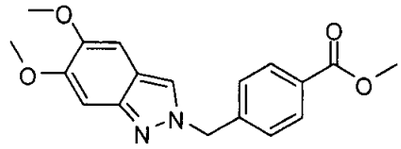
L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo,

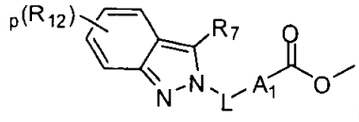
tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En una variante particular de la realización anterior, los compuestos comprenden:



En aún otra realización, los compuestos comprenden:



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

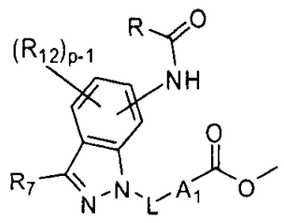
arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En otra realización, los compuestos comprenden:



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

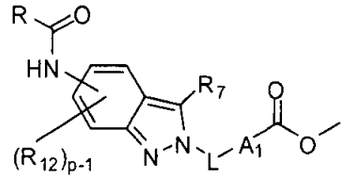
R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

En aún otra realización, los compuestos comprenden:



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

Sales, hidratos y prodrogas de inhibidores de HDAC

Debe reconocerse que los compuestos de la presente invención pueden estar

presentes, y pueden administrarse opcionalmente bajo la forma de sales hidratos y prodrogas, que se convierten *in vivo* en los compuestos de la presente invención. Por ejemplo, está dentro del alcance de la presente invención la conversión de compuestos de la presente invención y su uso en forma de sales aceptables para el uso farmacéutico, derivadas de varios ácidos y bases orgánicas e inorgánicas, de acuerdo con procedimientos bien conocidos en la técnica.

Cuando los compuestos de la presente invención poseen una forma de base libre, pueden preparare estos compuestos como una sal de adición ácida, haciendo reaccionar la forma de base libre del compuesto con un ácido inorgánico u orgánico aceptable para el uso farmacéutico, por ejemplo, halhidratos, tales como clorhidrato, bromhidrato, iodhidrato; otros ácidos minerales y sus sales correspondientes, tales como sulfato, nitrato, fosfato, etcétera; y alquil y monoarilsulfonatos, tales como etansulfonato, toluensulfonato y bencensulfonato; y otros ácidos orgánicos y sus sales correspondientes, tales como acetato, tartrato, maleato, succinato, citrato, benzoato, salicilato y ascorbato. Otras sales de adición ácida de la presente invención incluyen, sin limitaciones, adipato, alginato, arginato, aspartato, bisulfato, bisulfito, bromuro, butirato, canforato, canforsulfonato, caprilato, cloruro, clorobenzoato, ciclopentanpropionato, digluconato, dihidrógenfosfato, dinitrobenzoato, dodecilsulfato, fumarato, galacterato (de ácido múcico), galacturonato, glucoheptaoato, gluconato, glutamato, glicerofosfato, hemisuccinato, hemisulfato, heptanoato, hexanoato, hipurato, clorhidrato, bromhidrato, iodhidrato, 2-hidroxietansulfonato, ioduro, isetionato, iso-butirato, lactato, lactobionato, malato, malonato, mandelato, metafosfato, metansulfonato, metilbenzoato, monohidrógenfosfato, 2-naftalensulfonato, nicotinato, nitrato, oxalato, oleato, pamoato, pectinato, persulfato, fenilacetato, 3-fenilpropionato, fosfato, fosfonato y ftalato. Debe reconocerse que estas formas de bases libres diferirán típicamente en alguna medida de sus respectivas formas de sales, en lo que respecta a sus propiedades físicas, tales como su solubilidad en solventes polares, pero, en otros sentidos, las sales son equivalentes a sus formas de bases libres respectivas para los propósitos de la presente invención.

Cuando los compuestos de la presente invención poseen una forma de ácido libre, puede prepararse una sal de adición básica aceptable para el uso farmacéutico,

haciendo reaccionar la forma de ácido libre del compuesto con una base inorgánica u orgánica aceptable para el uso farmacéutico. Los ejemplos de dichas bases son los hidróxidos de metales alcalinos, incluyendo hidróxidos de potasio, sodio y litio; hidróxidos de metales alcalinos térreos, tales como hidróxido de bario y calcio; alcóxidos de metales alcalinos, por ejemplo, etanolato de potasio y propanolato de sodio; y varias bases orgánicas, tales como hidróxido de amonio, piperidina, dietanolamina y N-metilglutamina. También se incluyen las sales de aluminio de los compuestos de la presente invención. Otras sales básicas de la presente invención incluyen, sin limitaciones: sales de cobre, férricas, ferrosas, de litio, de magnesio, mangánicas, manganosas, de potasio, de sodio y de cinc. Las sales de bases orgánicas incluyen, sin limitaciones, sales de aminas primarias, secundarias y terciarias, aminas sustituidas, incluyendo aminas sustituidas de ocurrencia natural, aminas cíclicas y resinas de intercambio iónico básicas, por ejemplo, arginina, betaína, cafeína, cloroprocaína, colina, N,N'-dibenciletilendiamina (benzatina), diciclohexilamina, dietanolamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilendiamina, N-etilmorfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, iso-propilamina, lidocaína, lisina, meglumina, N-metil-D-glucamina, morfolina, piperazina, piperidina, resinas de poliamina, procaína, purinas, teobromina, trietanolamina, trietilamina, trimetilamina, tripropilamina y tris-(hidroximetil)-metilamina (trometamina). Debe reconocerse que las formas de ácido libre diferirán típicamente en alguna medida de sus respectivas formas de sales, en lo que respecta a sus propiedades físicas, tales como su solubilidad en solventes polares, pero, en otros sentidos, las sales son equivalentes a sus formas de bases libres respectivas para los propósitos de la presente invención.

Los compuestos de la presente invención que comprenden grupos básicos que contienen nitrógeno pueden cuaternizarse con agentes tales como haluros de (C_{1-4}) alquilo, por ejemplo, cloruros, bromuros e ioduros de metilo, etilo, iso-propilo y ter-butilo; sulfatos de di(C_{1-4}) alquilo, por ejemplo, sulfatos de dimetilo, dietilo y diamilo; haluros de (C_{10-18}) alquilo, por ejemplo, cloruros, bromuros e ioduros de decilo, dodecilo, laurilo, miristilo y estearilo; y haluros de (C_{1-4}) alquilo, por ejemplo, cloruro de bencilo y bromuro de fenetilo. Dichas sales permiten preparar compuestos de la presente invención solubles en agua y solubles en aceite.

Pueden prepararse *N*-óxidos de los compuestos de acuerdo con la presente invención empleando métodos conocidos por aquellos entrenados en la técnica. Por ejemplo, pueden prepararse *N*-óxidos tratando una forma no oxidada del compuesto con un agente oxidante (por ejemplo, ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido meta-cloroperoxibenzoico o semejantes) en un solvente orgánico inerte apropiado (por ejemplo, un hidrocarburo halogenado, tal como diclorometano) a aproximadamente 0°C. Como alternativa, pueden prepararse N-óxidos de los compuestos a partir del N-óxido de un material inicial apropiado.

Las prodrogas derivadas de los compuestos de acuerdo con la presente invención pueden prepararse modificando los sustituyentes de los compuestos de la presente invención, que luego se convierten *in vivo* en un sustituyente diferente. Debe destacarse que, en muchos casos, las prodrogas mismas están dentro del alcance del rango de los compuestos de acuerdo con la presente invención. Por ejemplo, pueden prepararse prodrogas haciendo reaccionar un compuesto con un agente carbamilante (por ejemplo, 1,1-aciloxialquilcarbonocloridato, carbonato de *para*-nitrofenilo o semejantes) o un agente acilante. Se describen otros ejemplos de métodos de para preparar prodrogas en Saulnier *et al.*(1994), *Bioorganic y Medicinal Chemistry Letters*, Vol. 4, p. 1985.

También pueden prepararse derivados protegidos de los compuestos de la presente invención. Pueden hallarse ejemplos de técnicas que pueden aplicarse a la creación de grupos protectores, y su remoción, en T.W. Greene, *Protecting Groups in Organic Synthesis*, 3ª edición, John Wiley & Sons, Inc. 1999.

Los compuestos de la presente invención también pueden prepararse o formarse convenientemente durante el proceso de la invención, como solvatos (por ejemplo, hidratos). Pueden prepararse convenientemente los hidratos de los compuestos de la presente invención efectuando una recristalización a partir de una mezcla de solventes acuosos/orgánicos, usando solventes orgánicos tal es como dioxina, tetrahidrofuranoo o metanol.

Una "sal aceptable para el uso farmacéutico", como se lo usa en la presente documentación, abarca cualquier compuesto de acuerdo con la presente invención que se utiliza bajo la forma de una sal, especialmente cuando la sal confiere propiedades farmacocinéticas mejoradas al compuesto, en comparación con la

forma libre del compuesto o una sal diferente del compuesto. La forma de sal aceptable para el uso farmacéutico puede también conferir inicialmente propiedades farmacocinéticas deseables al compuesto, ausentes previamente en éste, y aún puede afectar positivamente la farmacodinámica del compuesto, respecto de su actividad terapéutica en el cuerpo. Un ejemplo de una propiedad farmacocinética que puede ser afectada favorablemente es la forma en la que se transporta el compuesto a través de las membranas celulares, lo que, a su vez, puede afectar directa y positivamente la absorción, la distribución, la biotransformación y la excreción del compuesto. Si bien la ruta de administración de la composición farmacéutica es importante, y varios factores anatómicos, fisiológicos y patológicos pueden afectar en forma crítica la biodisponibilidd, la solubilidad del compuesto comúnmente depende del carácter de la sal particular del mismo utilizada. Aquellos entrenados en la técnica apreciarán que una solución acuosa del compuesto proporcionará la absorción más rápida del compuesto en el cuerpo de un sujeto tratado, mientras que las soluciones y las suspensiones de lípidos, así como las formas de dosificación sólidas, resultarán en una absorción menos rápida del compuesto.

Preparación de los inhibidores de HDAC

Se pueden desarrollar diversos métodos para sintetizar los compuestos acordes con la presente invención. Los métodos representativos para sintetizar estos compuestos se proveen en los Ejemplos. Sin embargo, se hace notar que los compuestos de la presente invención también se pueden sintetizar por otras rutas de síntesis que pudieran ser diseñadas por terceros.

Se puede ver fácilmente que determinados compuestos acordes con la presente invención tienen átomos con uniones a otros átomos que confieren una éstereoquímica particular al compuesto (por ejemplo, centros quirales). Se considera que la síntesis de los compuestos acordes con la presente invención pueden dar como resultado la creación de mezclas de diferentes estereoisómeros (es decir, enantiómeros y diastereómeros). A menos que se especifique una éstereoquímica particular, la descripción de un compuesto pretende abarcar todos los diferentes estereoisómeros posibles.

En la técnica se conocen diversos métodos para separar mezclas de diferentes estereoisómeros. Por ejemplo, se puede hacer reaccionar una mezcla racémica

de un compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diastereoisoméricos. Los diastereómeros se pueden separar luego con el fin de recuperar los ópticamente puros enantiómeros. Los complejos disociables también se pueden usar para resolver enantiómeros (por ejemplo, sales cristalinas diastereoisoméricas). Los diastereómeros poseen típicamente propiedades físicas suficientemente distintas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.) como para que se puedan separar aprovechando dichas diferencias. Por ejemplo, los diastereómeros se pueden separar típicamente por cromatografía o con de técnicas de separación/resolución basadas en las diferencias de solubilidad. Se puede consultar una descripción más detallada de las técnicas que se pueden usar para resolver los estereoisómeros de los compuestos a partir de su mezcla racémica en Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

Composiciones que comprenden inhibidores de HDAC

Puede usarse una amplia variedad de composiciones y métodos de administración en combinación con los compuestos de la presente invención. Dichas composiciones pueden incluir, además de los compuestos de la presente invención, excipientes farmacéuticos convencionales y otros agentes convencionales sin actividad farmacéutica. Adicionalmente, las composiciones pueden incluir agentes activos, además de los compuestos de la presente invención. Estos agentes activos adicionales pueden incluir compuestos adicionales de acuerdo con la invención, y/o uno o más agentes farmacéuticos activos adicionales.

Las composiciones pueden tomar una forma gaseosa, semilíquida o sólida, y pueden formularse de una manera apropiada para la ruta de administración a usar. Para una administración oral, se usan típicamente cápsulas y tabletas. Para una administración parenteral, se usa típicamente la reconstitución de un polvo liofilizado, preparado como se describe en la presente documentación.

Las composiciones que comprenden los compuestos de la presente invención pueden administrarse o coadministrarse por vía oral, parenteral, intraperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposomal, por inhalación, vaginal, intraocular, por

administración local (por ejemplo, empleando catéteres o stents), subcutánea, intraadiposal, intraarticular o intratecal. Los compuestos y/o las composiciones de acuerdo con la invención también pueden administrarse o coadministrarse en formas de dosificación de liberación lenta.

Los inhibidores de HDAC, y las composiciones que los comprenden, pueden administrarse o coadministrarse empleando cualquier forma de dosificación convencional. La co-administración, en el contexto de esta invención, representa la administración de más de un agente terapéutico, uno de los cuales incluye un inhibidor de HDAC, en el curso de un tratamiento coordinado, para obtener un resultado clínico mejorado. Dicha co-administración puede ser también coextensiva, es decir, puede°Currir durante períodos de tiempo superpuestos.

Las soluciones o suspensiones usadas para aplicaciones parenterales, intradérmicas, subcutáneas o tópicas puede incluir opcionalmente uno o más de los siguientes componentes: un diluyente estéril, tal como agua para inyección, solución salina, aceite fijo, polietilenglicol, glicerina, propilenglicol u otro solvente sintético; agentes antimicrobianos, tales como alcohol bencílico y metil parabenes; antioxidantes, tales como ácido ascórbico y bisulfito de sodio; agentes quelantes, tales como ácido etilendiaminotetraacético (EDTA); amortiguadores, tales como acetatos, citratos y fosfatos; agentes para ajustar la tonicidad, tales como cloruro de sodio o dextrosa, y agentes para ajustar la acidez o la alcalinidad de la composición, tales como agentes alcalinizantes o acidificantes, o amortiguadores, tales como carbonatos, bicarbonatos, fosfatos, ácido clorhídrico y ácidos orgánicos, tales como ácido acético y ácido cítrico. Las preparaciones parenterales pueden estar opcionalmente contenidas en ampollas, jeringas descartables o recipientes con una o varias dosis hechos de vidrio, plástico u otro material apropiado.

Cuando los compuestos de acuerdo con la presente invención presentan una solubilidad insuficiente, pueden usarse métodos para solubilizar los compuestos. Dichos métodos son conocidos por aquellos entrenados en la técnica, e incluyen, sin limitaciones, el uso de cosolventes, tales como dimetilsulfóxido (DMSO), el uso de agentes tensioactivos, tales como TWEEN, o la disolución en bicarbonato de sodio acuoso. Los derivados de los compuestos, tales como las prodrogas de los compuestos, también pueden usarse para formular composiciones farmacéuticas

efectivas.

Al mezclar o agregar compuestos de acuerdo con la presente invención a una composición, puede formarse una solución, una suspensión, una emulsión o semejantes. La forma de la composición resultante dependerá de una cantidad de factores, incluyendo el modo de administración pretendido, y la solubilidad del compuesto en el o los vehículos seleccionados. La concentración efectiva necesaria para mejorar la enfermedad a tratar puede determinarse en forma empírica.

Las composiciones de acuerdo con la presente invención pueden proporcionarse opcionalmente con el fin de administrarlas a seres humanos y animales, bajo la forma de unidades de dosificación, tales como tabletas, cápsulas, píldoras, polvos, polvos secos para inhalación, gránulos, soluciones o suspensiones parenterales estériles, y soluciones o suspensiones orales, y emulsiones de aceite-agua que contienen cantidades apropiadas de los compuestos, particularmente sus sales aceptables para el uso farmacéutico, preferiblemente sus sales de sodio. Los compuestos farmacéuticos con actividad terapéutica, y los derivados de los mismos, se formulan y administran típicamente como formas de dosificación unitaria, o como formas de dosificación múltiple. Las formas de dosificación unitaria, como se las usa en la presente documentación, hacen referencia unidades físicas discretas, apropiadas para sujetos humanos y animales, y envasadas en forma individual, como se conoce en la técnica. Cada dosificación unitaria contiene una cantidad predeterminada del compuesto con actividad terapéutica, suficiente para producir el efecto terapéutico deseado, en asociación con el vehículo, transporte o diluyente farmacéutico requerido. Los ejemplos de formas unitarias de dosificación incluyen ampollas y jeringas, y tabletas o cápsulas envasadas en forma individual. Las formas de dosificación unitarias pueden administrarse en fracciones o múltiplos. Una forma de dosificación múltiple es una pluralidad de formas de dosificación unitarias idénticas envasadas en un único recipiente, que pueden administrarse como formas unitarias de dosificación segregadas. Los ejemplos de formas de dosificación múltiples incluyen recipientes, botellas de tabletas o cápsulas, o botellas de pintas o galones. Por consiguiente, una forma de dosificación múltiple comprende varias dosificaciones individuales que no están segregadas en el envase.

Además de uno o más compuestos de acuerdo con la presente invención, la composición puede comprender un diluyente, tal como lactosa, sacarosa, fosfato de dicalcio o carboximetilcelulosa; un lubricante, tal como estearato de magnesio, estearato de calcio y talco; y un aglutinante, tal como almidón, gomas naturales, tal como goma acacia, gelatina, glucosa, molasas, polvinilpirrolidina, celulosas y derivados de las mismas, povidona, crospovidonas y otros aglutinantes conocidos por aquellos entrenados en la técnica. Pueden prepararse composiciones farmacéuticas de administración líquida, por ejemplo, disolviendo, dispersando o mezclando de otro modo un compuesto activo, como se definió previamente, y coadyuvantes farmacéuticos opcionales, en un vehículo, tal como, por ejemplo, agua, solución salina, dextrosa acuosa, glicerol, glicoles, etanol y semejantes, para formar una solución o una suspensión. Si se lo desea, la composición farmacéutica a administrar también puede contener cantidades menores de sustancias auxiliares, tales como agentes humectantes, agentes emulsificantes o agentes de solubilización, agentes amortiguadores del pH y semejantes, por ejemplo, acetato, citrato de sodio, derivados de ciclodextrina, monolaurato de sorbitan, acetato de trietanolamina de sodio, oleato de trietanolamina y otros agentes como tales. Los métodos actuales para preparar dichas formas de dosificación son conocidos en la técnica, o serán evidentes para aquellos entrenados en la técnica; por ejemplo, véase Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15ª edición, 1975. La composición o la formulación a administrar, en cualquier caso, contendrá una cantidad suficiente de un inhibidor de la presente invención, para reducir la actividad de HDAC *in vivo*, para tratar el estado de enfermedad en el sujeto.

Las formas de dosificación o las composiciones pueden comprender opcionalmente uno o más compuestos de acuerdo con la presente invención, en el rango de entre 0,005% y 100% (peso/peso), donde el resto comprende sustancias adicionales, tales como aquellas descriptas en la presente documentación. Para una administración oral, una composición aceptable para el uso farmacéutico puede comprender opcionalmente cualquier excipiente de uso común, tal como, por ejemplo, manitol de grado farmacéutico, lactosa, almidón, estearato de magnesio, talco, derivados de celulosa, croscarmellose sodio, glucosa, sacarosa, carbonato de magnesio, sacarina de sodio, talco. Dichas composiciones incluyen

soluciones, suspensiones, tabletas, cápsulas, polvos, polvos secos de inhalación y formulaciones de liberación sostenida, tales como, sin limitaciones, implantaes y sistemas de administración microencapsulados, y polímeros biodegradables, polímeros biocompatibles, tales como colágeno, acetato de etilen vinilo, polianhídridos, ácido poliglicólico, poliortoésteres, ácido polilláctico y otros. Los métodos para preparar estas formulaciones son conocidos por aquellos entrenados en la técnica. Las composiciones pueden contener opcionalmente 0,01%-100% (peso/peso) de uno o más inhibidores de HDAC, opcionalmente 0,1-95%, y opcionalmente 1-95%.

Pueden prepararse sales, preferiblemente sales de sodio, de los inhibidores , con vehículos que protejan el compuesto de la eliminación rápida del cuerpo, tales como las formulaciones o los recubrimientos de liberación demorada. Además, las formulaciones pueden incluir otros compuestos activos, para obtener combinaciones de propiedades deseadas.

Formulaciones de Administración Oral

Las formas de dosificación farmacéutica oral pueden tomar la forma de sólidos, geles o líquidos. Los ejemplos de formas de dosificación sólidas incluyen, sin limitaciones, tabletas, cápsulas, gránulos y polvos en lotes. Los ejemplos más específicos de tabletas orales incluyen tabletas comprimidas, pastillas masticables y tabletas que pueden presentar recubrimientos entéricos, recubrimientos azucarados o recubrimientos de película. Los ejemplos de cápsulas incluyen cápsulas de gelatina duras o blandas. Pueden proporcionarse los gránulos y los polvos en formas no efervescentes o efervescentes. Puede combinarse cada uno con otros ingredientes conocidos por aquellos entrenados en la técnica.

En determinadas realizaciones, pueden proporcionarse los compuestos de acuerdo con la presente invención como formas de dosificación sólidas, preferiblemente cápsulas o tabletas. Las tabletas, las píldoras, las cápsulas, las pastillas y semejantes pueden contener opcionalmente uno o más de los siguientes ingredientes, o compuestos de naturaleza similar: un aglutinante, un diluyente, un agente desintegrador, un lubricante, un deslizante, un agente edulcorante y un agente saborizante.

Los ejemplos de aglutinantes que pueden usarse incluyen, sin limitaciones,

celulosa microcristalina, goma tragacanto, solución de glucosa, mucílago de acacia, solución de gelatina, sacarosa y pasta de almidón.

Los ejemplos de lubricantes que pueden usarse incluyen, sin limitaciones, talco, almidón, estearato de magnesio o calcio, licopodio y ácido esteárico.

Los ejemplos de diluyentes que pueden usarse incluyen, sin limitaciones, lactosa, sacarosa, almidón, kaolina, sal, manitol y fosfato de dicalcio.

Los ejemplos de deslizantes que pueden usarse incluyen, sin limitaciones, dióxido de silicio coloidal.

Los ejemplos de agentes desintegradores que pueden usarse incluyen, sin limitaciones, croscarmellose sodio, glicolato de almidón de sodio, ácido algínico, almidón de maíz, almidón de papa, bentonita, metilcelulosa, agar y carboximetilcelulosa.

Los ejemplos de agentes colorantes que pueden usarse incluyen, sin limitaciones, cualquiera de los colorantes aprobados y certificados FD y C solubles en agua, mezclas de los mismos, y colorantes FD y C suspendidos en hidrato de alúmina.

Los ejemplos de agentes edulcorantes que pueden usarse incluyen, sin limitaciones, sacarosa, lactosa, manitol y agentes edulcorantes artificiales, tales como ciclamato de sodio y sacarina, y cualquier cantidad de sabores secados a chorro.

Los ejemplos de agentes saborizantes que pueden usarse incluyen, sin limitaciones, sabores naturales extraídos de plantas, tales como frutas, y mezclas sintéticas de compuestos que producen una sensación placentera, tales como, sin limitaciones, menta salvaje y salicilato de metilo.

Los ejemplos de agentes humectantes que pueden usarse incluyen, sin limitaciones, monoestearato de propilenglicol, monooleato de sorbitan, monolaurato de dietilenglicol y lauril éter de polioxietileno.

Los ejemplos de recubrimientos anti-eméticos que pueden usarse incluyen, sin limitaciones, ácidos grasos, grasas, ceras, shellac amoniado y ftalatos de acetato de celulosa.

Los ejemplos de recubrimientos de película que pueden usarse incluyen, sin limitaciones, hidroxietilcelulosa, carboximetilcelulosa de sodio, polietilenglicol 4000 y ftalato de acetato de celulosa.

Si se desea efectuar una administración oral, puede proporcionarse opcionalmente

la sal del compuesto en una composición que la proteja del ambiente ácido del estómago. Por ejemplo, puede formularse la composición en un recubrimiento entérico que mantenga su integridad en el estómago y libere el compuesto activo en el intestino. La composición también puede formularse en combinación con un antácido u otro ingrediente como tal.

Cuando la forma de dosificación unitaria es una cápsula, puede comprender opcionalmente un vehículo líquido, tal como un aceite graso. Además, las formas unitarias de dosificación pueden comprender adicionalmente varios otros materiales que modifiquen la forma física de la unidad de dosificación, por ejemplo, recubrimientos azucarados y otros agentes entéricos.

Los compuestos de acuerdo con la presente invención pueden administrarse también como componentes de un elixir, una suspensión, un jarabe, una pastilla, una gota, una goma de mascar o semejantes. Un jarabe puede comprender opcionalmente, además de los compuestos activos, sacarosa como agente edulcorante y determinados preservadores, colorantes y tinturas, y saborizantes.

Los compuestos de la presente invención también pueden mezclarse con otros materiales activos que no alteren la acción deseada, o con materiales que suplementen la acción deseada, tales como antácidos, bloqueadores de H2 y diuréticos. Por ejemplo, si se usa un compuesto para tratar el asma o la hipertensión, puede combinárselo con otros broncodilatadores y agentes antihipertensivos, respectivamente.

Los ejemplos de vehículos aceptables para el uso farmacéutico que pueden incluirse en las tabletas que comprenden los compuestos de la presente invención incluyen, sin limitaciones, aglutinantes, lubricantes, diluyentes, agentes desintegradores, agentes colorantes, agentes saborizantes y agentes humectantes. Las tabletas con recubrimientos entéricos, debido a estos mismos recubrimientos entéricos, resisten la acción de los ácidos estomacales y se disuelven o desintegran en el ambiente neutro o alcalino del intestino. Las tabletas recubiertas con azúcar pueden ser tabletas comprimidas, sobre las cuales se aplican distintas capas de sustancias aceptables para el uso farmacéutico. Las tabletas recubiertas con películas pueden ser tabletas comprimidas recubiertas con polímeros u otros recubrimientos apropiados. Las tabletas comprimidas múltiples pueden prepararse empleando más de un ciclo de compresión, con las

sustancias aceptables para el uso farmacéutico mencionadas previamente. También pueden usarse agentes colorantes en las tabletas. Pueden usarse agentes saborizantes y edulcorantes en las tabletas, y son especialmente útiles en la formación de tabletas y pastillas masticables.

Los ejemplos de formas de dosificación líquida oral que pueden usarse incluyen, sin limitaciones, soluciones acuosas, emulsiones, suspensiones, soluciones y/o suspensiones reconstituidas a partir de gránulos no efervescentes, y preparaciones efervescentes reconstituidas a partir de gránulos efervescentes.

Los ejemplos de soluciones acuosas que pueden usarse incluyen, sin limitaciones, elíxires y jarabes. Como se los usa en la presente documentación, los elíxires hacen referencia a preparaciones hidroalcohólicas transparentes edulcoradas. Los ejemplos de vehículos aceptables para el uso farmacéutico que pueden usarse en los elíxires incluyen, sin limitaciones, solventes. Los ejemplos particulares de solventes que pueden usarse incluyen glicerina, sorbitol, alcohol etílico y jarabe. Como se los usa en la presente documentación, los jarabes hacen referencia a soluciones acuosas concentradas de un azúcar, por ejemplo, sacarosa. Además, los jarabes pueden comprender opcionalmente un preservador.

Las emulsiones hacen referencia a sistemas de dos fases, donde se dispersa un líquido, bajo la forma de pequeños glóbulos, en otro líquido. Las emulsiones pueden ser opcionalmente emulsiones de aceite en agua o de agua en aceite. Los ejemplos de vehículos aceptables para el uso farmacéutico que pueden usarse en las emulsiones incluyen, sin limitaciones, líquidos no acuosos, agentes emulsificantes y preservadores.

Los ejemplos de sustancias aceptables para el uso farmacéutico que pueden usarse en los gránulos no efervescentes, que pueden reconstituirse en una forma de dosificación líquida oral, incluyen diluyentes, agentes edulcorantes y humectantes.

Los ejemplos de sustancias aceptables para el uso farmacéutico que pueden usarse en los gránulos efervescentes, los cuales pueden reconstituirse en una forma de dosificación líquida oral, incluyen ácidos orgánicos y una fuente de dióxido de carbono.

Pueden usarse opcionalmente agentes colorantes y saborizantes en todas las formas de dosificación mencionadas previamente.

Los ejemplos particulares de preservadores que pueden usarse incluyen glicerina, metil y propilparaben, ácido benzoico, benzoato de sodio y alcohol.

Los ejemplos particulares de líquidos no acuosos que pueden usarse en las emulsiones incluyen aceite mineral y aceite de semilla de algodón.

Los ejemplos particulares de agentes emulsificantes que pueden usarse incluyen gelatina, acacia, tragacanto, bentonita y agentes tensioactivos, tales como monooleato de polioxietilen sorbitan.

Los ejemplos particulares de agentes de suspensión que pueden usarse incluyen carboximetilcelulosa de sodio, pectina, tragacanto, Veegum y acacia. Los diluyentes incluyen lactosa y sacarosa. Los agentes edulcorantes incluyen sacarosa, jarabes, glicerina y agentes edulcorantes artificiales, tales como ciclamato de sodio y sacarina.

Los ejemplos particulares de agentes humectantes que pueden usarse incluyen monoestearato de propilenglicol, monooleato de sorbitan, monolaurato de dietilenglicol y lauril éter de polioxietileno.

Los ejemplos particulares de ácidos orgánicos que pueden usarse incluyen ácido cítrico y ácido tartárico.

Las fuentes de dióxido de carbono que pueden usarse en las composiciones efervescentes incluyen bicarbonato de sodio y carbonato de sodio. Los agentes colorantes incluyen cualquiera de los colorantes apropiados y certificados FD y C solubles en agua, y mezclas de los mismos.

Los ejemplos particulares de agentes saborizantes que pueden usarse incluyen sabores naturales extraídos de plantas, tales como frutas, y mezclas sintéticas de compuestos que producen una sensación de sabor placentera.

Para una forma de dosificación sólida, la solución o suspensión, por ejemplo, en carbonato de propileno, aceites vegetales o triglicéridos, se encapsula preferiblemente en una cápsula de gelatina. Se describen dichas soluciones, y su preparación y encapsulación, en las Patentes de los EEUU Nº 4328245, 4409239 y 4410545. Para una forma de dosificación líquida, la solución, por ejemplo, por ejemplo, en polietilenglicol, puede diluirse con una cantidad suficiente de un vehículo líquido aceptable para el uso farmacéutico, por ejemplo agua, que debe medirse fácilmente antes de administrarse.

Como alternativa, pueden prepararse formulaciones orales líquidas o semi-sólidas

disolviendo o dispersando el compuesto o la sal activa en aceites vegetales, glicoles, triglicéridos, ésteres de propilenglicol (por ejemplo, carbonato de propileno) y otros vehículos como tales, y encapsulando estas soluciones o suspensiones en recubrimientos de cápsulas de gelatina duras o blandas. Otras formulaciones útiles incluyen aquellas detalladas en las Patentes de los EEUU Nº Re 28.819 y 4.358.603.

Inyectables, Soluciones y Emulsiones

La presente invención también hace referencia a composiciones diseñadas para administrar los compuestos de la presente invención por administración parenteral, generalmente caracterizada por inyección subcutánea, intramuscular o intravenosa. Pueden prepararse inyectables de cualquier forma convencional, por ejemplo, como soluciones o suspensiones líquidas, como formas sólidas apropiadas para disolver o suspender en un líquido antes de inyectarlo, o como emulsiones.

Los ejemplos de excipientes que pueden usarse en combinación con los inyectables de acuerdo con la presente invención incluyen, sin limitaciones, agua, solución salina, dextrosa, glicerol o etanol. Las composiciones inyectables también pueden comprender opcionalmente cantidades menores de sustancias auxiliares no tóxicas, tales como agentes humectantes o emulsificantes, agentes amortiguadores del pH, estabilizadores, potenciadores de la solubilidad y otros agentes como los mencionados, tales como, por ejemplo, acetato de sodio, monolaurato de sorbitan, oleato de trietanolamina y ciclodextrinas. En la presente documentación también se contempla el implantae de un sistema de liberación lenta o liberación sostenida, de modo de mantener un nivel de dosificación constante (véase, por ejemplo, la Patente de los EEUU Nº 3710795). El porcentaje de compuesto activo contenido en dichas composiciones parenterales depende en gran medida de la naturaleza específica del mismo, así como de la actividad del compuesto y las necesidades del sujeto.

La administración parenteral de las formulaciones incluye la administración intravenosa, subcutánea e intramuscular. Las preparaciones de administración parenteral incluyen soluciones estériles listas para inyectar, productos secos solubles estériles, tales como los polvos liofilizados descriptos en la presente documentación, listos para combinar con un solvente justo antes de usarse,

incluyendo tabletas hipodérmicas, suspensiones estériles listas para inyectar, productos insolubles estériles secos, listos para combinar con un vehículo justo antes de usarse, y emulsiones estériles. Las soluciones pueden ser acuosas o no acuosas.

Cuando se los administra por vía intravenosa, los ejemplos de vehículos apropiados incluyen, sin limitaciones, solución salina fisiológica o solución salina amortiguada con fosfato (PBS), y soluciones que contienen agentes espesadores y solubilizadores, tales como glucosa, polietilenglicol y polipropilenglicol, y mezclas de los mismos.

Los ejemplos de vehículos aceptables para el uso farmacéutico que pueden usarse opcionalmente en las preparaciones parenterales incluyen, sin limitaciones, vehículos acuosos, vehículos no acuosos, agentes antimicrobianos, agentes isotónicos, amortiguadores, antioxidantes, anestésicos locales, agentes de suspensión o dispersión, agentes emulsificadores, agentes secuestrantes o quelantes, y otras sustancias aceptables para el uso farmacéutico.

Los ejemplos de vehículos acuosos que pueden usarse opcionalmente incluyen inyecciones de cloruro de sodio, inyecciones de Ringer, inyecciones de dextrosa isotónica, inyecciones de agua estéril, inyecciones de dextrosa e inyecciones de Ringer lactadas.

Los ejemplos de vehículos parenterales no acuosos que pueden usarse opcionalmente incluyen aceites fijos de origen vegetal, aceite de semilla de algodón, aceite de maíz, aceite de sésamo y aceite de maní.

Pueden agregarse agentes antimicrobianos, en concentraciones bacteriostáticas o fungistáticas, a las preparaciones parenterales, particularmente cuando se envasan las preparaciones en recipientes de dosis múltiples, y, por consiguiente, se los diseña de modo que puedan almacenarse y puedan extraerse varias alícuotas. Los ejemplos de agentes antimicrobianos que pueden usarse incluyen fenoles o cresoles, mercurianos, alcohol bencílico, clorobutanol, ésteres de ácido metil y propil p-hidroxibenzoico, timerosal, cloruro de benzalconio y cloruro de benzetonio.

Los ejemplos de agentes isotónicos que pueden usarse incluyen cloruro de sodio y dextrosa. Los ejemplos de amortiguadores que pueden usarse incluyen fosfato y citrato. Los ejemplos de antioxidantes que pueden usarse incluyen bisulfato de

sodio. Los ejemplos de anestésicos locales que pueden usarse incluyen clorhidrato de procaína. Los ejemplos de agentes de suspensión y dispersión que pueden usarse incluyen carboximetilcelulosa de sodio, hidroxipropil metilcelulosa y polivinilpirrolidona. Los ejemplos de agentes emulsificantes que pueden usarse incluyen Polisorbato 80 (TWEEN 80). Un agente secuestrante o quelante de iones metálicos incluye EDTA.

Los vehículos farmacéuticos también incluyen opcionalmente alcohol etílico, polietilenglicol y propilenglicol para vehículos miscibles en agua, e hidróxido de sodio, ácido clorhídrico, ácido cítrico o ácido láctico para ajustar el pH.

Puede ajustarse la concentración de un inhibidor en la formulación parenteral, de modo que una inyección pueda administrar una cantidad eficaz para el uso farmacéutico, suficiente para producir el efecto farmacológico deseado. La concentración de extracto de un inhibidor, y/o la dosificación a usar, dependerá finalmente de la edad, el peso y la condición del paciente o el animal, como es conocido en la técnica.

Las preparaciones de dosificaciones unitarias parenterales pueden envasarse en una ampolla, un recipiente o una jeringa con una aguja. Todas las preparaciones para administración parenteral deberán ser estériles, como es conocido y practicado en la técnica.

Pueden diseñarse los inyectables para una administración local y sistémica. Típicamente, se formula una dosificación efectiva para el uso terapéutico de modo que contenga una concentración de al menos entre aproximadamente 0,1% p/p y aproximadamente 90% p/p o más, preferiblemente más de 1% p/p del inhibidor de HDAC, que se administrará a los tejidos a tratar. El inhibidor puede administrarse de una vez, o puede dividirse en una cantidad de dosis menores, que se administrarán separadas por intervalos de tiempo. Se comprende que la dosificación precisa y la duración del tratamiento dependerá de la localización de la administración parenteral de la composición, del vehículo y de otras variables que podrán determinarse en forma empírica, usando protocolos de prueba conocidos, o realizando extrapolaciones a partir de datos de prueba *in vivo* o *in vitro*. Debe destacarse que los valores de las concentraciones y las dosificaciones variarán también con la edad del individuo a tratar. Además, debe comprenderse que, para un sujeto en particular, puede ser necesario ajustar regímenes de

dosificación específicos con el correr del tiempo, de acuerdo con las necesidades individuales y el juicio profesional del encargado de la administración o la supervisión de la administración de las formulaciones. Por consiguiente, los rangos de concentración detallados en la presente documentación son solamente ejemplos, y no pretenden limitar el alcance o la práctica de las formulaciones reivindicadas.

El inhibidor de HDAC puede suspenderse opcionalmente en formas micronizadas, o en otras formas apropiadas, o puede derivatizarse para producir un producto activo más soluble o producir una prodroga. La forma de la mezcla resultante depende de una cantidad de factores, incluyendo el modo de administración deseado y la solubilidad del compuesto en el vehículo o los vehículos deseados. La concentración efectiva es suficiente para mejorar los síntomas del estado de enfermedad, y puede determinarse en forma empírica.

Polvos liofilizados

Los compuestos de la presente invención pueden prepararse también como polvos liofilizados, que pueden reconstituirse para administrarlos como soluciones, emulsiones y otras mezclas. También pueden formularse los polvos liofilizados como sólidos o geles..

Puede prepararse un polvo estéril liofilizado disolviendo el compuesto en una solución amortiguadora de fosfato de sodio que contiene dextrosa u otro excipiente apropiado. La filtración estéril subsiguiente de la solución, seguida por una liofilización bajo condiciones estándar conocidas por aquellos entrenados en la técnica, permite obtener la formulación deseada. Brevemente, puede prepararse opcionalmente el polvo liofilizado disolviendo dextrosa, sorbitol, fructosa, jarabe de maíz, xilitol, glicerina, glucosa, sacarosa u otro agente apropiado, aproximadamente 1-20%, preferiblemente entre aproximadamente 5 y 15%, en un amortiguador apropiado, tal como citrato, fosfato de sodio o potasio, u otro amortiguador como tales, conocido por aquellos entrenados en la técnica, típicamente a aproximadamente pH neutro. Luego se agrega un inhibidor de HDAC a la mezcla resultante, preferiblemente una temperatura mayor que la temperatura ambiente, más preferiblemente a aproximadamente 30-35°C, y se agita hasta disolverlo. Se diluye la mezcla resultante agregando más amortiguador hasta una concentración deseada. La mezcla resultante se filtra en forma estéril o

se trata para eliminar los particulados y asegurar la ésterilidad, y se separa en porciones en distintos recipientes para liofilizarla. Cada recipiente puede contener una única dosificación o múltiples dosificaciones del inhibidor de DPP-IV.

Administración tópica

Los compuestos de la presente invención también pueden administrarse como mezclas tópicas. Pueden usarse mezclas tópicas para efectuar una administración local y sistémica. La mezcla resultante puede ser una solución, una suspensión una emulsión o semejantes, y se formula como una crema, un gel, un ungüento, una emulsión, una solución, un elíxir, una loción, una suspensión, una tintura, una pasta, una espuma, un aerosol, una irrigación, un rocío, un supositorios, una venda, una parche dérmico o cualquier otra formulación apropiada para una administración tópica.

Los inhibidores de HDAC pueden formularse como aerosoles para administración tópica, tal como por inhalación (véanse las Patentes de los EEUU Nº 4044126, 4414209 y 4364923, que describen aerosoles para administrar un ésteroide útil para tratar enfermedades inflamatorias, particularmente el asma). Estas formulaciones para administrar en el tracto respiratorio pueden tomar la forma de un aerosol o una solución de un nebulizador, o como un polvo microfino para insuflar, solo o en combinación con un vehículo inerte, tal como lactosa. En tal caso, las partículas de la formulación típicamente tendrán diámetros menores que 50 micrones, preferiblemente menores que 10 micrones.

Los inhibidores pueden formularse también para una aplicación local o tópica, tal como una aplicación tópica a la piel y las membranas mucosas, tal como sobre el ojo, bajo la forma de geles, cremas y lociones, y para aplicar sobre el ojo o para aplicaciones intracistérnicas intraespinales. Se contempla la administración tópica para la administración transdérmica, y también para administraciones a los ojos o las mucosas, o para terapias de inhalación. También pueden administrarse soluciones nasales del inhibidor de HDAC, solo o en combinación con otros excipientes aceptables para el uso farmacéutico. También pueden administrarse soluciones nasales del inhibidor de HDAC, solo o en combinación con otros excipientes aceptables para el uso farmacéutico.

Formulaciones para otras rutas de administración

Dependiendo del estado de enfermedad a tratar, también pueden usarse otras rutas de administración, tales como aplicación tópica, parches transdérmicos y administración rectal. Por ejemplo, las formas de dosificación farmacéutica para administración rectal son los supositorios rectales, las cápsulas y las tabletas de efecto sistémico. Los supositorios rectales, como se los usa en la presente documentación, representan cuerpos sólidos que se insertan en el recto y se derriten a la temperatura del cuerpo, liberando uno o más ingredientes terapéuticos activos. Las sustancias aceptables para el uso farmacéutico utilizadas en los supositorios rectales son bases o vehículos, y agentes que elevan el punto de fusión. Los ejemplos de bases incluyen manteca de cacao (aceite de teobroma), glicerina-gelatina, carbocera, (polioxietilenglicol) y mezclas apropiadas de mono, di y triglicéridos de ácidos grasos. Pueden usarse combinaciones de varias bases. Los agentes para elevar el punto de fusión de los supositorios incluyen spermaceti y cera. Pueden prepararse los supositorios rectales empleando un método de compresión o moldeado. El peso típico de un supositorio rectal es de aproximadamente 2 ó 3 g. Las tabletas y las cápsulas para administración rectal pueden fabricarse usando la misma sustancia aceptable para el uso farmacéutico y los mismos métodos que los usados para las formulaciones de administración oral.

Ejemplos de formulaciones

Los siguientes son ejemplos particulares de formulaciones orales, intravenosas y en tabletas, que pueden usarse opcionalmente con los compuestos de la presente invención. Debe destacarse pueden variarse que estas formulaciones dependiendo del compuesto particular usado y la indicación para la cual se usará la formulación.

FORMULACIÓN ORAL	
Compuesto de la presente invención	10-100 mg
Monohidrato de ácido cítrico	105 mg
Hidróxido de sodio	18 mg
Saborizantes	
Agua	c.s. hasta completar 100 ml
FORMULACIÓN INTRAVENOSA	
Compuesto de la presente invención	0,1-10 mg

Monohidrato de dextrosa	hasta obtener isotonicidad
Monohidrato de ácido cítrico	1,05 mg
Hidróxido de sodio	0,18 mg
Agua para inyección	hasta 1,0 ml
FORMULACIÓN EN TABLETA	
Compuesto de la presente invención	1%
Celulosa microcristalina	73%
Ácido esteárico	25%
Sílice coloidal	1%.

Equipos que comprenden inhibidores de HDAC

La invención también se relaciona con equipos y otros artículos manufacturados para tratar enfermedades asociadas con la HDAC. Debe destacarse que estas enfermedades abarcan todas las condiciones donde los HDAC poseen una actividad que contribuye a la patología y/o la sintomatología de la condición.

En una realización, se proporciona un equipo que comprende una composición que comprende al menos un inhibidor de la presente invención, en combinación con instrucciones. Las instrucciones pueden indicar el estado de enfermedad para el que puede administrarse la composición, información de almacenamiento, información de dosificación y/o instrucciones acerca de cómo administrar la composición. El equipo también puede comprender materiales de envasado. El material de envasado puede comprender un recipiente para alojar la composición. El equipo también puede comprender opcionalmente componentes adicionales, tales como jeringas para administrar la composición. El equipo puede comprender la composición, bajo la forma de dosis individuales o múltiples.

En otra realización, se proporciona un artículo de manufactura que comprende una composición que comprende al menos un inhibidor de la presente invención, en combinación con materiales de envasado. El material de envasado puede comprender un recipiente para alojar la composición. El recipiente puede comprender opcionalmente una marca que indique el estado de enfermedad para el que puede administrarse la composición, información de almacenamiento, información de dosificación y/o instrucciones acerca de cómo administrar la composición. El equipo también puede comprender opcionalmente componentes opcionales, tales como jeringas para administrar la composición. El equipo puede

comprender la composición, bajo la forma de dosis individuales o múltiples.

Debe destacarse que el material envasado usado en los equipos y los artículos manufacturados de acuerdo con la presente invención pueden formar una pluralidad de recipientes divididos, tales como una botella dividida o un paquete de aluminio dividido. El recipiente puede tomar cualquier forma convencional, o cualquier forma conocida en la técnica, compuesta por un material aceptable para el uso farmacéutico, por ejemplo, una caja de papel o cartón, una botella o un vaso de vidrio o plástico, una bolsa re-sellable (por ejemplo, para contener un "relleno" de tabletas que se pueden colocar un recipiente diferente), o un paquete tipo ampolla con dosificaciones individuales, para presionar el paquete de acuerdo con un cronograma terapéutico. El recipiente empleado dependerá de la forma de dosificación exacta empleada, por ejemplo, no se usará generalmente una caja de cartón convencional para contener una suspensión líquida. Es factible usar más de un recipiente en un único envase para comercializar una única forma de dosificación. Por ejemplo, las tabletas pueden estar contenidas en una botella que, a su vez, esté contenida en una caja. Típicamente el equipo incluye direcciones para administrar los componentes Separados. La forma del equipo es particularmente ventajosa cuando se administran los componentes separados, preferiblemente en distintas formas de dosificación (por ejemplo, oral, tópica, transdérmica y parenteral), cuando se los administra con intervalos diferentes o cuando el médico a cargo desea titular los componentes individuales de la combinación.

Un ejemplo particular de un equipo de acuerdo con la presente invención es el denominado envase tipo ampolla. Los envases tipo ampolla son bien conocidos en la industria del envasado, y se usan ampliamente para envasar formas de dosificación farmacéutica unitarias (tabletas, cápsulas y semejantes). Los envases tipo ampolla generalmente consisten en una lámina de un material relativamente rígido, recubierto con una lámina de un material plástico preferiblemente transparente. Durante el proceso de envasado, se forman concavidades en la lámina plástica. Las concavidades tienen el tamaño y la forma de las tabletas o las cápsulas individuales que se envasarán, y tienen un tamaño que permite acomodar múltiples tabletas y/o cápsulas. Luego se colocan las tabletas o las cápsulas en las concavidades creadas con tal fin, y se sella la lámina de material

relativamente rígido contra la lámina plástica, en la cara opuesta a la dirección en la que se hubieron formado las concavidades. Como resultado, las tabletas o las cápsulas se sellan individualmente o se sellan en forma colectiva, según se lo desee, en las concavidades entre la lámina plástica y la lámina. Preferiblemente, la longitud de la lámina es tal que pueden extraerse las tabletas o las cápsulas del envase tipo ampolla, aplicando presión manual en las concavidades, donde se forma una abertura en la lámina a la altura de las concavidades. Puede extraerse la tableta o la cápsula a través de dicha abertura.

Otro ejemplo específico de un equipo es un sistema de administración diseñado para administrar las dosis diarias, una por vez, en el orden en que se pretende usarlas. Preferiblemente, el sistema está equipado con un ayuda memoria, de modo de facilitar el seguimiento del régimen. Un ejemplo de dicho ayuda memoria es un contador mecánico que indica la cantidad de dosis que hubieron sido administradas. Otro ejemplo de dicho ayuda memoria es un microchip de memoria operado a batería unido a un lector de cristal líquido, o una señal audible recordatoria que, por ejemplo, presenta la fecha de la última dosis diaria tomada y/o avisa cuándo debe tomarse la siguiente dosis.

Terapia combinada

Una amplia variedad de agentes terapéuticos puede tener efectos terapéuticos aditivos o sinérgicos con los inhibidores de HDAC de acuerdo con la presente invención. Dichos agentes terapéuticos se pueden combinar de formar aditiva o sinérgica con los inhibidores de HDAC para inhibir el crecimiento celular indeseado, tal como un crecimiento celular inapropiado que da como resultado condiciones benignas o un crecimiento tumoral indeseado.

En una realización, se provee un método de tratamiento para un estado de enfermedad con proliferación celular que comprende tratar a las células con un compuesto acorde con la presente invención en combinación con un agente antiproliferativo, en donde las células son tratadas con el compuesto acorde con la presente invención antes, al mismo tiempo y/o después de haber tratado a las células con dicho agente antiproliferativo, denominado terapia combinada en el presente. Cabe destacar que el tratamiento con un agente antes del otro se denomina terapia secuencial en la presente, aún si los agentes también se

administran juntos. Se debe tener en cuenta que la terapia combinada pretende abarcar la situación en que los agentes se administran antes o después del uno o del otro (terapia secuencial) así como cuando los agentes se administran al mismo tiempo.

Los ejemplos de agentes terapéuticos que se pueden usar en combinación con los inhibidores de HDAC incluyen, en un sentido no limitativo, agentes anticancerosos, agentes alquilantes, agentes antibióticos, agentes antimetabólicos, agentes hormonales, agentes derivados de plantas y agentes biológicos.

Los agentes alquilantes son compuestos polifuncionales que tienen la capacidad de sustituir grupos alquilo por iones hidrógeno. Los ejemplos de agentes alquilantes incluyen, en un sentido no limitativo, bicloroetilaminas (mostazas de nitrógeno, por ejemplo clorambucilo, ciclofosfamida, ifosfamida, mecloretamina, melfalán, mostaza de uracilo), aziridinas (por ejemplo tiotepa), sulfonatos de alquilalcano (por ejemplo, busulfano), nitrosoureas (por ejemplo carmustina, lomustina, estreptozocina), agentes alquilantes no clásicos (altretamina, dacarbazina y procarbazina), compuestos de platino (carboplatino y cisplatino). Estos compuestos reaccionan con grupos fosfato, amino, hidroxilo, sulfhidrilo, carboxilo e imidazol. Bajo condiciones fisiológicas, estas drogas se ionizan y producen iones de carga positiva que se unen a ácidos nucleicos y proteínas susceptibles, lo que conduce a un arresto del ciclo celular y/o a la muerte celular. La terapia combinada que incluye un inhibidor de HDAC y un agente alquilante puede tener efectos sinérgicos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes antibióticos constituyen un grupo de drogas que se producen de manera similar a los antibióticos como una modificación de productos naturales. Los ejemplos de agentes antibióticos incluyen, en un sentido no limitativo, antraciclinas (por ejemplo, doxorubicina, daunorubicina, epirubicina, idarubicina y antracenediona), mitomicina C, bleomicina, dactinomicina, plicatomicina. Estos agentes antibióticos interfieren con el crecimiento celular al atacar diferentes componentes celulares. Por ejemplo, se cree que las antraciclinas interfieren en general con la acción de la ADN topoisomerasa II en las regiones de ADN en transcripción activa, lo que conduce a cortes en la cadena de ADN. Se considera en general que la bleomicina actúa quelando el hierro y formando un complejo

activado, que luego se une a las bases del ADN, causando cortes en las cadenas y muerte celular. La terapia combinada que incluye un inhibidor de HDAC y un agente antibiótico puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes antimetabólicos con un grupo de drogas que interfiere con los procesos metabólicos que son vitales para la fisiología y proliferación de células cancerosas. Las células cancerosas en proliferación activa requieren de la síntesis continua de grandes cantidades de ácidos nucleicos, proteínas, lípidos y otros constituyente celulares vitales. Muchos de los antimetabolitos inhiben la síntesis de los nucleósidos purina o pirimidina o inhiben las enzimas de replicación del ADN. Algunos antimetabolitos también interfieren con la síntesis de ribonucleósidos y ARN y/o con el metabolismo de aminoácidos así como con la síntesis de proteínas. Al interferir con la síntesis de los constituyente celulares vitales, los antimetabolitos pueden demorar o detener el crecimiento de las células cancerosas. Los ejemplos de agentes antimetabólicos incluyen, en un sentido no limitativo, fluorouracilo (5-FU), floxuridina (5-FUdR), metotrexato, leucovorina, hidroxiurea, tioguanina (6-TG), mercaptopurina (6-MP), citarabina, pentostatina, fosfato de fludarabina, cladribina (2-CDA), asparaginasa y gemcitabina. La terapia combinada que incluye un inhibidor de HDAC y un agente antimetabólico puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes hormonales constituyen un grupo de drogas que regula el crecimiento y desarrollo de sus órganos de interés. La mayoría de los agentes hormonales son esteroides sexuales y derivados y análogos de los mismos, tales como estrógenos, andrógenos y progestinas. Estos agentes hormonales pueden servir como antagonistas de los receptores de los esteroides sexuales para subsensibilizar la expresión del receptor y la transcripción de genes vitales. Los ejemplos de dichos agentes hormonales son estrógenos sintéticos (por ejemplo, dietilestibestrol), antiestrógenos (por ejemplo, tamoxifeno, toremifeno, fluoximesterol y raloxifeno), antiandrógenos (bicalutamida, nilutamida, flutamida), inhibidores de aromatasa (por ejemplo, aminoglutetimida, anastrozol y tetrazol), ketoconazol, acetato de goserelina, leuprolida, acetato de megestrol y mifepristona. La terapia combinada que incluye un inhibidor de HDAC y un agente

hormonal puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes derivados de plantas constituyen un grupo de drogas que derivan de plantas o que están modificados sobre la base de la estructura molecular de los agentes. Los ejemplos de agentes derivados de plantas incluyen, en un sentido no limitativo, vinca alcaloides (por ejemplo, vincristina, vinblastina, vindesina, vinzolidina y vinorelbina), podofilotoxinas (por ejemplo, etopósido (VP-16) y tenipósido (VM-26)), taxanos (por ejemplo, paclitaxel y docetaxel). Estos agentes derivados de plantas actúan generalmente como agentes antimitóticos que se unen a la tubulina e inhiben la mitosis. Se cree que las podofilotoxinas, tal como etopósido, interfieren con la síntesis de ADN por interacción con la topoisomerasa II, lo que conduce a cortes de la cadena de ADN. La terapia combinada que incluye un inhibidor de HDAC y un agente derivado de plantas puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes biológicos son un grupo de biomoléculas que provocan la regresión del cáncer/tumor cuando se usan solos o en combinación con quimioterapia y/o radioterapia. Los ejemplos de agentes biológicos incluyen, en un sentido no limitativo, proteínas inmunomoduladoras tales como citoquinas, anticuerpos monoclonales contra antígenos tumorales, genes supresores tumorales y vacunas contra el cáncer. La terapia combinada que incluye un inhibidor de HDAC y un agente biológico puede tener efectos sinérgicos terapéuticos sobre el cáncer, mejorar las respuestas inmunes de los pacientes a señales tumorigénicas y reducir los efectos secundarios potenciales asociados con este agente quimioterapéutico.

Las citoquinas poseen una gran actividad inmunomoduladora. Algunas citoquinas, tales como interleuquina-2 (IL-2, aldesleuquina) e interferón, han demostrado actividad antitumoral y han sido aprobadas para el tratamiento de pacientes con carcinoma de células renales metastásicas y melanoma maligno metastásico. La IL-2 es un factor de crecimiento de células T que es fundamental para las respuestas inmunes mediadas por células T. Se cree que los efectos antitumorales selectivos de IL-2 en algunos pacientes son el resultado de una respuesta inmune mediada por células que puede discriminar entre propios y no

propios. Los ejemplos de interleuquinas que se pueden usar junto con un inhibidor de HDAC incluyen, en un sentido no limitativo, interleuquina 2 (IL-2) e interleuquina 4 (IL-4), interleuquina 12 (IL-12).

El γ-interferón incluye más de 23 subtipos relacionados con actividades superpuestas, donde todos dichos subtipos de IFN se encuentran dentro del alcance de la presente invención. Se ha demostrado que el γ-IFN tiene actividad contra muchas formas malignas sólidas y hematológicas, siendo éstas últimas particularmente sensibles.

Otras citoquinas que se pueden usar junto con un inhibidor de HDAC incluyen aquellas citoquinas que ejercen efectos importantes sobre la hematopoyesis y las funciones inmunes. Los ejemplos de dichas citoquinas incluyen, en un sentido no limitativo, eritropoyetina, CSF de granulocitos (filgrastina) y CSF de granulocitos, macrófagos (sargramostim). Estas citoquinas se pueden usar junto con un inhibidor de HDAC para reducir la toxicidad mielopoyética inducida por quimioterapia.

También se pueden usar otros agentes inmunomoduladores distintos de las citoquinas junto con un inhibidor de HDAC para inhibir un crecimiento celular anormal. Los ejemplos de dichos agentes inmunomoduladores incluyen, en un sentido no limitativo, el bacilo de Calmette-Guerin, levamisol y octreotida, un octapéptido de acción prolongada que imita los efectos de la hormona somatostatina natural.

Los anticuerpos monoclonales contra antígenos tumorales son anticuerpos generados contra los antígenos expresados por tumores, preferentemente antígenos específicos del tumor. Por ejemplo, el anticuerpo monoclonal HERCEPTIN® (Trastruzumab) es generado contra el receptor 2 del factor de crecimiento epidérmico humano (HER2) que se sobreexpresa en algunos tumores de mama, incluyendo cáncer de mama metastásico. La sobreexpresión de la proteína HER2 está asociada con una enfermedad más agresiva y una prognosis más pobre en la clínica. HERCEPTIN® se usa como agente único para el tratamiento de pacientes con cáncer de mama metastásico cuyos tumores sobreexpresan la proteína HER2. La terapia combinada que incluye un inhibidor de HDAC y HERCEPTIN® puede tener efectos sinérgicos terapéuticos sobre tumores, en especial en distintos tipos de cáncer metastásico.

Otro ejemplo de anticuerpos monoclonales contra antígenos tumorales es el RITUXAN® (Rituximab) generado contra el CD20 sobre células de linfoma y que reduce selectivamente células B maduras y pre-B CD20+ normales y malignas. El RITUXAN® se usa como agente único para el tratamiento de pacientes con linfoma no Hodgkin de células B CD20+ recurrente o refractario de bajo grado o folicular. La terapia combinada que incluye un inhibidor de HDAC y RITUXAN® puede tener efectos sinérgicos terapéuticos no sólo sobre el linfoma, sino también sobre otras formas o tipos de tumores malignos.

Los genes supresores tumorales son genes cuya función es inhibir los ciclos de crecimiento y división celulares, impidiendo de esa manera el desarrollo de neoplasias. Las mutaciones en los genes supresores tumorales hacen que la célula omite uno o más de los componentes de la red de señales inhibidoras, pasa de largo por los puntos de comprobación del ciclo celular y da como resultado un mayor índice de cáncer-crecimiento celular controlado. Los ejemplos de genes supresores tumorales incluyen, en un sentido no limitativo, DPC-4, NF-1, NF-2, RB, p53, WT1, BRCA1 y BRCA2.

El DPC-4 está relacionado con el cáncer de páncreas y participa en una vía citoplasmática que inhibe la división celular. El NF-1 codifica una proteína que inhibe Ras, una proteína inhibidora citoplasmática. El NF-1 está relacionado con neurofibromas y feocromocitomas del sistema nervioso y con la leucemia mieloide. El NF-2 codifica una proteína nuclear relacionada con meningioma, schwanoma y ependimoma de sistema nervioso. El RB codifica la proteína pRB, una proteína nuclear que es un gran inhibidor del ciclo celular. El RB está relacionado con el retinoblastoma así como con cáncer de huesos, vejiga, de pulmón de células pequeñas y de mama. El P53 codifica la proteína p53 que regula la división celular y puede inducir apoptosis. La mutación y/o inactividad de p53 se observa en un amplio grupo de distintos tipos de cáncer. El WT1 está relacionado con el tumor de Wilms de los riñones. El BRCA1 está relacionada con el cáncer de mama y ovario y el BRCA2 está relacionado con el cáncer de mama. El gen supresor tumoral puede ser transferido a las células tumorales donde ejerce sus funciones supresoras del tumor. La terapia combinada que incluye un inhibidor de HDAC y un supresor de tumores puede tener efectos sinérgicos terapéuticos en pacientes que sufren de diversas formas de cáncer.

Las vacunas contra cáncer constituyen un grupo de agentes que induce en el cuerpo una respuesta inmune específica para los tumores. La mayoría de las vacunas contra cáncer bajo investigación y desarrollo y en estudios clínicos son antígenos asociados a tumores (TAA). Los TAA son estructuras (es decir proteínas, enzimas o carbohidratos) que están presentes sobre las células tumorales y relativamente ausentes o reducidos sobre las células normales. En virtud de ser bastante únicos para la célula tumoral, los TAA proveen blancos para su reconocimiento por el sistema inmune y causan su destrucción. Los ejemplo de TAA incluyen, en un sentido no limitativo, gangliósidos (GM2), el antígeno específico de próstata (PSA), la alfa-fetoproteína (AFP), el antígeno carcinoembrionario (CEA) (producido por el cáncer de colon y otros adenocarcinomas, por ejemplo el cáncer de mama, pulmón, gástrico y de páncreas), los antígenos asociados a melanomas (MART-1, gp100, MAGE 1,3 tirosinasa), fragmentos de papilomavirus E6 y E7, células completas o porciones/lisados de células tumorales autólogas y células tumorales alogénicas.

Se puede usar un adyuvante para aumentar la respuesta inmune a los TAA. Los ejemplos de adyuvantes incluyen, en un sentido no limitativo, el bacilo de Calmette-Guerin (BCG), lipopolisacáridos de endotoxinas, hemocianina de lapa (GKLH), interleuquina-2 (IL-2), factor estimulante de colonias de granulocitos-macrófagos (GM-CSF) y citoxano, un agente quimioterapéutico que se cree que reduce la supresión inducida por tumores cuando se administran dosis bajas del mismo.

EJEMPLOS

Preparación de inhibidores de HDAC

Pueden desarrollarse varios métodos para sintetizar los compuestos de acuerdo con la presente invención. Se proporcionan métodos representativos para sintetizar estos compuestos en los ejemplos. Debe destacarse, sin embargo, que también pueden sintetizarse los compuestos de la presente invención empleando otras rutas sintéticas, que puedan ser ideadas por aquellos entrenados en la técnica.

Se reconocerá fácilmente que determinados compuestos de acuerdo con la presente invención tienen átomos con conexiones con otros átomos, que confieren una éstereoquímica particular al compuesto (por ejemplo, centros quirales). Se

reconoce que la síntesis de los compuestos de acuerdo con la presente invención puede resultar en la creación de mezclas de distintos éstereoisómeros (es decir,enantiómeros y diastereómeros). A menos que se especifique una éstereoquímica particular, la mención de un compuesto abarca todos los distintos éstereoisómeros posibles.

Se conocen varios métodos para separar mezclas de distintos éstereoisómeros en la técnica. Por ejemplo, puede hacerse reaccionar una mezcla racémica de un compuesto con un agente de resolución con actividad óptica para formar un par de compuestos diastereoisoméricos. Luego pueden separarse los diastereómeros para recuperar los enantiómeros ópticamente puros. También pueden usarse los complejos disociables para resolver enantiómeros (por ejemplo, sales diastereoisoméricas cristalinas). Los diastereómeros típicamente tienen propiedades físicas suficientemente diferentes (por ejemplo, puntos de fusión, puntos de ebullición, solubilidad, reactividad, etcétera) y pueden separarse fácilmente, aprovechando estas diferencias. Por ejemplo, pueden separarse típicamente los diastereómeros por cromatografía o empleando procedimientos de separación/resolución, basados en las diferencias de solubilidad. Puede hallarse una descripción más detallada de los procedimientos que pueden usarse para resolver éstereoisómeros de compuestos de su mezcla racémica en Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates y Resolutions, John Wiley & Sons, Inc. (1981).

También pueden prepararse los compuestos de acuerdo con la presente invención como sales de adición ácida aceptables para el uso farmacéutico, haciendo reaccionar la base libre del compuesto con un ácido inorgánico u orgánico aceptable para el uso farmacéutico. Como alternativa, puede prepararse una sal de adición básica de un compuesto haciendo reaccionar la forma de ácido libre del compuesto con una base inorgánica u orgánica aceptable para el uso farmacéutico. Se describen los ácidos y las bases inorgánicas y orgánicas apropiadas para preparar las sales aceptables para el uso farmacéutico de los compuestos en la sección de definiciones de esta Solicitud. Como alternativa, pueden prepararse las formas desales de los compuestos usando sales de los materiales iniciales o los intermediarios.

Pueden prepararse las formas de ácidos o bases libres de los compuestos a partir de la forma correspondiente de sal de adición básica o sal de adición ácida. Por ejemplo, puede convertirse un compuesto en una forma de sal de adición ácida en la correspondiente base libre, tratándolo con una base apropiada (por ejemplo, una solución de hidróxido de amonio, hidróxido de sodio y semejantes). Puede convertirse un compuesto en forma de sal de adición básica en el ácido libre correspondiente, tratándolo con un ácido apropiado (por ejemplo, ácido clorhídrico, etcétera).

Pueden prepararse *N*-óxidos de los compuestos de acuerdo con la presente invención empleando métodos conocidos por aquellos entrenados en la técnica. Por ejemplo, pueden prepararse *N*-óxidos tratando una forma no oxidada del compuesto con un agente oxidante (por ejemplo, ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido meta-cloroperoxibenzoico o semejantes) en un solvente orgánico inerte apropiado (por ejemplo, un hidrocarburo halogenado, tal como diclorometano) a aproximadamente 0°C. Como alternativa, pueden prepararse N-óxidos de los compuestos a partir del N-óxido de un material inicial apropiado.

Pueden prepararse compuestos en formas no oxidadas a partir de los *N*-óxidos de los compuestos, tratándolos con un agente reductor (por ejemplo, azufre, dióxido de azufre, trifenil fosfina, borohidruro de litio, borohidruro de sodio, tricloruro o otribromuro fosforoso, o semejantes) en un solvente orgánico inerte apropiado (por ejemplo, acetonitrilo, etanol, dioxano acuoso o semejantes) a 0-80°C.

Pueden prepararse las prodrogas derivadas de los compuestos empleando métodos conocidos por aquellos entrenados en la técnica (por ejemplo, para hallar detalles adicionales, véase Saulnier *et al.* (1994), *Bioorganic y Medicinal Chemistry Letters*, Vol. 4, p. 1985). Por ejemplo, pueden prepararse prodrogas apropiadas haciendo reaccionar un compuesto no derivatizado con un agente carbamilante apropiado (por ejemplo, clohidrato de 1,1-aciloxialquilcarbono, carbonato de para-nitrofenilo o semejantes).

Pueden preparare los derivados protegidos de los compuestos empleando métodos conocidos por aquellos entrenados en la técnica. Se proporciona una descripción detallada de los procedimientos disponibles para crear y eliminar

grupos protectores en T.W. Greene, *Protecting Groups in Organic Synthesis*, 3ª edición, John Wiley & Sons, Inc. 1999.

Los compuestos de la presente invención también pueden prepararse o formarse convenientemente durante el proceso de la invención, como solvatos (por ejemplo, hidratos). Pueden prepararse convenientemente los hidratos de los compuestos de la presente invención efectuando una recristalización a partir de una mezcla de solventes acuosos/orgánicos, usando solventes orgánicos tal es como dioxina, tetrahidrofurano o metanol.

También pueden prepararse los compuestos de acuerdo con la presente invención como sus éstereoisómeros individuales, haciendo reaccionar una mezcla racémica del compuesto con un agente de resolución activa, para formar un par de compuestos diastereoisoméricos, separando los diastereómeros y recuperando el enantiómero ópticamente puro. Si bien puede efectuarse la resolución de enantiómeros usando derivados diastereoméricos covalentes de los compuestos, se prefieren los complejos disociables (por ejemplo, sales diastereoisoméricas cristalinas). Los diastereómeros tienen propiedades físicas diferentes (por ejemplo, puntos de fusión, puntos de ebullición, solubilidades, reactividades, etcétera), y puede separárselos fácilmente aprovechando estas diferencias. Pueden separarse los diastereómeros por cromatografía o empleando procedimientos de separación/resolución, basados en las diferencias de solubilidad. Luego se recuperan los enantiómeros ópticamente puros, junto con el agente de resolución, empleando cualquier medio apropiado que no produzca racemización. Puede hallarse una descripción más detallada de los procedimientos que pueden usarse para resolver éstereoisómeros de compuestos de su mezcla racémica en Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates y Resoluciones, John Wiley & Sons, Inc. (1981).

Como se los usa en la presente documentación, los símbolos y las convenciones usadas en estos procesos, esquemas y ejemplos son consistentes con aquellos usadas en la literatura científica contemporánea, por ejemplo, Journal of the American Chemical Society o Journal of Biological Chemistry. Se usan generalmente las abreviaturas convencionales de una letra o tres letras para designar residuos de aminoácidos, de los que se asume que están en la configuración L, a menos que se indique lo contrario. También, a menos que se

indique lo contrario, se obtuvieron todos los materiales iniciales en proveedores de sustancias químicas, y se los usó sin purificaciones adicionales. Específicamente, pueden usarse las siguientes abreviaturas en los ejemplos y a lo largo de la memoria descriptiva:

µl (microlitos)	Ac (acetilo)
atm (atmósfera)	ATP (adenosintrifosfatasa)
BOC (ter-butiloxicarbonilo)	BOP (cloruro bi(2-oxo-3-oxazolidinil)fosfínico)
BSA (albúmina de suero bovino)	CBZ (benciloxicarbonilo)
CDI (1,1-carbonildiimidazol)	DCC (diciclohexilcarbodiimida)
DCE (dicloroetano)	DCM (diclorometano)
DMAP (4-dimetilaminopiridina)	DME (1,2-dimetoxietano)
DMF (N,N-dimetilformamida)	DMPU (N,N'-dimetilpropilenurea)
DMSO (dimetilsulfóxido)	EDCI (clorhidrato de etilcarbodiimida)
EDTA (ácido etilendiamintetracético)	Et (etilo)
Et_2O (dietil éter)	EtOAc (acetato de etilo)
FMOC (9-fluorenilmetoxicarbonilo)	g (gramos)
h (horas)	HOAc o AcOH (ácido acético)
HOBT (1-hidroxibenzotriazol)	HOSu (N-hidroxisuccinimida)
HPLC (cromatografía líquida de alta presión)	Hz (Hertz)
i.v. (intravenoso)	IBCF (cloroformiato de isobutilo)
i-PrOH (isopropanol)	L (litros)
M (molar)	mCPBA (ácido meta-cloroperbenzoico)
Me (metilo)	MeOH (metanol)
mg (miligramos)	MHz (megahertz)
min (minutos)	mL (mililitros)
mM (milimolar)	mmol (milimoles)
mol (moles)	MOPS (ácido morfolinpropansulfónico)
mp (punto de fusión)	NaOAc (acetato de sodio)
OMe (metoxi)	psi (libras por pulgada cuadrada)
RP (fase reversa)	RT (temperatura ambiente)

SPA (Ensayo de Proximidad de Centelleo)	TBAF (fluoruro de tetra-n-butilamonio)
TBS (t-butildimetilsililo)	tBu (ter-butilo)
TEA (trietilamina)	TFA (ácido trifluoroacético)
TFAA (anhídrido trifluoroacético)	THF (tetrahidrofurano)
TIPS (triisopropilsililo)	TLC (cromatografía en capa delgada)
TMS (trimetilsililo)	TMSE (2-(trimetilsilil)etilo)
Tr (tiempo de retención)	

Todas las referencias a éter o Et_2O representan dietil éter; y solución salina hace referencia a una solución acuosa saturada de NaCl. A menos que se indique lo contrario, todas las temperaturas se expresan en °C (grados centígrados). Todas las reacciones se efectúan bajo una atmósfera inerte a RT, a menos que se indique lo contrario..

Se registraron los espectros de ^1H NMR en un dispositivo Bruker Avance 400. Se expresan los desplazamientos químicos en partes por millón (ppm). Las constantes de unión se expresan en unidades de hertz (Hz). Los patrones de separación describen multiplicidades aparentes, y se denominan s (singulete), d (doblete), t (triplete), q (cuarteto), m (multiplete), br (ancho).

Se adquirieron los espectros de masa de baja resolución (MS) y los datos de pureza de los compuestos en un dispositivo Aguas ZQ LC/MS de cuadrupolo simple, equipado con una fuente de ionización de electrorrocío (ESI), un detector UV (220 y 254 nm), y un detector de dispersión lumínica evaporativa (ELSD). Se efectuó la cromatografía en capa delgada en placas de gel de sílice de 0,25 mm de E. Merck (60F-254), se visualizó con luz UV, 5% de ácido fosfomolíbdico etanólico, Ninhidrina o solución de p-anisaldehído. Se efectuó la cromatografía en columna instantánea en gel de sílice (malla 230-400, Merck).

Los materiales iniciales y reactivos usados en la preparación de estos compuestos se pueden obtener de proveedores comerciales, tales como Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), o se pueden preparar mediante métodos bien conocidos por el especialista en la técnica, de acuerdo con los procedimientos que se describen referencias estándar tales como *Reactives for Organic Synthesis* de Fieser y Fieser, volúmenes. 1-17,

John Wiley y Sons, Nueva York, NY, 1991; *Chemistry of Carbon Compounds* de Rodd, volúmenes. 1-5 y suplementos., Elsevier Science Publishers, 1989; *Organic Reactions*, volúmenes. 1-40, John Wiley y Sons, Nueva York, NY, 1991; March J.: *Advanced Organic Chemistry*, 4ª. ed., John Wiley y Sons, Nueva York, NY; y Larock: *Comprehensive Organic Transformations*, VCH Publishers, Nueva York, 1989.

La descripción completa de todos los documentos citados en toda esta solicitud se incorpora en la presente a modo de referencia.

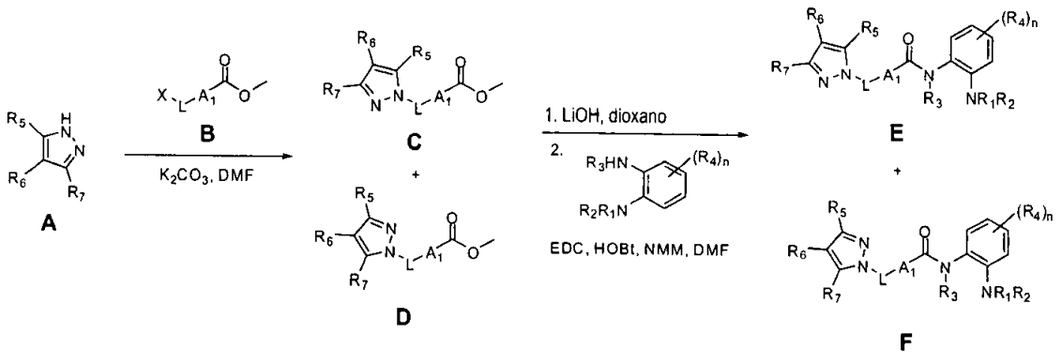
Esquemas de síntesis para los compuestos de la presente invención

Los compuestos acordes con la presente invención se pueden sintetizar según los esquemas de reacción que se muestran a continuación. Los especialistas en la técnica podrán diseñar rápidamente otros esquemas de reacción. También se debe tener en cuenta que es posible emplear una variedad de solventes, temperaturas y otras condiciones de reacción diferentes para optimizar los rendimientos de las reacciones.

En las reacciones descritas a continuación puede ser necesario proteger grupos funcionales reactivos, por ejemplo grupo hidroxi, amino, imino, tio o carboxi, cuando se desea que éstos se encuentren en el producto final, para evitar su participación indeseada en las reacciones. Pueden utilizarse grupos protectores convencionales de acuerdo con la práctica estándar, para consultar ejemplos véase T.W. Greene y P. G. M. Wuts en "Protective Groups in Organic Chemistry" John Wiley y Sons, 1991.

Las rutas de síntesis generales para producir los compuestos de la presente invención se muestran en los siguientes esquemas.

Esquema 1



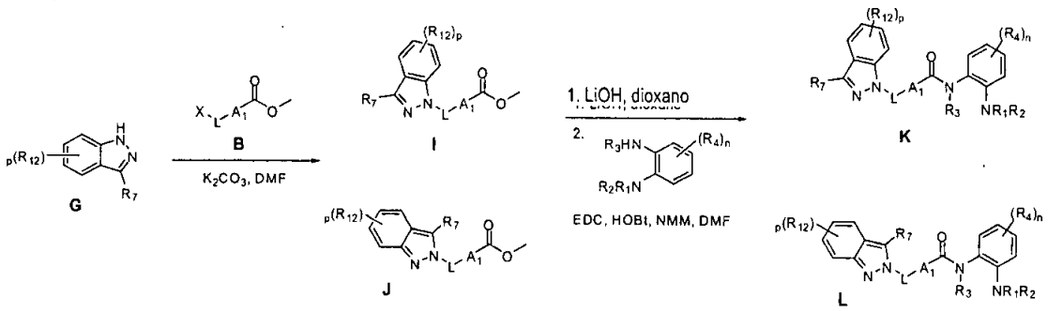
Se trata una solución de **B** (0,5 mmol) en DMF (2,5 ml) con un heterocíclico apropiado **A** (0,5 mmol) y K_2CO_3 sólido (0,6 mmol). Después de agitar a 23 °C

durante 18 hs, la reacción se vierte en agua (10 ml) y el sólido resultante se aísla por filtración. La torta de filtrado se puede lavar con agua y dejar secar bajo vacío para obtener una mezcla de productos de alquilación regioisoméricos **C** y **D**, y **E** que se pueden separar by cromatografía instantánea. Si no se forma ningún sólido, la mezcla de DMF/agua se puede extraer con acetato de etilo. Los extractos combinados se pueden secar ($MgSO_4$), concentrar bajo vacío y purificar por cromatografía instantánea.

Se trata una solución de los productos de alquilación **C, D** y/o **E** (0,25 mmol) en dioxano (1 ml) con LiOH acuoso (1 M, 1,0 ml). Después de agitar a 23 °C durante 2 hs, la reacción se neutraliza con HCl acuoso (1 M, 2,0 ml) y el sólido resultante se aísla por filtración. La torta de filtrado se puede lavar con agua y dejar secar bajo vacío para obtener el correspondiente ácido carboxílico.

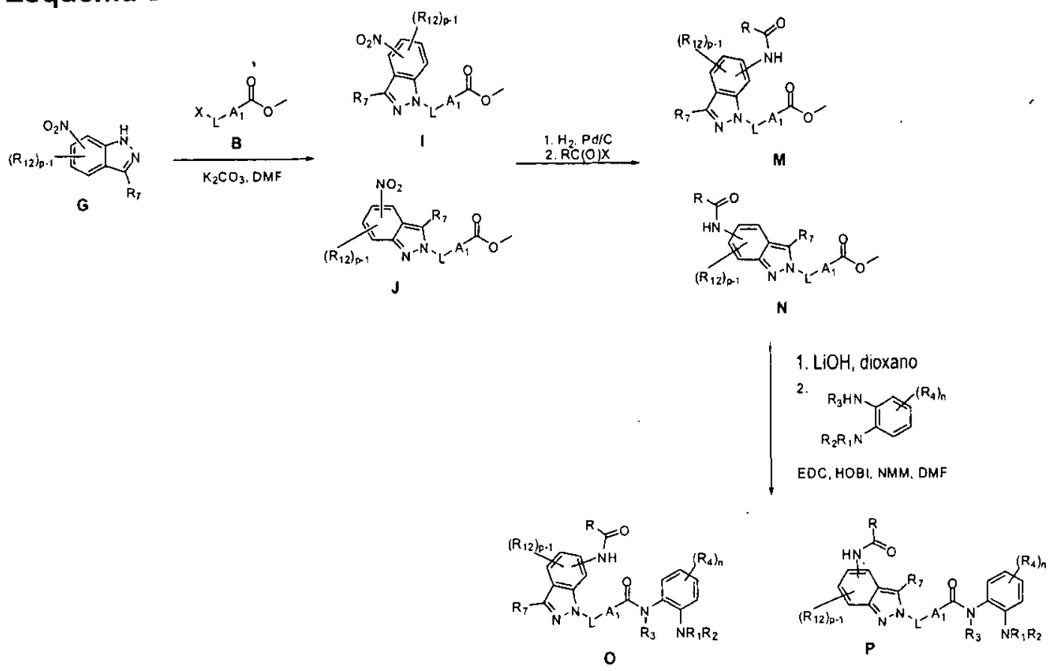
Se trata, sucesivamente, una solución del ácido carboxílico formado antes (0,1 mmol) en DMF (1 ml) con EDC (0,12 mmol), HOBt (0,12 mmol), una 1,2-fenilendiamina sustituida o no sustituida (0,12 mmol) y NMM (0,3 mmol). Después de agitar a 23 °C durante 4 h, la reacción se vierte en agua (10 ml) y el sólido resultante se aísla por filtración. La torta de filtrado se puede lavar con agua y dejar secar bajo vacío para obtener la correspondiente amida **F, G** y/o **H**.

Esquema 2



Con relación al Esquema 2, la alquilación de **I** con **B**, la hidrólisis de **J** y/o **K** y el acoplamiento con la 1,2-fenilendiamina para obtener **L** y/o **M** se realizan como se describe en el Esquema 1.

Esquema 3



Con relación al Esquema 3, los nitrobencenos **J'** y **K'** se pueden preparar como se describe con relación a los Esquemas 1 y 2.

Se agita vigorosamente una solución del nitrobenceno (**J'** y/o **K'**) (1,0 mmol) en MeOH (10 ml) con Pd/C (10% en peso, 50 mg) bajo hidrógeno durante 4 hs. La reacción se filtra y se concentra bajo vacío para obtener la correspondiente anilina que se puede usar en reacciones subsiguientes.

Se trata, sucesivamente, una solución de la anilina (1,0 mmol) en diclorometano (10 ml) con el cloruro ácido o cloroformiato apropiado (RC(O)Cl, en donde R es, por ejemplo, un grupo alcoxi, alquilo, heterocicloalquilo o arilo opcionalmente sustituido) (1,1 mmol) y trietilamina (2,2 mmol). Después de agitar a 23 °C durante 4 hs, la reacción se concentra bajo vacío para obtener el correspondiente producto de acilación (**N** y/o **O**). Si fuera necesario, se puede realizar una purificación por cromatografía instantánea o recristalización.

Los compuestos **N** y/o **O** se pueden acoplar con una 1,2-fenilendiamina sustituida o no sustituida para obtener **P** y/o **Q**, según se describe con relación a los Esquemas 1 y 2.

Los componentes quirales se pueden separar y purificar usando cualquiera entre una variedad de técnicas conocidas por los especialistas en la técnica. Por ejemplo, los componentes quirales se pueden purificar usando cromatografía de fluidos supercríticos (SFC). En una variación particular, los análisis analíticos quirales SFC/MS se conducen usando un sistema de SFC analítico Berger

(AutoChem, Newark, DE) que consiste de un módulo de control de fluido de bomba doble SFC Berger con una bomba de fluido supercrítico FCM 1100/1200 Berger y un modificador para la bomba de fluido FCM 1200, un horno TCM 2000 Berger y un dosificador automático Alcott 718. El sistema integrado se puede controlar con el software Chemstation BI-SFC versión 3.4. La detección se puede efectuar con un detector Watrers ZQ 2000 operado en modalidad positiva con una interfase ESI y un rango de barrido de 200-800 Da con 0,5 segundos por barrido. Las separaciones cromatográficas se pueden efectuar con una columna ChiralPak AD-H, ChiralPak AS-H, ChiralCel OD-H, o ChiralCel OJ-H (5□4,6 x 250 mm; Chiral Technologies, Inc. West Chester, PA) con 10 a 40% metanol como modificador y con o sin acetato de amonio (10 mM). Se puede emplear cualquiera de diversas velocidades de flujo incluyendo, por ejemplo, 1,5 o 3,5 ml/min con una presión de entrada definida en 100 bar. Además, se puede usar una variedad de condiciones de inyección de la muestra incluyendo, por ejemplo, inyecciones de muestras de 5 ó 10 μl en metanol a 0,1 mg/ml en concentración.

En otra variación, las separaciones quirales preparativas se efectúan usando un sistema de purificación MultiGram II SFC Berger. Por ejemplo, las muestras se pueden cargar sobre una columna ChiralPak AD (21 x 250 mm, 10 μ). En variaciones particulares, la velocidad de flujo para la separación puede ser de 70 ml/min, el volumen de inyección de hasta 2 ml y la presión de entrada definida en 130 bar. Se pueden aplicar inyecciones acumuladas para incrementar la eficacia.

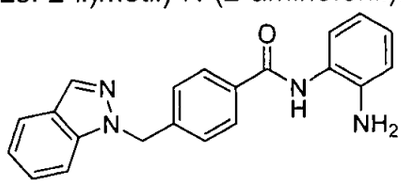
En cada uno de los procedimientos o esquemas de reacción anteriores, los diversos sustituyentes se pueden seleccionar entre los distintos sustituyentes descritos en otra parte en la presente.

Las descripciones de las síntesis de los compuestos particulares acordes con la presente invención basados en el esquema de reacción anterior se muestran en la presente.

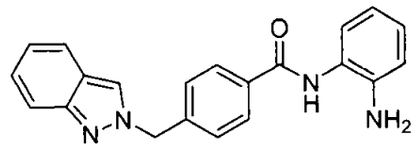
Ejemplos de inhibidores de HDAC

La presente invención se ejemplifica además, pero en un sentido no limitativo, con los siguientes ejemplos que describen la síntesis de compuestos particulares acordes con la invención.

Ejemplos 1 y 2: 4-((1*H*-indazol-1-il)metil)-N-(2-aminofenil)benzamida *y* 4-((2*H*-indazol-2-il)metil)-N-(2-aminofenil)benzamida



Ejemplo 1



Ejemplo 2

Los compuestos del título se prepararon usando el procedimiento descrito en el Esquema 2. En particular, se trató una solución de 4-bromometilbenzoato de metilo (0,5 mmol) en DMF (2,5 ml) con indazol (0,5 mmol) y K_2CO_3 sólido (0,6 mmol). Después de agitar a 23 °C durante 18 h, la reacción se vertió en agua (10 ml) y el sólido resultante se aisló por filtración. La torta de filtrado se lavó con agua y se dejó secar bajo vacío para obtener una mezcla de productos de alquilación regioisoméricos, que fueron separados por cromatografía instantánea.

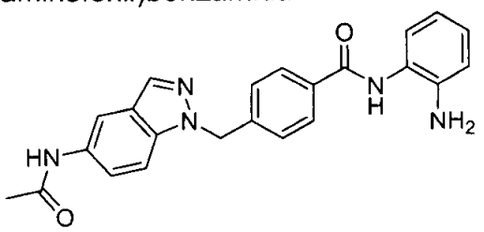
Se trató una solución del metil éster (0,25 mmol) en dioxano (1 ml) con LiOH acuoso (1 M, 1,0 ml). Después de agitar a 23 °C durante 2 hs, la reacción se neutralizó con HCl acuoso (1 M, 2,0 ml) y el sólido resultante se aisló por filtración. La torta de filtrado se lavó con agua y se secó bajo vacío para obtener el correspondiente ácido benzoico.

Se trató, sucesivamente, una solución del ácido benzoico apropiado (0,1 mmol) en DMF (1 ml) con EDC (0,12 mmol), HOBt (0,12 mmol), 1,2-fenilendiamina (0,12 mmol) y NMM (0,3 mmol). Después de agitar a 23 °C durante 4 hs, la reacción se vertió en agua (10 ml) y el sólido resultante se aisló por filtración. La torta de filtrado se lavó con agua y se dejó secar bajo vacío para obtener la correspondiente amida.

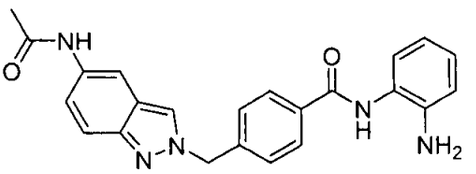
Ejemplo 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,85 (s, 2 H) 5,74 (s, 2 H) 6,53 - 6,58 (m, 1 H) 6,73 (dd, J=7,83, 1,26 Hz, 1 H) 6,91 - 6,96 (m, 1 H) 7,09 - 7,16 (m, 2 H) 7,28 - 7,39 (m, 3 H) 7,70 (d, J=8,34 Hz, 1 H) 7,77 (d, J=8,34 Hz, 1 H) 7,87 (d, J=8,08 Hz, 2 H) 8,13 (s, 1 H) 9,56 (s, 1 H).ESI-MS: m/z 343,4 $(M + H)^+$.

Ejemplo 2: ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,94 (s, 2 H) 5,72 (s, 2 H) 6,57 (t, J=7,58 Hz, 1 H) 6,74 - 6,77 (m, 1 H) 6,95 (td, J=7,58, 1,52 Hz, 1 H) 7,00 - 7,05 (m, 1 H) 7,13 (d, J=7,58 Hz, 1 H) 7,22 (dd, J=8,21, 7,20 Hz, 1 H) 7,41 (d, J=8,08 Hz, 2 H) 7,58 (d, J=8,59 Hz, 1 H) 7,71 (d, J=8,59 Hz, 1 H) 7,93 (d, J=8,08 Hz, 2 H) 8,51 (s, 1 H) 9,62 (s, 1 H)ESI-MS: m/z 343,4 $(M + H)^+$.

Ejemplos 3 y 4: 4–((5-acetamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida y 4–((5-acetamido-2*H*-indazol-2-il)metil)–N–(2-aminofenil)benzamida



Ejemplo 3



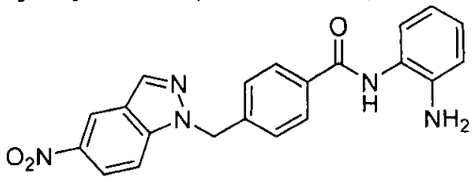
Ejemplo 4

Los compuestos del título se prepararon usando un procedimiento análogo al descrito en los Ejemplos 1 y 2 excepto que el nitrobenceno se redujo y la anilina se aciló como se describe en el Esquema 2. Específicamente, la alquilación con 4–bromometilbenzoato de metilo, la hidrólisis de benzoato de metilo, y el acoplamiento con 1,2-fenilenodiamina se efectuaron como se describe en conexión con los Ejemplos 1 y 2. Una solución del nitrobenceno (1,0 mmol) en MeOH (10 mL) con Pd/C (10 % en peso, 50 mg) luego se agitó vigorosamente bajo hidrógeno por 4 h. La reacción se filtró y se concentró al vacío para dar la anilina correspondiente que se llevó a la siguiente reacción. Una solución de la anilina (1,0 mmol) en diclorometano (10 mL) se trató en forma consecutiva don el cloruro ácido o cloroformato adecuado (1,1 mmol) y trietilamina (2,2 mmol). Después de agitar a 23 °C durante 4 h, la reacción se concentró al vacío para dar el correspondiente producto de acilación. Si es necesario, la purificación se puede conducer por cromatografía flash o recritalización.

Ejemplo 3: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,02 (s, 3 H) 4,85 (s, 2 H) 5,69 (s, 2 H) 6,49 - 6,60 (m, 1 H) 6,73 (d, J=8,08 Hz, 1 H) 6,87 - 6,99 (m, 2 H) 7,11 (d, J=8,08 Hz, 1 H) 7,29 (d, J=8,08 Hz, 2 H) 7,39 (dd, J=9,09, 1,77 Hz, 1 H) 7,61 (d, J=8,84 Hz, 1 H) 7,87 (d, J=8,08 Hz, 2 H) 8,06 (s, 1 H) 8,12 (s, 1 H) 9,56 (s, 1 H)ESI-MS: m/z 400,5 $(M + H)^+$.

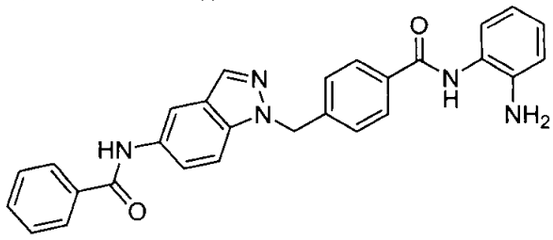
Ejemplo 4: ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 2,03 (s, 3 H) 4,87 (s, 2 H) 5,67 (s, 2 H) 6,45 - 6,65 (m, 1 H) 6,74 (d, J=8,08 Hz, 1 H) 6,86 - 7,02 (m, 1 H) 7,13 (d, J=7,33 Hz, 1 H) 7,20 (dd, J=9,35, 1,77 Hz, 1 H) 7,39 (d, J=8,08 Hz, 2 H) 7,52 (d, J=9,09 Hz, 1 H) 7,92 (d, J=8,08 Hz, 2 H) 8,12 (s, 1 H) 8,41 (s, 1 H) 9,61 (s, 1 H) 9,85 (s, 1 H)ESI-MS: m/z 400,5 $(M + H)^+$.

Ejemplo 5: N-(2-aminofenil)-4–((5-nitro-1H-indazol-1-il)metil)benzamida



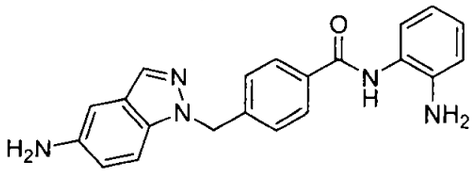
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido trifluoroacético: δ ppm 5,86 (s, 2 H) 6,96 (s, 1 H) 7,05 (d, J=7,58 Hz, 1 H) 7,13 (d, J=7,33 Hz, 1 H) 7,25 (d, J=7,83 Hz, 1 H) 7,37 (d, J=8,08 Hz, 2 H) 7,92 (d, J=8,34 Hz, 2 H) 7,96 (d, J=9,09 Hz, 1 H) 8,24 (dd, J=9,35, 2,27 Hz, 1 H) 8,47 (s, 1 H) 8,85 (d, J=2,02 Hz, 1 H) 9,99 (s, 1 H) ESI-MS: m/z 388,4 $(M + H)^+$.

Ejemplo 6: 4–((5-benzamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida



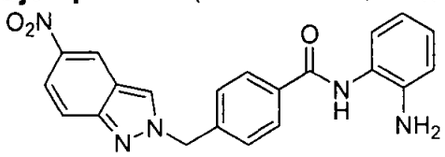
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,86 (s, 2 H) 5,73 (s, 2 H) 6,49 - 6,62 (m, 1 H) 6,73 (d, J=7,83 Hz, 1 H) 6,85 - 6,97 (m, 1 H) 7,11 (d, J=7,83 Hz, 1 H) 7,30 (d, J=8,08 Hz, 2 H) 7,45 - 7,62 (m, 3 H) 7,61 - 7,74 (m, 2 H) 7,88 (d, J=8,34 Hz, 2 H) 7,96 (d, J=6,82 Hz, 2 H) 8,12 (s, 1 H) 8,26 (s, 1 H) 9,57 (s, 1 H) 10,28 (s, 1 H)ESI-MS: m/z 462,5 $(M + H)^+$.

Ejemplo 7: 4–((5-amino-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida



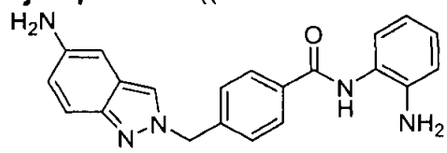
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,85 (bs, 4 H) 5,59 (s, 2 H) 6,55 (s, 1 H) 6,71 - 6,80 (m, 3 H) 6,93 (d, J=6,32 Hz, 1 H) 7,11 (d, J=6,82 Hz, 1 H) 7,26 (d, J=7,58 Hz, 2 H) 7,30 - 7,40 (m, 1 H) 7,73 - 7,83 (m, 1 H) 7,86 (d, J=7,58 Hz, 2 H) 9,56 (s, 1 H)ESI-MS: m/z 358,4 $(M + H)^+$.

Ejemplo 8: N-(2-aminofenil)-4–((5-nitro-2*H*-indazol-2-il)metil)benzamida



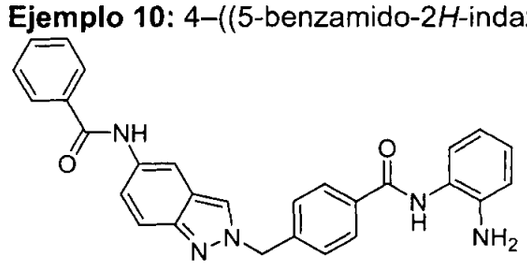
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,87 (br. s., 2 H) 5,75 - 5,88 (m, 2 H) 6,51 - 6,61 (m, 1 H) 6,74 (d, J=7,33 Hz, 1 H) 6,90 - 6,98 (m, 1 H) 7,13 (d, J=7,58 Hz, 1 H) 7,46 (d, J=8,08 Hz, 2 H) 7,77 (d, J=9,60 Hz, 1 H) 7,94 (d, J=8,08 Hz, 2 H) 7,97 - 8,04 (m, 1 H) 8,91 (d, 1 H) 8,94 - 9,01 (m, 1 H) 9,62 (s, 1 H)ESI-MS: m/z 388,4 $(M + H)^+$.

Ejemplo 9: 4–((5-amino-2*H*-indazol-2-il)metil)–N–(2-aminofenil)benzamida



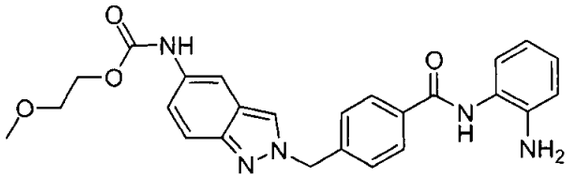
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido trifluoroacético: δ ppm 5,76 (s, 2 H) 6,84 - 6,95 (m, 1 H) 7,01 (d, J=7,83 Hz, 1 H) 7,08 - 7,20 (m, 2 H) 7,24 (s, 1 H) 7,44 (d, J=8,08 Hz, 2 H) 7,69 - 7,79 (m, 2 H) 7,96 (d, J=7,83 Hz, 2 H) 8,64 (s, 1 H) 9,96 (s, 1 H) ESI-MS: m/z 358,4 $(M + H)^+$

Ejemplo 10: 4–((5-benzamido-2*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida



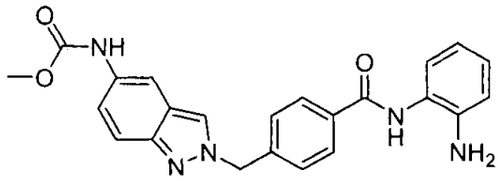
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,87 (s, 2 H) 5,61 - 5,76 (s, 2 H) 6,56 (t, J=7,33 Hz, 1 H) 6,75 (d, J=8,08 Hz, 1 H) 6,88 - 7,00 (m, 1 H) 7,13 (d, J=8,08 Hz, 1 H) 7,41 (d, J=7,07 Hz, 2 H) 7,45 - 7,63 (m, 3 H) 7,83 - 8,02 (m, 4 H) 8,26 (s, 1 H) 8,49 (s, 1 H) 9,61 (s, 1 H) 10,20 (s, 1 H)ESI-MS: m/z 462,5 $(M + H)^+$.

Ejemplo 11: 2-(4–((2-aminofenil)carbamoil)bencil)-2*H*-indazol-5-ilcarbamato de 2-Metoxietilo



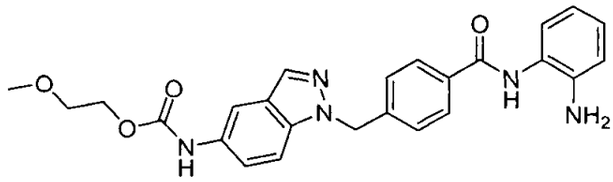
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3,52 - 3,60 (m, 2 H) 4,13 - 4,22 (m, 2 H) 4,86 (bs, 2 H) 5,66 (s, 2 H) 6,56 (m, 1 H) 6,75 (m, 1 H) 6,93 (d, J=6,82 Hz, 1 H) 7,13 (m, 1 H) 7,21 (d, J=2,02 Hz, 1 H) 7,39 (d, J=7,83 Hz, 2 H) 7,52 (s, 1 H) 7,82 - 7,89 (m, 2 H) 7,91 (s, 1 H) 8,40 (s, 1 H) 9,60 (s, 1 H) 9,64 (s, 1 H)ESI-MS: m/z 460,5 $(M + H)^+$.

Ejemplo 12: 2-(4–((2-aminofenil)carbamoil)bencil)-2*H*-indazol-5-ilcarbamato de metilo



El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3,32 (s, 3 H) 4,87 (s, 2 H) 5,58 - 5,73 (m, 2 H) 6,48 - 6,62 (m, 1 H) 6,74 (d, J=8,08 Hz, 1 H) 6,88 - 7,00 (m, 1 H) 7,07 - 7,17 (m, 1 H) 7,18 - 7,24 (m, 1 H) 7,39 (dd, J=8,08, 4,55 Hz, 2 H) 7,46 - 7,57 (m, 1 H) 7,88 - 8,00 (m, 2 H) 8,39 (d, J=6,32 Hz, 1 H) 8,56 (s, 1 H) 9,54 (s, 1 H) 9,61 (s, 1 H)ESI-MS: m/z 416,5 $(M + H)^+$.

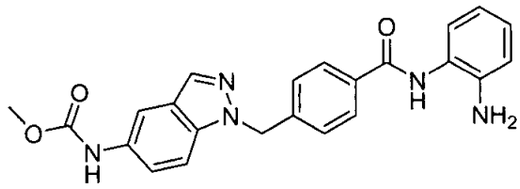
Ejemplo 13: 1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de 2-Metoxietilo



El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3,31 (s, 3 H) 3,47 - 3,61 (m, 2 H) 4,12 - 4,23 (m, 2 H) 4,85 (s, 2 H) 5,69 (s, 2 H) 6,55 (t, J=7,58 Hz, 1 H) 6,69 - 6,78 (m, 1 H) 6,86 - 7,01 (m, 1 H) 7,11 (d, J=7,83 Hz, 1 H) 7,28 (d, J=8,34

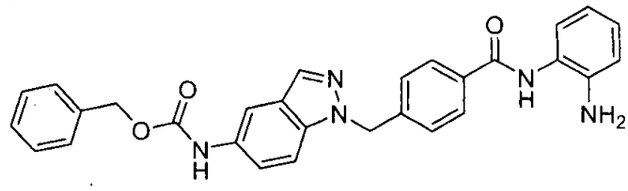
Hz, 2 H) 7,33 - 7,45 (m, 1 H) 7,61 (d, J=9,09 Hz, 1 H) 7,87 (m, 3 H) 8,05 (s, 1 H) 9,56 (s, 1 H) 9,71 (s, 1 H)ESI-MS: m/z 460,5 $(M + H)^+$.

Ejemplo 14: 1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de metilo



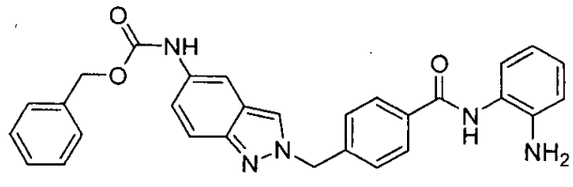
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido trifluoroacético: δ ppm 3,65 (s, 3 H) 5,70 (s, 2 H) 6,90 (s, 1 H) 6,99 (s, 1 H) 7,11 (s, 1 H) 7,23 (d, J=7,83 Hz, 1 H) 7,31 (d, J=8,08 Hz, 2 H) 7,38 (s, 1 H) 7,61 (d, J=9,09 Hz, 1 H) 7,89 (d, J=7,83 Hz, 3 H) 8,06 (s, 1 H) 9,61 (s, 1 H) 9,91 (s, 1 H)ESI-MS: m/z 416,5 $(M + H)^+$.

Ejemplo 15: 1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de bencilo



El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido trifluoroacético: δ ppm 4,85 (s, 2 H) 5,14 (s, 2 H) 5,69 (s, 2 H) 6,55 (s, 1 H) 6,73 (d, J=8,08 Hz, 1 H) 6,93 (s, 1 H) 7,04 - 7,18 (m, 1 H) 7,22 - 7,49 (m, 7 H) 7,61 (s, 1 H) 7,79 - 8,00 (m, 4 H) 8,05 (s, 1 H) 9,56 (s, 1 H) 9,74 (s, 1 H)ESI-MS: m/z 492,5 $(M + H)^+$.

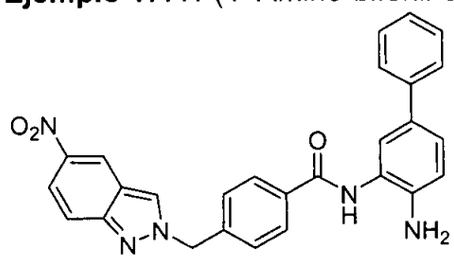
Ejemplo 16: 2-(4–((2-aminofenil)carbamoil)bencil)-2*H*-indazol-5-ilcarbamato de bencilo



El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido trifluoroacético: δ ppm 5,14 (s, 2 H) 5,68 (s, 2 H) 6,81 - 6,94 (m, 1 H) 6,95 - 7,05

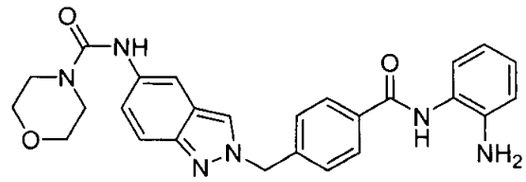
(m, 1 H) 7,10 (s, 1 H) 7,22 (dd, J=9,35, 1,77 Hz, 2 H) 7,29 - 7,47 (m, 7 H) 7,51 (d, J=9,35 Hz, 2 H) 7,94 (d, J=8,08 Hz, 2 H) 8,41 (s, 1 H) 9,68 (s, 1 H) 9,94 (s, 1 H)ESI-MS: m/z 492,5 $(M + H)^+$.

Ejemplo 17: *N*-(4–Amino-bifenil-3-il)-4–(5-nitro-indazol-2-ilmetil)-benzamida



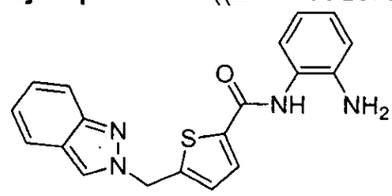
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido trifluoroacético: δ ppm 5,84 (s, 2 H) 6,97 (s, 1 H) 7,25 (s, 1 H) 7,39 (s, 3 H) 7,44 - 7,62 (m, 5 H) 7,79 (s, 1 H) 7,99 (s, 3 H) 8,98 (s, 2 H) 9,89 (s, 1 H)ESI-MS: m/z 464,5 $(M + H)^+$.

Ejemplo 18: N-(2-(4–((2-Aminofenil)carbamoil)bencil)-2*H*-indazol-5-il)morfolin-4–carboxamida



El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido trifluoroacético: δ ppm 3,34 - 3,45 (m, 4 H) 3,59 (m, 4 H) 4,86 (s, 2 H) 5,66 (s, 2 H) 6,75 (m, 1 H) 6,86 - 6,98 (m, 1 H) 7,06 - 7,16 (m, 1 H) 7,20 - 7,30 (m, 1 H) 7,38 (d, 2 H) 7,46 (m, 1 H) 7,78 (s, 1 H) 7,91 (d, 2 H) 8,36 (s, 1 H) 8,40 - 8,48 (m, 1 H) 9,61 (s, 1 H)ESI-MS: m/z 471,5 $(M + H)^+$.

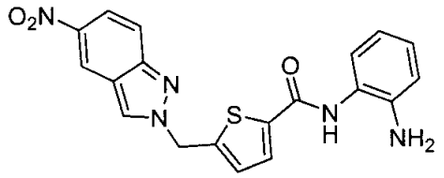
Ejemplo 19: 5-((2*H*-Indazol-2-il)metil)–N–(2-aminofenil)tiofen-2-carboxamida



El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,88 (s, 2 H) 5,89 (s, 2 H) 6,54 - 6,60 (m, 1 H) 6,75 (d, J=8,08 Hz, 1 H) 6,94 - 6,99 (m, 1 H) 7,02 - 7,10 (m,

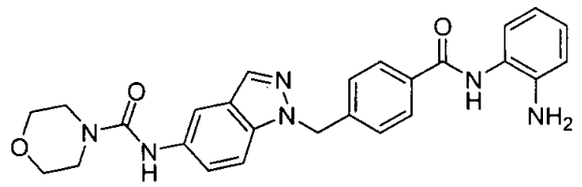
2 H) 7,22 - 7,30 (m, 2 H) 7,62 (d, J=8,84 Hz, 1 H) 7,72 (d, J=8,59 Hz, 1 H) 7,83 (d, J=3,03 Hz, 1 H) 8,51 (s, 1 H) 9,68 (s, 1 H)ESI-MS: m/z 349,4 $(M + H)^+$.

Ejemplo 20: N-(2-Aminofenil)-5-((5-nitro-2*H*-indazol-2-il)metil)tiofen-2-carboxamida



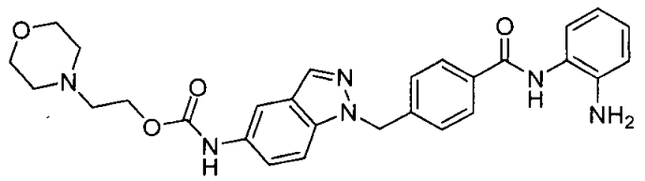
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,89 (s, 2 H) 6,01 (s, 2 H) 6,55 - 6,59 (m, 1 H) 6,75 (d, J=8,08 Hz, 1 H) 6,95 (d, J=7,83 Hz, 1H) 7,07 (d, J=7,83 Hz, 1 H) 7,30 (s, 1 H) 7,82 (d, J=9,35 Hz, 2 H) 8,01 - 8,05 (m, 1 H) 8,93 - 8,97 (m, 2 H) 9,70 (s, 1 H)ESI-MS: m/z 394,4 $(M + H)^+$.

Ejemplo 21: N-(1-(4–((2-Aminofenil)carbamoil)bencil)-1*H*-indazol-5-il)morfolin-4–carboxamida



El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3,37 - 3,47 (m, 4 H) 3,50 - 3,66 (m, 4 H) 5,62 (s, 2 H) 6,56 (m, 1 H) 6,74 (d, J=8,59 Hz, 1 H) 6,94 (m, 1 H) 7,11 (m, 1 H) 7,29 (d, J=8,08 Hz, 2 H) 7,39 (dd, J=9,09, 1,77 Hz, 1 H) 7,57 (d, J=9,09 Hz, 1 H) 7,74 - 7,89 (m, 3 H) 7,96 - 8,05 (m, 1 H) 8,52 (s, 1 H) 9,57 (s, 1 H)ESI-MS: m/z 471,5 $(M + H)^+$.

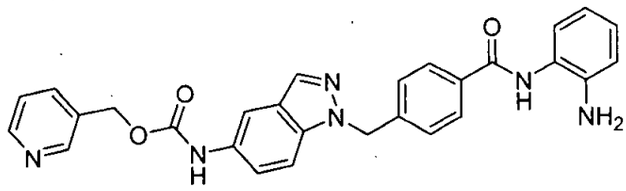
Ejemplo 22: 1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de 2-Morfolinoetilo



El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 2,41 (m, 2 H) 2,56 (m, 2 H) 3,55 (m, 4 H) 4,18 (m, 4 H) 4,85 (s, 2 H) 5,68 (s, 2 H) 6,47 - 6,63 (m, 1 H) 6,73 (d, J=8,08 Hz, 1 H) 6,85 - 6,99 (m, 1 H) 7,10 (s, 1 H) 7,28 (d, J=8,34 Hz, 2 H) 7,39

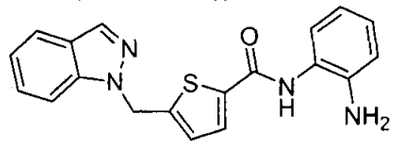
(d, J=8,84 Hz, 1 H) 7,61 (d, J=9,09 Hz, 1 H) 7,87 (d, J=8,08 Hz, 3 H) 8,04 (s, 1 H) 9,55 (s, 1 H) 9,60 - 9,71 (m, 1 H)ESI-MS: m/z 515,6 $(M + H)^+$.

Ejemplo 23: 1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de Piridin-3-ilmetilo



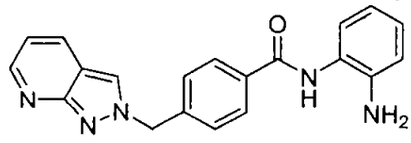
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 3 y 4. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,85 (bs, 2 H) 5,18 (s, 2 H) 5,69 (s, 2 H) 6,48 - 6,59 (m, 1 H) 6,73 (dd, J=8,08, 1,26 Hz, 1 H) 6,87 - 6,98 (m, 1 H) 7,11 (d, J=7,33 Hz, 1 H) 7,28 (d, J=8,34 Hz, 2 H) 7,34 - 7,47 (m, 2 H) 7,62 (d, J=9,09 Hz, 2 H) 7,77 - 7,94 (m, 3 H) 8,03 - 8,08 (m, 1 H) 8,54 (dd, J=4,80, 1,52 Hz, 1 H) 8,65 (d, J=1,77 Hz, 1 H) 9,56 (s, 1 H) 9,78 (s, 1 H)ESI-MS: m/z 493,5 $(M + H)^+$.

Ejemplo 24: 5-((1*H*-Indazol-1-il)metil)–N–(2-aminofenil)tiofen-2-carboxamida



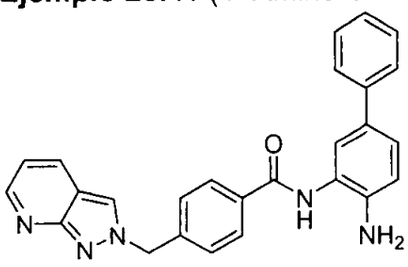
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,86 (s, 2 H) 5,90 (s, 2 H) 6,52 - 6,59 (m, 1 H) 6,74 (d, J=7,33 Hz, 1 H) 6,91 - 6,99 (m, 1 H) 7,05 (d, J=7,33 Hz, 1 H) 7,13 - 7,23 (m, 2 H) 7,42 (s, 1 H) 7,79 (m, 3 H) 8,15 (s, 1 H) 9,62 (s, 1 H)ESI-MS: m/z 349,4 $(M + H)^+$.

Ejemplo 25: 4–((2*H*-Pirazolo[3,4–b]piridin-2-il)metil)–N–(2-aminofenil)benzamida



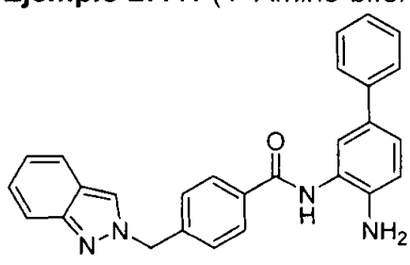
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido bis-trifluoroacético: δ ppm 6,11 (s, 2 H) 6,79 (d, J=8,08 Hz, 1 H) 6,92 (d, J=8,08 Hz, 1 H) 7,02 - 7,10 (m, 1 H) 7,19 (d, J=7,58 Hz, 1 H) 7,63 (d, J=8,08 Hz, 2H) 7,79 (dd, J=8,08, 5,81 Hz, 1 H) 7,97 (d, J=8,34 Hz, 2 H) 9,11 - 9,19 (m, 1 H) 9,23 (d, J=7,83 Hz, 1 H) 9,40 (d, J=4,80 Hz, 1 H) 9,86 (s, 1 H)ESI-MS: m/z 344,4 $(M + H)^+$.

Ejemplo 26: *N*-(4–Amino-bifenil-3-il)-4–pirazolo[3,4–*b*]piridin-2-ilmetil-benzamida



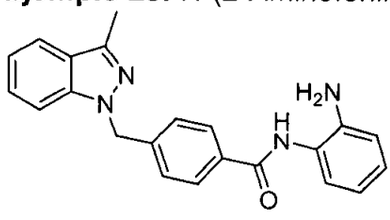
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido bis-trifluoroacético: δ ppm 6,11 (s, 2H) 6,91 (d, J=8,34 Hz, 1 H) 7,24 (t, J=7,33 Hz, 1 H) 7,33 - 7,41 (m, 3 H) 7,48 - 7,56 (m, 3 H) 7,64 (d, J=8,34 Hz, 2 H) 7,79 (dd, J=8,08, 5,81 Hz, 1 H) 8,00 (d, J=8,34 Hz, 2 H) 9,16 (br. s., 1 H) 9,23 (d, J=7,83 Hz, 1 H) 9,35 - 9,45 (m, 1 H) 9,82 (s, 1 H)ESI-MS: m/z 420,5 $(M + H)^+$.

Ejemplo 27: *N*-(4–Amino-bifenil-3-il)-4–indazol-2-ilmetil-benzamida



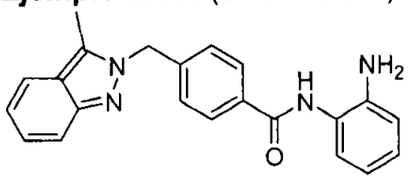
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido trifluoroacético: δ ppm 5,74 (s, 2 H) 6,98 - 7,06 (m, 1 H) 7,08 (d, J=8,34 Hz, 1 H) 7,18 - 7,25 (m, 1 H) 7,28 (t, 1 H) 7,35 - 7,48 (m, 5 H) 7,58 (m, 4 H) 7,71 (d, J=8,34 Hz, 1 H) 7,98 (d, J=8,08 Hz, 2 H) 8,53 (s, 1 H) 10,02 (s, 1 H)ESI-MS: m/z 419,5 $(M + H)^+$.

Ejemplo 28: N-(2-Aminofenil)-4–((3-metil-1*H*-indazol-1-il)metil)benzamida



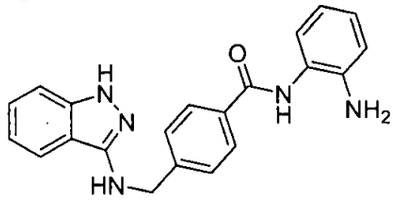
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 2,48 (s, 3 H) 4,87 (s, 2 H) 5,66 (s, 2 H) 6,54 - 6,61 (m, 1 H) 6,76 (dd, J=7,83, 1,26 Hz, 1 H) 6,91 - 6,99 (m, 1 H) 7,09 - 7,17 (m, 2 H) 7,31 (d, J=8,34 Hz, 2 H) 7,34 - 7,40 (m, 1 H) 7,64 (d, J=8,34 Hz, 1 H) 7,73 (d, J=8,08 Hz, 1 H) 7,89 (d, J=8,34 Hz, 2 H) 9,57 (s, 1 H)ESI-MS: m/z 357,4 $(M + H)^+$.

Ejemplo 29: N-(2-Aminofenil)-4–((3-metil-2*H*-indazol-2-il)metil)benzamida



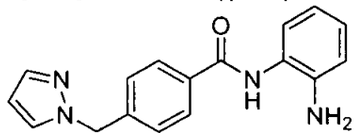
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 2,61 (s, 3 H) 4,88 (s, 2 H) 5,72 (s, 2 H) 6,50 - 6,64 (m, 1 H) 6,72 - 6,82 (m, 1 H) 6,93 - 7,03 (m, 2 H) 7,12 - 7,17 (m, 1 H) 7,20 - 7,31 (m, 3 H) 7,55 (d, J=8,59 Hz, 1 H) 7,68 (d, J=8,59 Hz, 1 H) 7,93 (d, J=8,08 Hz, 2 H) 9,62 (s, 1 H)ESI-MS: m/z 357,4 $(M + H)^+$.

Ejemplo 30: 4–((1H-indazol-3-ilamino)metil)–N–(2-aminofenil)benzamida



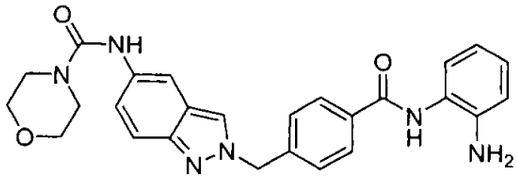
El compuesto del título se preparó usando un procedimiento análogo al descrito en los Ejemplos 1 y 2. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,56 (d, J=6,15 Hz, 2 H) 4,88 (s, 2 H) 6,49 - 6,63 (m, 1 H) 6,63 - 6,73 (m, 1 H) 6,77 (d, J=7,98 Hz, 1 H) 6,84 - 7,01 (m, 2 H) 7,16 (d, J=7,48 Hz, 1 H) 7,20 - 7,29 (m, 2 H) 7,52 (d, J=8,14 Hz, 2 H) 7,77 (d, J=8,14 Hz, 1 H) 7,92 (d, J=8,14 Hz, 2 H) 9,60 (s, 1 H) 11,40 (s, 1 H)ESI-MS: m/z 358,4 $(M + H)^+$.

Ejemplo 31: 4–((1H-pirazol-1-il)metil)–N–(2-aminofenil)benzamida



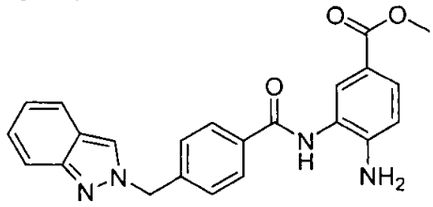
^{1}H NMR (499 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 5,38 (s, 2 H), 6,25 - 6,33 (m, 2 H), 7,18 - 7,26 (m, 3 H), 7,31 - 7,38 (m, 3 H), 7,46 - 7,53 (m, 1 H), 7,84 - 7,89 (m, 1 H), 7,92 - 7,99 (m, 1 H), 10,09 (s, 1 H). ESI-MS: *m/z* 293,3 $(M + H)^+$.

Ejemplo 32: N-(2-(4–((2-Aminofenil)carbamoil)bencil)-2*H*-indazol-5-il)morfolin-4–carboxamida



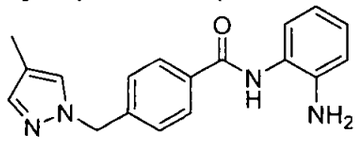
^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3,36 - 3,47 (m, 4 H) 3,61 (m, 4 H) 4,85 (s, 2 H) 5,69 (s, 2 H) 6,77 (m, 1 H) 6,94 (m, 1 H) 7,12 (m, 1 H) 7,27 (m, 1 H) 7,37 (d, 2 H) 7,46 (m, 1 H) 7,78 (s, 1 H) 7,87 (d, 2 H) 8,36 (s, 1 H) 8,46 (m, 1 H) 9,56 (s, 1 H)ESI-MS: *m/z* 471,5 $(M + H)^+$.

Ejemplo 33: 3-(4–((2H-indazol-2-il)metil)benzamido)-4–aminobenzoato de metilo



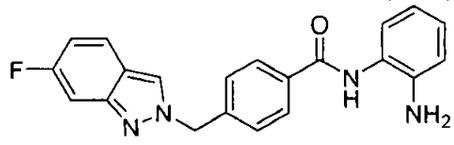
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,73 (s, 14 H), 5,72 (s, 10 H), 5,81 (s, 10 H), 6,74 (d, *J*=8,59 Hz, 6 H), 6,98 - 7,07 (m, 6 H), 7,17 - 7,26 (m, 6 H), 7,41 (d, *J*=8,34 Hz, 10 H), 7,51 - 7,61 (m, 11 H), 7,67 - 7,77 (m, 11 H), 7,94 (d, *J*=8,08 Hz, 10 H), 8,52 (s, 6 H), 9,60 (s, 1 H). ESI-MS: *m/z* 401,4 $(M + H)^+$.

Ejemplo 34: N-(2-aminofenil)-4–((4–metil-1H-pirazol-1-il)metil)benzamida



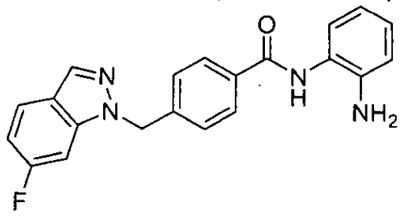
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,00 (s, 3 H), 4,87 (s, 2 H), 5,29 - 5,33 (m, 2 H), 6,54 - 6,60 (m, 1 H), 6,73 - 6,78 (m, 1 H), 6,92 - 6,97 (m, 1 H), 7,13 (d, *J*=7,58 Hz, 1 H), 7,25 - 7,30 (m, 3 H), 7,58 (s, 1 H), 7,91 (d, *J*=8,08 Hz, 2 H), 9,60 (s, 1 H). ESI-MS: *m/z* 307,4 $(M + H)^+$.

Ejemplo 35: N-(2-aminofenil)-4–((6-fluoro-2H-indazol-2-il)metil)benzamida



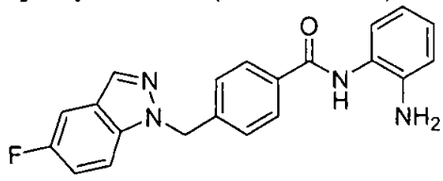
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,87 (s, 2 H), 5,70 (s, 2 H), 6,53 - 6,60 (m, 1 H), 6,75 (d, *J*=8,08 Hz, 1 H), 6,91 - 6,99 (m, 2 H), 7,13 (d, *J*=8,08 Hz, 1 H), 7,31 (d, *J*=10,36 Hz, 1 H), 7,41 (d, *J*=8,08 Hz, 2 H), 7,76 - 7,83 (m, 1 H), 7,93 (d, *J*=8,08 Hz, 2 H), 8,58 (s, 1 H), 9,61 (s, 1 H). ESI-MS: *m/z* 361,4 $(M + H)^+$.

Ejemplo 36: N-(2-aminofenil)-4–((6-fluoro-1H-indazol-1-il)metil)benzamida



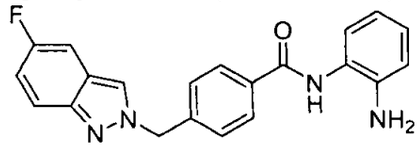
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,86 (s, 2 H), 5,67 - 5,72 (m, 2 H), 6,53 - 6,59 (m, 1 H), 6,74 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,91 - 6,96 (m, 1 H), 6,99 - 7,06 (m, 1 H), 7,11 (d, *J*=7,33 Hz, 1 H), 7,33 (d, *J*=8,08 Hz, 2 H), 7,59 - 7,66 (m, 1 H), 7,81 (dd, *J*=8,84, 5,31 Hz, 1 H), 7,88 (d, *J*=8,08 Hz, 2 H), 8,13 - 8,16 (m, 1 H), 9,57 (s, 1 H). ESI-MS: *m/z* 361,4 $(M + H)^+$.

Ejemplo 37: N-(2-aminofenil)-4–((5-fluoro-1H-indazol-1-il)metil)benzamida



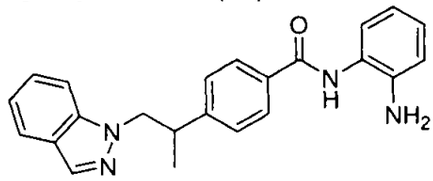
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,86 (s, 2 H), 5,75 (s, 2 H), 6,55 (s, 1 H), 6,74 (d, *J*=7,83 Hz, 1 H), 6,92 (d, *J*=7,58 Hz, 1 H), 7,10 (s, 1 H), 7,23 - 7,33 (m, 3 H), 7,49 - 7,59 (m, 1 H), 7,75 (s, 1 H), 7,87 (s, 2 H), 8,11 (s, 1 H), 9,57 (s, 1 H). ESI-MS: *m/z* 361,4 $(M + H)^+$.

Ejemplo 38: N-(2-aminofenil)-4–((5-fluoro-2H-indazol-2-il)metil)benzamida



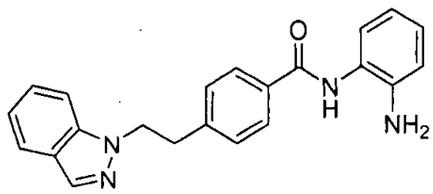
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,87 (s, 2 H), 5,68 (s, 2 H), 6,52 - 6,59 (m, 1 H), 6,71 - 6,77 (m, 1 H), 6,91 - 6,98 (m, 1 H), 7,09 - 7,17 (m, 2 H), 7,37 - 7,48 (m, 3 H), 7,62 - 7,68 (m, 1 H), 7,93 (d, *J*=8,34 Hz, 2 H), 8,50 (s, 1 H), 9,60 (s, 1 H). ESI-MS: *m/z* 361,4 $(M + H)^+$.

Ejemplo 39: 4–(1-(1H-indazol-1-il)propan-2-il)–N–(2-aminofenil)benzamida



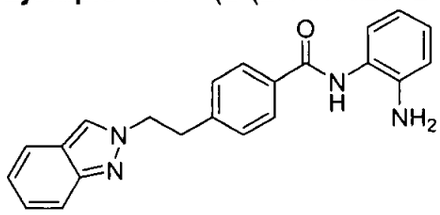
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 1,20 (d, *J*=6,82 Hz, 3 H), 3,51 - 3,62 (m, 1 H), 4,54 - 4,65 (m, 2 H), 6,95 (s, 2 H), 7,01 - 7,13 (m, 3 H), 7,25 (d, *J*=7,58 Hz, 1 H), 7,29 - 7,35 (m, 1 H), 7,44 (d, *J*=8,34 Hz, 2 H), 7,65 - 7,72 (m, 2 H), 7,85 (d, *J*=8,08 Hz, 2 H), 8,02 (s, 1 H), 9,84 - 10,01 (m, 1 H). ESI-MS: *m/z* 371,4 $(M + H)^+$.

Ejemplo 40: 4–(2-(1H-indazol-1-il)etil)–N–(2-aminofenil)benzamida



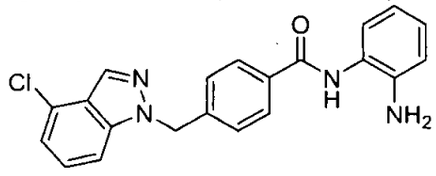
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,17 - 3,28 (m, 2 H), 4,68 (t, *J*=7,07 Hz, 2 H), 4,85 (s, 2 H), 6,51 - 6,62 (m, 1 H), 6,75 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,88 - 7,00 (m, 1 H), 7,03 - 7,18 (m, 2 H), 7,26 - 7,38 (m, 3 H), 7,62 (d, *J*=8,34 Hz, 1 H), 7,72 (d, *J*=8,08 Hz, 1 H), 7,78 - 7,86 (m, 2 H), 8,04 (s, 1 H), 9,56 (s, 1 H). ESI-MS: *m/z* 357,4 $(M + H)^+$.

Ejemplo 41: 4–(2-(2H-indazol-2-il)etil)–N–(2-aminofenil)benzamida



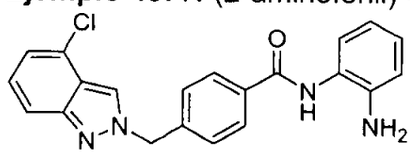
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,34 (t, *J*=7,07 Hz, 2 H), 4,72 (t, *J*=7,07 Hz, 2 H), 4,85 (s, 2 H), 6,51 - 6,62 (m, 1 H), 6,74 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,88 - 7,03 (m, 2 H), 7,11 (d, *J*=7,33 Hz, 1 H), 7,15 - 7,25 (m, 1 H), 7,29 (d, *J*=8,08 Hz, 2 H), 7,54 - 7,68 (m, 2 H), 7,84 (d, *J*=8,08 Hz, 2 H), 8,19 - 8,30 (m, 1 H), 9,56 (s, 1 H). ESI-MS: *m/z* 357,4 $(M + H)^+$.

Ejemplo 42: N-(2-aminofenil)-4–((4–cloro-1H-indazol-1-il)metil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,85 (s, 2 H), 5,74 - 5,81 (m, 2 H), 6,52 - 6,59 (m, 1 H), 6,71 - 6,77 (m, 1 H), 6,90 - 6,97 (m, 1 H), 7,11 (d, *J*=7,07 Hz, 1 H), 7,23 (d, *J*=7,58 Hz, 1 H), 7,31 (d, *J*=8,34 Hz, 2 H), 7,35 - 7,42 (m, 1 H), 7,74 (d, *J*=8,59 Hz, 1 H), 7,89 (d, *J*=8,08 Hz, 2 H), 8,18 - 8,23 (m, 1 H), 9,57 (s, 1 H). ESI-MS: *m/z* 377,8 $(M + H)^+$.

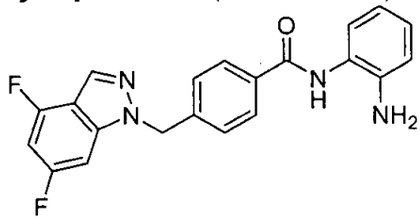
Ejemplo 43: N-(2-aminofenil)-4–((4–cloro-2H-indazol-2-il)metil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,87 (s, 2 H), 5,70 - 5,78 (m, 2 H), 6,53 - 6,61 (m, 1 H), 6,75 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,91 - 6,98 (m, 1 H), 7,13 (d, *J*=7,07 Hz, 2 H), 7,22 (dd, *J*=8,59, 7,07 Hz, 1 H), 7,41 - 7,49 (m, 2 H), 7,58 (d, *J*=8,59 Hz, 1

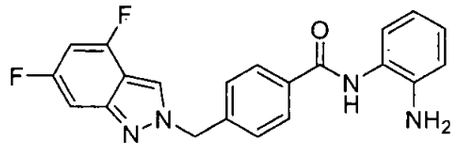
H), 7,93 (d, *J*=8,08 Hz, 2 H), 8,67 - 8,71 (m, 1 H), 9,61 (s, 1 H). ESI-MS: *m/z* 377,8 $(M + H)^+$.

Ejemplo 44: N-(2-aminofenil)-4–((4,6-difluoro-1H-indazol-1-il)metil)benzamida



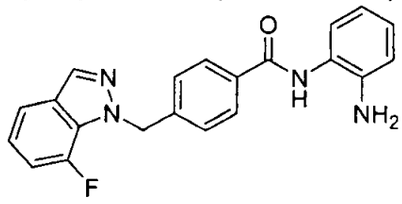
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,86 (s, 2 H), 5,67 - 5,75 (m, 2 H), 6,52 - 6,59 (m, 1 H), 6,74 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,91 - 6,96 (m, 1 H), 7,00 - 7,07 (m, 1 H), 7,12 (d, *J*=7,58 Hz, 1 H), 7,34 (d, *J*=8,08 Hz, 2 H), 7,60 (d, *J*=9,35 Hz, 1 H), 7,89 (d, *J*=8,08 Hz, 2 H), 8,25 - 8,30 (m, 1 H), 9,58 (s, 1 H). ESI-MS: *m/z* 379,4 $(M + H)^+$.

Ejemplo 45: N-(2-aminofenil)-4–((4,6-difluoro-2H-indazol-2-il)metil)benzamida



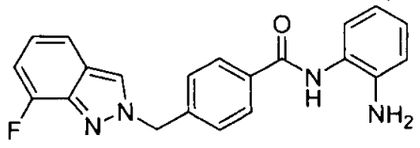
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,87 (s, 2 H), 5,67 - 5,74 (m, 2 H), 6,52 - 6,61 (m, 1 H), 6,75 (dd, *J*=7,83, 1,26 Hz, 1 H), 6,88 - 6,98 (m, 2 H), 7,13 (d, *J*=7,07 Hz, 1 H), 7,25 (d, *J*=8,84 Hz, 1 H), 7,44 (d, *J*=8,34 Hz, 2 H), 7,93 (d, *J*=8,08 Hz, 2 H), 8,82 (s, 1 H), 9,61 (s, 1 H). ESI-MS: *m/z* 379,4 $(M + H)^+$.

Ejemplo 46: N-(2-aminofenil)-4–((7-fluoro-1H-indazol-1-il)metil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,86 (s, 2 H), 5,78 (s, 2 H), 6,51 - 6,58 (m, 1 H), 6,71 - 6,76 (m, 1 H), 6,89 - 6,96 (m, 1 H), 7,07 - 7,14 (m, 2 H), 7,17 - 7,25 (m, 3 H), 7,61 (d, *J*=7,83 Hz, 1 H), 7,88 (d, *J*=8,08 Hz, 2 H), 8,24 (d, *J*=2,53 Hz, 1 H), 9,56 (s, 1 H). ESI-MS: *m/z* 361,4 $(M + H)^+$.

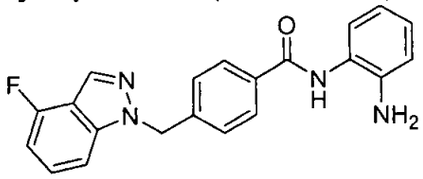
Ejemplo 47: N-(2-aminofenil)-4–((7-fluoro-2H-indazol-2-il)metil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,87 (s, 2 H), 5,72 - 5,78 (m, 2 H), 6,52 - 6,60 (m, 1 H), 6,75 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,92 - 7,04 (m, 3 H), 7,13 (d, *J*=7,33 Hz,

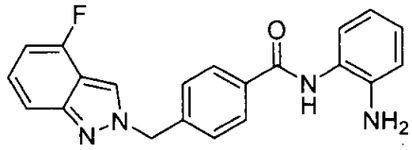
1 H), 7,43 (d, *J*=8,08 Hz, 2 H), 7,51 - 7,57 (m, 1 H), 7,94 (d, *J*=8,08 Hz, 2 H), 8,66 (d, *J*=2,78 Hz, 1 H), 9,62 (s, 1 H). ESI-MS: *m/z* 361,4 $(M + H)^+$.

Ejemplo 48: N-(2-aminofenil)-4–((4–fluoro-1H-indazol-1-il)metil)benzamida



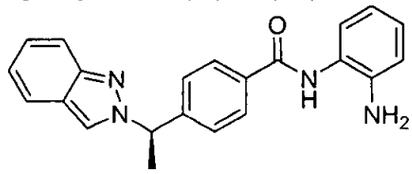
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 4,86 (s, 2 H), 5,77 (s, 2 H), 6,50 - 6,60 (m, 1 H), 6,73 (d, J=8,34 Hz, 1 H), 6,88 - 6,97 (m, 2 H), 7,11 (d, J=7,58 Hz, 1 H), 7,32 (d, J=8,08 Hz, 2 H), 7,34 - 7,42 (m, 1 H), 7,58 (d, J=8,34 Hz, 1 H), 7,89 (d, J=7,83 Hz, 2 H), 8,25 (s, 1 H), 9,57 (s, 1 H). ESI-MS: m/z 361,4 (M + H)+.

Ejemplo 49: N-(2-aminofenil)-4–((4–fluoro-2H-indazol-2-il)metil)benzamida



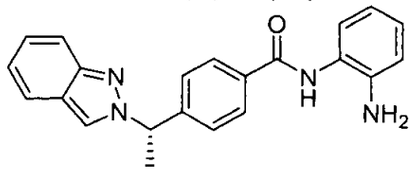
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,87 (s, 2 H), 5,69 - 5,75 (m, 2 H), 6,52 - 6,60 (m, 1 H), 6,72 - 6,82 (m, 2 H), 6,91 - 6,97 (m, 1 H), 7,12 (d, *J*=7,33 Hz, 1 H), 7,17 - 7,24 (m, 1 H), 7,39 - 7,46 (m, 3 H), 7,93 (d, *J*=8,08 Hz, 2 H), 8,74 (s, 1 H), 9,61 (s, 1 H). ESI-MS: *m/z* 361,4 $(M + H)^+$.

Ejemplo 50: (R)-4–(1-(2H-indazol-2-il)etil)–N–(2-aminofenil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,18 (d, *J*=7,07 Hz, 4 H), 3,36 (d, *J*=5,05 Hz, 2 H), 4,29 (q, 1 H), 5,07 (s, 2 H), 6,24 (d, *J*=7,07 Hz, 1 H), 6,76 (s, 1 H), 6,96 (s, 1 H), 7,13 (s, 1 H), 7,24 (d, *J*=8,59 Hz, 2 H), 7,32 (s, 1 H), 7,39 - 7,44 (m, 1 H), 7,63 (d, *J*=8,08 Hz, 3 H), 7,80 (d, *J*=8,84 Hz, 2 H), 7,90 (d, *J*=8,34 Hz, 1 H), 8,11 (d, *J*=8,34 Hz, 3 H), 8,75 (s, 1 H), 9,79 (s, 1 H). ESI-MS: *m/z* 357,4 $(M + H)^+$.

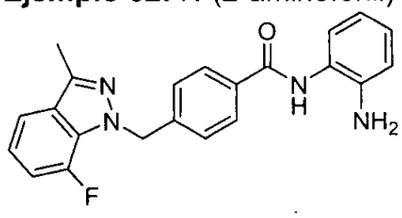
Ejemplo 51: (S)-4–(1-(2H-indazol-2-il)etil)–N–(2-aminofenil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,18 (d, *J*=7,07 Hz, 4 H), 3,36 (d, *J*=5,05 Hz, 2 H), 4,29 (q, 1 H), 5,07 (s, 2 H), 6,24 (d, *J*=7,07 Hz, 1 H), 6,76 (s, 1 H), 6,96 (s, 1

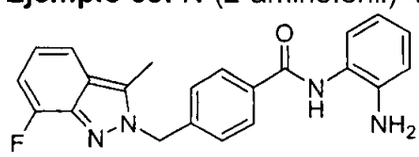
H), 7,13 (s, 1 H), 7,24 (d, *J*=8,59 Hz, 2 H), 7,32 (s, 1 H), 7,39 - 7,44 (m, 1 H), 7,63 (d, *J*=8,08 Hz, 3 H), 7,80 (d, *J*=8,84 Hz, 2 H), 7,90 (d, *J*=8,34 Hz, 1 H), 8,11 (d, *J*=8,34 Hz, 3 H), 8,75 (s, 1 H), 9,79 (s, 1 H). ESI-MS: *m/z* 357,4 $(M + H)^+$.

Ejemplo 52: N-(2-aminofenil)-4–((7-fluoro-3-metil-1H-indazol-1-il)metil)benzamida



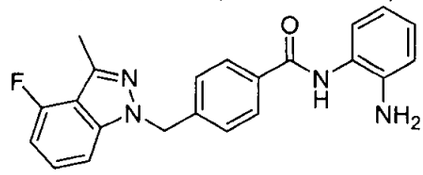
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,51 (s, 3 H), 4,86 (s, 2 H), 5,62 - 5,71 (m, 2 H), 6,51 - 6,59 (m, 1 H), 6,73 (d, *J*=7,83 Hz, 1 H), 6,89 - 6,97 (m, 1 H), 7,04 - 7,14 (m, 2 H), 7,15 - 7,25 (m, 3 H), 7,56 (d, *J*=8,08 Hz, 1 H), 7,87 (d, *J*=7,83 Hz, 2 H), 9,56 (s, 1 H). ESI-MS: *m/z* 375,4 $(M + H)^+$.

Ejemplo 53: N-(2-aminofenil)-4–((7-fluoro-3-metil-2H-indazol-2-il)metil)benzamida



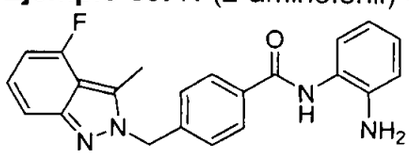
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,61 (s, 3 H), 4,87 (s, 2 H), 5,74 (s, 2 H), 6,53 - 6,59 (m, 1 H), 6,74 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,91 - 7,02 (m, 3 H), 7,12 (d, *J*=7,58 Hz, 1 H), 7,29 (d, *J*=8,08 Hz, 2 H), 7,51 (d, *J*=8,34 Hz, 1 H), 7,93 (d, *J*=8,08 Hz, 2 H), 9,61 (s, 1 H). ESI-MS: *m/z* 375,4 $(M + H)^+$.

Ejemplo 54: N-(2-aminofenil)-4–((4–fluoro-3-metil-1H-indazol-1-il)metil)benzamida



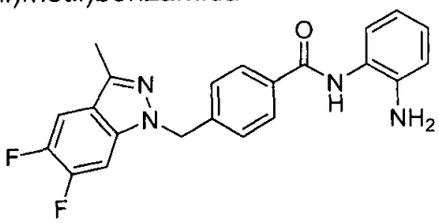
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,53 - 2,58 (m, 3 H), 4,86 (s, 2 H), 5,65 (s, 2 H), 6,51 - 6,59 (m, 1 H), 6,74 (dd, *J*=7,83, 1,26 Hz, 1 H), 6,84 (dd, *J*=10,86, 7,58 Hz, 1 H), 6,90 - 6,97 (m, 1 H), 7,11 (d, *J*=7,83 Hz, 1 H), 7,25 - 7,36 (m, 3 H), 7,48 (d, *J*=8,59 Hz, 1 H), 7,88 (d, *J*=8,08 Hz, 2 H), 9,56 (s, 1 H). ESI-MS: *m/z* 375,4 $(M + H)^+$.

Ejemplo 55: N-(2-aminofenil)-4–((4–fluoro-3-metil-2H-indazol-2-il)metil)benzamida



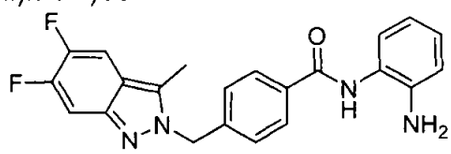
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,65 - 2,71 (m, 3 H), 4,87 (s, 2 H), 5,71 (s, 2 H), 6,53 - 6,60 (m, 1 H), 6,66 - 6,77 (m, 2 H), 6,91 - 6,98 (m, 1 H), 7,09 - 7,19 (m, 2 H), 7,29 (d, *J*=8,08 Hz, 2 H), 7,36 (d, *J*=8,59 Hz, 1 H), 7,92 (d, *J*=8,34 Hz, 2 H), 9,61 (s, 1 H). ESI-MS: *m/z* 375,4 $(M + H)^+$.

Ejemplo 56: N-(2-aminofenil)-4–((5,6-difluoro-3-metil-1H-indazol-1-il)metil)benzamida



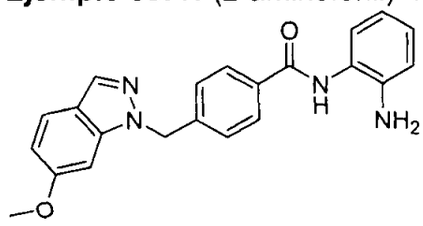
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,45 (s, 3 H), 4,86 (s, 2 H), 5,60 (s, 2 H), 6,51 - 6,60 (m, 1 H), 6,74 (d, *J*=8,08 Hz, 1 H), 6,89 - 6,98 (m, 1 H), 7,12 (d, *J*=7,83 Hz, 1 H), 7,32 (d, *J*=7,83 Hz, 2 H), 7,78 - 7,84 (m, 1 H), 7,85 - 7,91 (m, 3 H), 9,56 (s, 1 H). ESI-MS: *m/z* 393,4 $(M + H)^+$.

Ejemplo 57: N-(2-aminofenil)-4–((5,6-difluoro-3-metil-2H-indazol-2-il)metil)benzamida



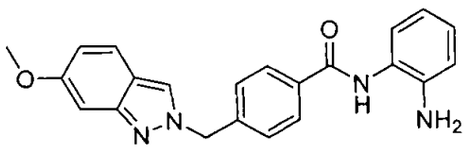
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,57 (s, 3 H), 4,98 (s, 1 H), 5,67 (s, 2 H), 6,58 (s, 1 H), 6,76 (s, 1 H), 6,95 (s, 1 H), 7,13 (s, 1 H), 7,27 (s, 2 H), 7,55 (s, 1 H), 7,75 (s, 1 H), 7,90 (s, 3 H), 9,62 (s, 1 H). ESI-MS: *m/z* 393,4 $(M + H)^+$.

Ejemplo 58: N-(2-aminofenil)-4–((6-metoxi-1H-indazol-1-il)metil)benzamida



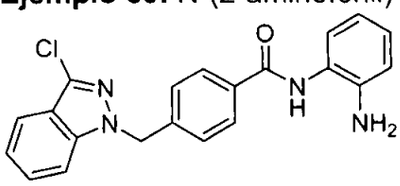
^{1}H NMR (400 MHz, CLOROFORM-*d*) δ ppm 3,31 (s, 3 H), 4,85 (s, 2 H), 5,68 (s, 2 H), 6,56 (s, 1 H), 6,72 - 6,79 (m, 2 H), 6,93 (s, 1 H), 7,11 (s, 1 H), 7,20 (s, 1 H), 7,30 (d, *J*=8,08 Hz, 2 H), 7,61 (s, 1 H), 7,88 (d, *J*=8,08 Hz, 2 H), 7,98 (s, 1 H), 9,56 (s, 1 H). ESI-MS: *m/z* 373,4 $(M + H)^+$.

Ejemplo 59: N-(2-aminofenil)-4–((6-metoxi-2H-indazol-2-il)metil)benzamida



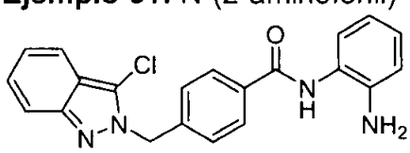
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,71 - 3,79 (m, 3 H), 4,87 (s, 2 H), 5,63 (s, 2 H), 6,51 - 6,62 (m, 1 H), 6,64 - 6,71 (m, 1 H), 6,72 - 6,78 (m, 1 H), 6,90 (d, *J*=1,77 Hz, 1 H), 6,91 - 6,97 (m, 1 H), 7,13 (d, *J*=7,83 Hz, 1 H), 7,38 (d, *J*=8,34 Hz, 2 H), 7,57 (d, *J*=9,09 Hz, 1 H), 7,92 (d, *J*=8,08 Hz, 2 H), 8,38 (s, 1 H), 9,60 (s, 1 H). ESI-MS: *m/z* 373,4 $(M + H)^+$.

Ejemplo 60: N-(2-aminofenil)-4–((3-cloro-1H-indazol-1-il)metil)benzamida



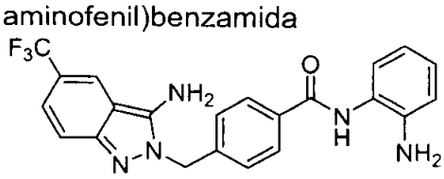
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 4,86 (s, 2 H), 5,72 (s, 2 H), 6,52 - 6,59 (m, 1 H), 6,74 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,90 - 6,97 (m, 1 H), 7,11 (d, *J*=6,57 Hz, 1 H), 7,22 - 7,30 (m, 1 H), 7,35 (d, *J*=8,34 Hz, 2 H), 7,47 - 7,54 (m, 1 H), 7,68 (d, *J*=8,08 Hz, 1 H), 7,82 (d, J=8,59 Hz, 1 H), 7,89 (d, J=8,34 Hz, 2 H), 9,57 (s, 1 H). ESI-MS: m/z 377,8 (M + H)+.

Ejemplo 61: N-(2-aminofenil)-4–((3-cloro-2H-indazol-2-il)metil)benzamida



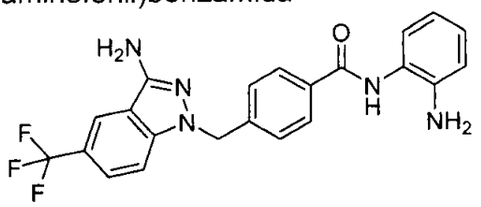
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,87 (s, 2 H), 5,73 - 5,82 (m, 2 H), 6,51 - 6,61 (m, 1 H), 6,74 (d, *J*=8,08 Hz, 1 H), 6,90 - 6,99 (m, 1 H), 7,10 - 7,19 (m, 2 H), 7,29 - 7,37 (m, 3 H), 7,53 (s, 1 H), 7,57 - 7,68 (m, 2 H), 7,93 (d, *J*=7,83 Hz, 2 H), 9,61 (s, 1 H). ESI-MS: *m/z* 377,8 $(M + H)^+$.

Ejemplo 62: 4–((3-amino-5-(trifluorometil)-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida



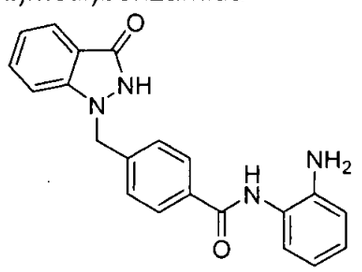
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,86 (s, 2 H), 5,47 (s, 2 H), 6,53 - 6,60 (m, 1 H), 6,73 - 6,80 (m, 3 H), 6,90 - 6,97 (m, 1 H), 7,13 (d, *J*=7,58 Hz, 1 H), 7,20 - 7,25 (m, 1 H), 7,25 - 7,34 (m, 3 H), 7,90 (d, *J*=8,08 Hz, 2 H), 8,17 (s, 1 H), 9,59 (s, 1 H). ESI-MS: *m/z* 425,5 $(M + H)^+$.

Ejemplo 63: 4–((3-amino-5-(trifluorometil)-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida



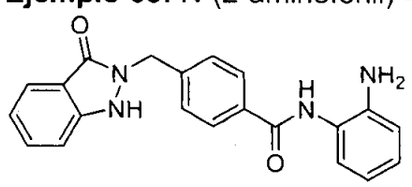
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,85 (s, 2 H), 5,45 (s, 2 H), 5,85 (s, 2 H), 6,56 (td, *J*=7,58, 1,26 Hz, 1 H), 6,74 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,89 - 6,97 (m, 1 H), 7,10 (s, 1 H), 7,28 (d, *J*=8,08 Hz, 2 H), 7,50 - 7,57 (m, 1 H), 7,66 (d, *J*=8,84 Hz, 1 H), 7,87 (d, *J*=8,08 Hz, 2 H), 8,20 (s, 1 H), 9,55 (s, 1 H). ESI-MS: *m/z* 425,5 $(M + H)^+$.

Ejemplo 64: N-(2-aminofenil)-4–((3-oxo-2,3-dihidro-1H-indazol-1-il)metil)benzamida



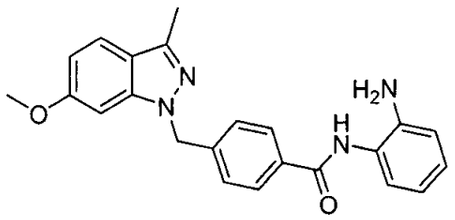
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 5,46 (s, 2 H), 6,92 (s, 1 H), 7,01 (t, *J*=7,33 Hz, 2 H), 7,12 (s, 1 H), 7,25 (s, 1 H), 7,33 (d, *J*=7,83 Hz, 3 H), 7,55 (d, *J*=8,34 Hz, 1 H), 7,64 (d, *J*=8,08 Hz, 1 H), 7,90 (d, *J*=7,58 Hz, 2 H), 9,92 (s, 1 H). ESI-MS: *m/z* 359,3 $(M + H)^+$.

Ejemplo 65: N-(2-aminofenil)-4–((3-oxo-1H-indazol-2(3H)-il)metil)benzamida



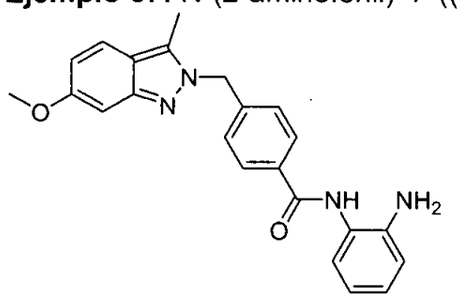
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 5,51 (s, 2 H), 6,89 (s, 1 H), 7,02 (s, 2 H), 7,15 (s, 1 H), 7,27 (s, 1 H), 7,37 (s, 2 H), 7,66 (s, 3 H), 8,02 (d, *J*=7,33 Hz, 2 H), 9,96 (s, 1 H), 11,98 (s, 1 H). ESI-MS: *m/z* 359,3 $(M + H)^+$.

Ejemplo 66: N-(2-aminofenil)-4–((6-metoxi-3-metil-1H-indazol-1-il)metil)benzamida



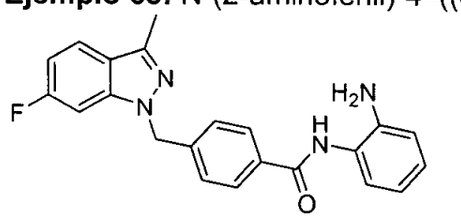
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,41 - 2,46 (m, 3 H), 3,78 - 3,84 (m, 3 H), 4,88 (s, 2 H), 5,60 (s, 2 H), 6,54 - 6,62 (m, 1 H), 6,72 - 6,79 (m, 2 H), 6,92 - 6,99 (m, 1 H), 7,11 - 7,18 (m, 2 H), 7,32 (d, *J*=8,34 Hz, 2 H), 7,58 (d, *J*=8,59 Hz, 1 H), 7,90 (d, *J*=8,34 Hz, 2 H), 9,58 (s, 1 H). ESI-MS: *m/z* 387,2 $(M + H)^+$.

Ejemplo 67: N-(2-aminofenil)-4–((6-metoxi-3-metil-2H-indazol-2-il)metil)benzamida



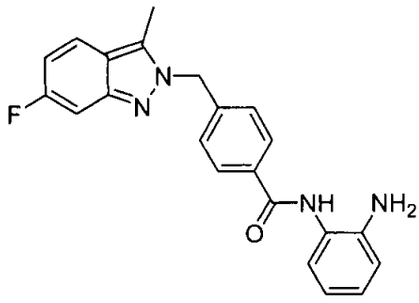
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,55 (s, 3 H), 3,79 (s, 3 H), 4,88 (s, 2 H), 5,63 (s, 2 H), 6,55 - 6,62 (m, 1 H), 6,62 - 6,68 (m, 1 H), 6,77 (dd, *J*=7,83, 1,26 Hz, 1 H), 6,86 (d, *J*=2,02 Hz, 1 H), 6,93 - 7,00 (m, 1 H), 7,14 (d, *J*=7,33 Hz, 1 H), 7,27 (d, *J*=8,34 Hz, 2 H), 7,55 (d, *J*=9,09 Hz, 1 H), 7,93 (d, *J*=8,08 Hz, 2 H), 9,62 (s, 1 H). ESI-MS: *m/z* 387,2 $(M + H)^+$.

Ejemplo 68: N-(2-aminofenil)-4–((6-fluoro-3-metil-1H-indazol-1-il)metil)benzamida



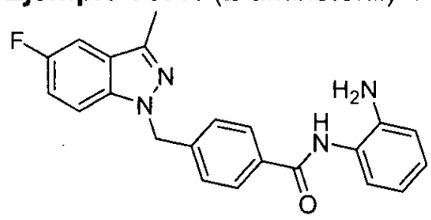
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,47 - 2,49 (m, 3 H), 4,87 (s, 2 H), 5,61 (s, 2 H), 6,55 - 6,61 (m, 1 H), 6,76 (dd, *J*=8,08, 1,52 Hz, 1 H), 6,93 - 7,02 (m, 2 H), 7,14 (d, *J*=7,83 Hz, 1 H), 7,34 (d, *J*=8,34 Hz, 2 H), 7,54 - 7,61 (m, 1 H), 7,77 (dd, *J*=8,84, 5,31 Hz, 1 H), 7,90 (d, *J*=8,34 Hz, 2 H), 9,57 (s, 1 H). ESI-MS: *m/z* 375,3 $(M + H)^+$.

Ejemplo 69: N-(2-aminofenil)-4–((6-fluoro-3-metil-2H-indazol-2-il)metil)benzamida



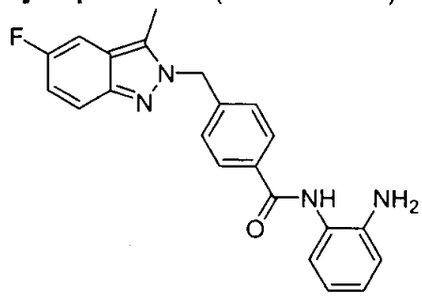
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,59 - 2,63 (m, 3 H), 4,88 (s, 2 H), 5,69 (s, 2 H), 6,53 - 6,62 (m, 1 H), 6,78 (dd, *J*=7,75, 1,52 Hz, 1 H), 6,87 - 6,99 (m, 2 H), 7,15 (d, *J*=7,33 Hz, 1 H), 7,24 - 7,35 (m, 3 H), 7,77 (dd, *J*=9,09, 5,56 Hz, 1 H), 7,94 (d, *J*=8,08 Hz, 2 H), 9,62 (s, 1 H). ESI-MS: *m/z* 375,3 $(M + H)^+$.

Ejemplo 70: N-(2-aminofenil)-4–((5-fluoro-3-metil-1H-indazol-1-il)metil)benzamida



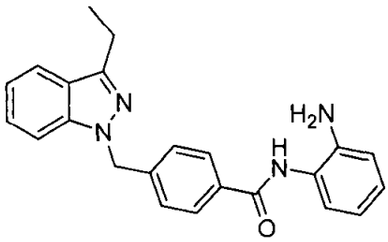
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,46 - 2,49 (m, 3 H), 4,87 (s, 2 H), 5,66 (s, 2 H), 6,53 - 6,62 (m, 1 H), 6,77 (d, *J*=1,26 Hz, 1 H), 6,91 - 7,01 (m, 1 H), 7,14 (d, *J*=7,07 Hz, 1 H), 7,25 - 7,35 (m, 3 H), 7,55 (d, *J*=2,27 Hz, 1 H), 7,70 (dd, *J*=9,09, 4,29 Hz, 1 H), 7,89 (d, *J*=8,08 Hz, 2 H), 9,57 (s, 1 H). ESI-MS: *m/z* 375,3 $(M + H)^+$.

Ejemplo 71: N-(2-aminofenil)-4–((5-fluoro-3-metil-2H-indazol-2-il)metil)benzamida



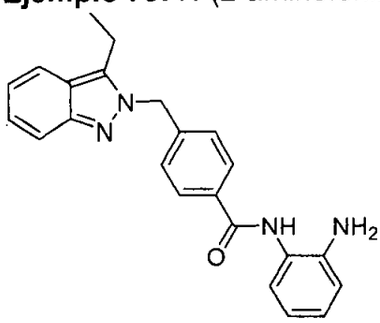
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,58 (s, 3 H), 4,88 (s, 2 H), 5,72 (s, 2 H), 6,55 - 6,62 (m, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,93 - 7,00 (m, 1 H), 7,14 (td, *J*=9,35, 2,53 Hz, 2 H), 7,29 (d, *J*=8,34 Hz, 2 H), 7,46 (dd, *J*=9,60, 2,02 Hz, 1 H), 7,62 (dd, *J*=9,35, 4,55 Hz, 1 H), 7,94 (d, *J*=8,34 Hz, 2 H), 9,62 (s, 1 H). ESI-MS: *m/z* 375,4 $(M + H)^+$.

Ejemplo 72: N-(2-aminofenil)-4–((3-etil-1H-indazol-1-il)metil)benzamida



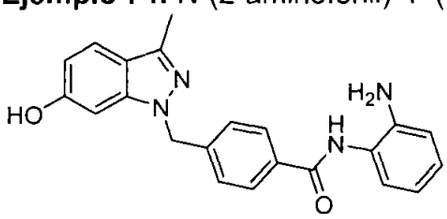
1H NMR (400 MHz, DMSO-d_6) δ ppm 1,29 - 1,36 (m, 3 H), 2,95 (q, *J*=7,58 Hz, 2 H), 4,87 (s, 2 H), 5,67 (s, 2 H), 6,53 - 6,62 (m, 1 H), 6,72 - 6,81 (m, 1 H), 6,91 - 7,00 (m, 1 H), 7,08 - 7,18 (m, 2 H), 7,27 - 7,39 (m, 3 H), 7,63 (d, *J*=8,34 Hz, 1 H), 7,77 (d, *J*=8,08 Hz, 1 H), 7,89 (d, *J*=8,08 Hz, 1 H), 9,57 (s, 1 H). ESI-MS: *m/z* 371,4 $(M + H)^+$.

Ejemplo 73: N-(2-aminofenil)-4–((3-etil-2H-indazol-2-il)metil)benzamida



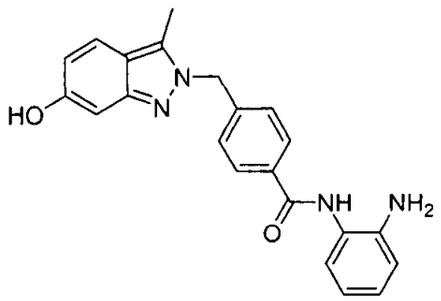
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,09 - 1,20 (m, 3 H), 3,09 (q, *J*=7,58 Hz, 2 H), 4,89 (s, 2 H), 5,75 (s, 2 H), 6,55 - 6,62 (m, 1 H), 6,74 - 6,80 (m, 1 H), 6,93 - 7,03 (m, 2 H), 7,14 (d, *J*=7,58 Hz, 1 H), 7,21 - 7,31 (m, 3 H), 7,56 (d, *J*=8,84 Hz, 1 H), 7,72 (d, *J*=8,59 Hz, 1 H), 7,93 (d, *J*=8,34 Hz, 2 H), 9,63 (s, 1 H). ESI-MS: *m/z* 371,4 $(M + H)^+$.

Ejemplo 74: N-(2-aminofenil)-4–((6-hidroxi-3-metil-1H-indazol-1-il)metil)benzamida



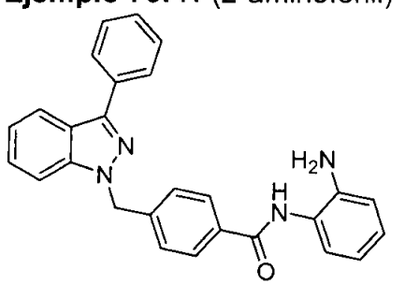
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,42 (s, 3 H), 5,52 (s, 2 H), 6,59 - 6,69 (m, 1 H), 6,74 (d, *J*=1,77 Hz, 1 H), 6,94 (s, 1 H), 7,04 (s, 1 H), 7,08 - 7,20 (m, 2 H), 7,23 - 7,34 (m, 3 H), 7,50 (d, *J*=8,84 Hz, 1 H), 7,92 (d, *J*=8,34 Hz, 2 H), 9,95 (s, 1 H). ESI-MS: *m/z* 373,3 $(M + H)^+$.

Ejemplo 75: N-(2-aminofenil)-4–((6-hidroxi-3-metil-2H-indazol-2-il)metil)benzamida



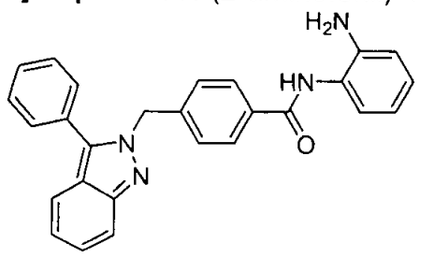
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 2,54 (s, 3 H), 3,97 (s, 1 H), 5,62 (s, 2 H), 6,56 - 6,65 (m, 1 H), 6,69 (d, *J*=1,52 Hz, 1 H), 7,01 (s, 1 H), 7,10 (d, *J*=7,83 Hz, 1 H), 7,14 - 7,23 (m, 1 H), 7,30 (d, *J*=8,08 Hz, 3 H), 7,52 (d, *J*=8,84 Hz, 1 H), 7,96 (d, *J*=8,34 Hz, 2 H), 10,07 (s, 1 H). ESI-MS: *m/z* 373,3 $(M + H)^+$.

Ejemplo 76: N-(2-aminofenil)-4–((3-fenil-1H-indazol-1-il)metil)benzamida



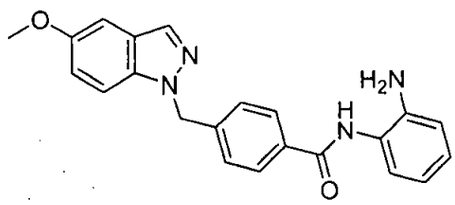
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,86 (s, 2 H), 5,78 - 5,87 (m, 2 H), 6,53 - 6,61 (m, 1 H), 6,75 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,91 - 6,99 (m, 1 H), 7,13 (d, *J*=7,83 Hz, 1 H), 7,22 - 7,30 (m, 1 H), 7,38 - 7,49 (m, 3 H), 7,50 - 7,57 (m, 2 H), 7,80 (d, *J*=8,34 Hz, 1 H), 7,91 (d, *J*=8,34 Hz, 2 H), 8,00 (d, *J*=7,07 Hz, 2 H), 8,11 (d, *J*=8,08 Hz, 1 H), 9,57 (s, 1 H). ESI-MS: *m/z* 419,4 $(M + H)^+$.

Ejemplo 77: N-(2-aminofenil)-4–((3-fenil-2H-indazol-2-il)metil)benzamida



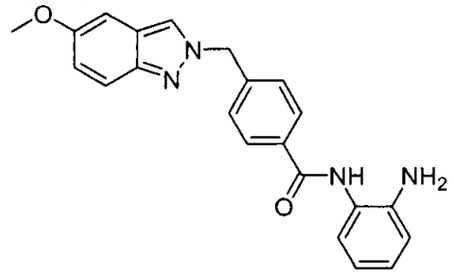
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,87 (s, 2 H), 5,77 (s, 2 H), 6,54 - 6,61 (m, 1 H), 6,76 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,92 - 6,99 (m, 1 H), 7,09 - 7,17 (m, 3 H), 7,30 - 7,37 (m, 1 H), 7,52 - 7,63 (m, 3 H), 7,69 (d, *J*=8,84 Hz, 1 H), 7,89 (d, *J*=8,08 Hz, 2 H), 9,60 (s, 1 H). ESI-MS: *m/z* 419,4 $(M + H)^+$.

Ejemplo 78: N-(2-aminofenil)-4–((5-metoxi-1H-indazol-1-il)metil)benzamida



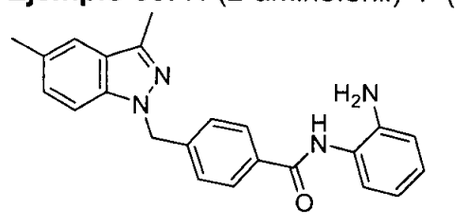
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 3,78 (s, 3 H), 5,71 (s, 2 H), 6,53 - 6,64 (m, 1 H), 6,78 (s, 1 H), 6,91 - 7,00 (m, 1 H), 7,01 - 7,08 (m, 1 H), 7,13 (s, 1 H), 7,20 (d, *J*=2,27 Hz, 1 H), 7,30 (d, *J*=8,08 Hz, 2 H), 7,61 (d, *J*=9,09 Hz, 1 H), 7,89 (d, *J*=8,08 Hz, 2 H), 8,01 (s, 1 H), 9,59 (s, 1 H). ESI-MS: *m/z* 373,3 $(M + H)^+$.

Ejemplo 79: N-(2-aminofenil)-4–((5-metoxi-2H-indazol-2-il)metil)benzamida



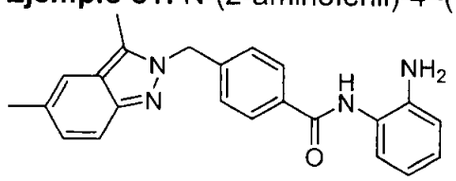
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,77 (s, 3 H), 5,69 (s, 2 H), 6,84 - 6,95 (m, 2 H), 6,95 - 7,05 (m, 2 H), 7,07 - 7,15 (m, 1 H), 7,26 (d, *J*=7,58 Hz, 1 H), 7,42 (d, *J*=8,34 Hz, 2 H), 7,51 (d, *J*=9,09 Hz, 1 H), 7,96 (d, *J*=8,34 Hz, 2 H), 8,35 (s, 1 H), 9,91 (s, 1 H). ESI-MS: *m/z* 373,3 $(M + H)^+$.

Ejemplo 80: N-(2-aminofenil)-4–((3,5-dimetil-1H-indazol-1-il)metil)benzamida



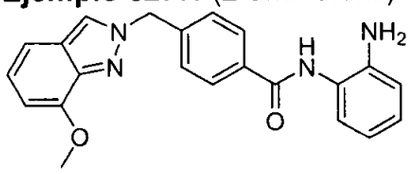
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,40 (s, 3 H), 2,44 - 2,48 (m, 3 H), 4,87 (s, 2 H), 5,62 (s, 2 H), 6,54 - 6,61 (m, 1 H), 6,76 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,92 - 6,99 (m, 1 H), 7,13 (d, *J*=7,07 Hz, 1 H), 7,20 (dd, *J*=8,59, 1,26 Hz, 1 H), 7,28 (d, *J*=8,08 Hz, 2 H), 7,49 (s, 1 H), 7,52 (d, *J*=8,59 Hz, 1 H), 7,88 (d, *J*=8,08 Hz, 2 H), 9,57 (s, 1 H). ESI-MS: *m/z* 371,4 $(M + H)^+$.

Ejemplo 81: N-(2-aminofenil)-4–((3,5-dimetil-2H-indazol-2-il)metil)benzamida



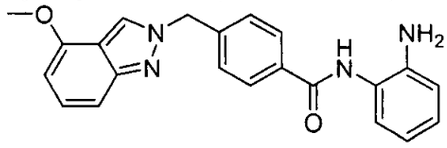
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,36 (s, 3 H), 2,56 (s, 3 H), 4,88 (s, 2 H), 5,69 (s, 2 H), 6,54 - 6,62 (m, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,93 - 7,00 (m, 1 H), 7,07 (dd, *J*=8,84, 1,52 Hz, 1 H), 7,14 (d, *J*=7,07 Hz, 1 H), 7,26 (d, *J*=8,34 Hz, 2 H), 7,41 (s, 1 H), 7,45 (d, *J*=8,84 Hz, 1 H), 7,93 (d, *J*=8,08 Hz, 2 H), 9,62 (s, 1 H). ESI-MS: *m/z* 371,4 $(M + H)^+$.

Ejemplo 82: N-(2-aminofenil)-4–((7-metoxi-2H-indazol-2-il)metil)benzamida



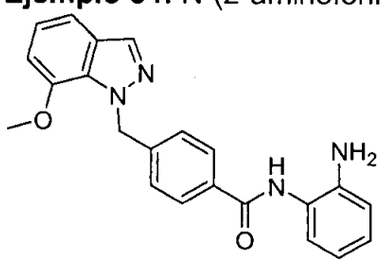
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,88 (s, 3 H), 4,89 (s, 2 H), 5,70 (s, 2 H), 6,54 - 6,65 (m, 2 H), 6,76 (d, *J*=7,58 Hz, 1 H), 6,90 - 7,01 (m, 2 H), 7,15 (s, 1 H), 7,24 (d, *J*=8,34 Hz, 1 H), 7,41 (d, *J*=7,58 Hz, 2 H), 7,95 (d, *J*=8,08 Hz, 2 H), 8,47 (s, 1 H), 9,62 (s, 1 H). ESI-MS: *m/z* 373,1 $(M + H)^+$.

Ejemplo 83: N-(2-aminofenil)-4–((4–metoxi-2H-indazol-2-il)metil)benzamida



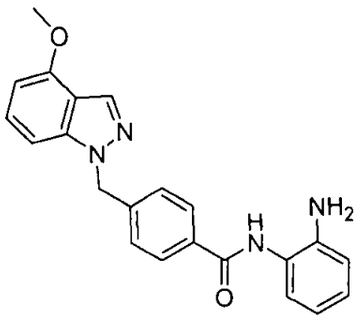
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,89 (s, 3 H), 4,89 (s, 2 H), 5,69 (s, 2 H), 6,36 - 6,46 (m, 1 H), 6,53 - 6,64 (m, 1 H), 6,76 (d, *J*=8,08 Hz, 1 H), 6,91 - 7,02 (m, 1 H), 7,11 - 7,20 (m, 3 H), 7,42 (d, *J*=7,83 Hz, 2 H), 7,94 (d, *J*=7,83 Hz, 2 H), 8,55 (s, 1 H), 9,62 (s, 1 H). ESI-MS: *m/z* 373,2 $(M + H)^+$.

Ejemplo 84: N-(2-aminofenil)-4–((7-metoxi-1H-indazol-1-il)metil)benzamida



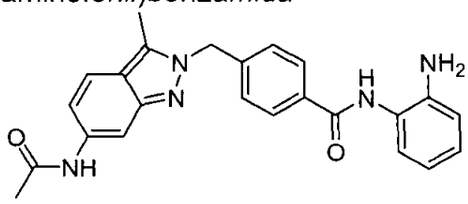
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,92 (s, 3 H), 4,87 (s, 2 H), 5,85 (s, 2 H), 6,54 - 6,61 (m, 1 H), 6,76 (d, *J*=7,83 Hz, 1 H), 6,87 (d, *J*=7,58 Hz, 1 H), 6,92 - 6,99 (m, 1 H), 7,03 - 7,10 (m, 1 H), 7,13 (d, *J*=7,83 Hz, 1 H), 7,24 (d, *J*=7,83 Hz, 2 H), 7,32 (d, *J*=8,08 Hz, 1 H), 7,88 (d, *J*=7,58 Hz, 2 H), 8,09 (s, 1 H), 9,56 (s, 1 H). ESI-MS: *m/z* 373,3 $(M + H)^+$.

Ejemplo 85: N-(2-aminofenil)-4–((4–metoxi-1H-indazol-1-il)metil)benzamida



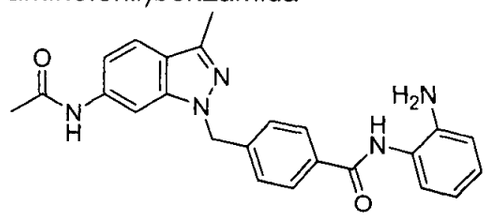
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,93 (s, 3 H), 4,87 (s, 2 H), 5,72 (s, 2 H), 6,54 - 6,63 (m, 2 H), 6,76 (d, *J*=7,83 Hz, 1 H), 6,90 - 7,00 (m, 1 H), 7,13 (d, *J*=7,83 Hz, 1 H), 7,23 - 7,33 (m, 4 H), 7,89 (d, *J*=7,83 Hz, 2 H), 8,10 (s, 1 H), 9,58 (s, 1 H). ESI-MS: *m/z* 373,3 $(M + H)^+$.

Ejemplo 86: 4–((6-acetamido-3-metil-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida



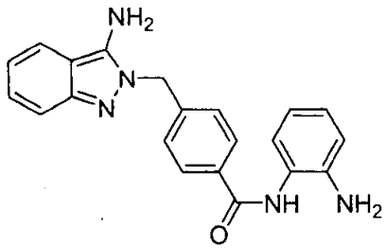
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,06 (s, 3 H), 2,53 - 2,57 (m, 2 H), 4,88 (s, 2 H), 5,66 (s, 2 H), 6,53 - 6,63 (m, 1 H), 6,76 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,93 - 7,04 (m, 2 H), 7,14 (d, *J*=7,07 Hz, 1 H), 7,27 (d, *J*=8,08 Hz, 2 H), 7,59 (d, *J*=9,09 Hz, 1 H), 7,93 (d, *J*=8,08 Hz, 2 H), 7,99 (s, 1 H), 9,62 (s, 1 H), 9,91 (s, 1 H). ESI-MS: *m/z* 414,3 $(M + H)^+$.

Ejemplo 87: 4–((6-acetamido-3-metil-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida



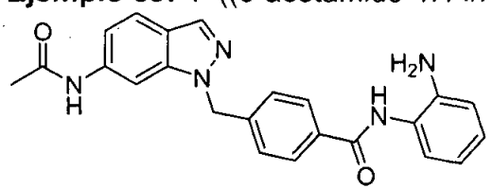
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,06 (s, 3 H), 2,44 - 2,48 (m, 3 H), 4,88 (s, 2 H), 5,56 (s, 2 H), 6,53 - 6,63 (m, 1 H), 6,73 - 6,81 (m, 1 H), 6,91 - 7,01 (m, 1 H), 7,08 - 7,19 (m, 2 H), 7,24 (d, *J*=8,08 Hz, 2 H), 7,63 (d, *J*=8,59 Hz, 1 H), 7,89 (d, *J*=8,08 Hz, 2 H), 8,01 (s, 1 H), 9,58 (s, 1 H), 10,09 (s, 1 H). ESI-MS: *m/z* 414,3 $(M + H)^+$.

Ejemplo 88: 4–((3-amino-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida



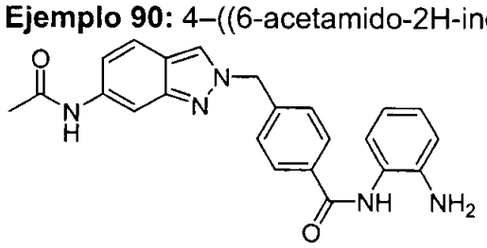
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,88 (s, 2 H), 5,46 (s, 2 H), 6,27 (s, 2 H), 6,58 (t, *J*=7,45 Hz, 1 H), 6,65 (t, *J*=7,33 Hz, 1 H), 6,76 (d, *J*=8,08 Hz, 1 H), 6,96 (t, *J*=7,58 Hz, 1 H), 7,05 (t, *J*=7,58 Hz, 1 H), 7,12 - 7,20 (m, 2 H), 7,29 (d, *J*=7,83 Hz, 2 H), 7,63 (d, *J*=8,34 Hz, 1 H), 7,91 (d, *J*=7,83 Hz, 2 H), 9,6 (s, 1H). ESI-MS: *m/z* 358,2 $(M + H)^+$.

Ejemplo 89: 4–((6-acetamido-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida



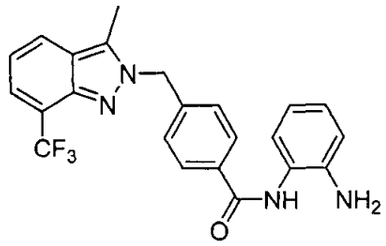
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,93 - 2,13 (m, 3 H), 4,87 (s, 2 H), 5,66 (s, 2 H), 6,53 - 6,61 (m, 1 H), 6,75 (dd, *J*=7,96, 1,39 Hz, 1 H), 6,91 - 6,98 (m, 1 H), 7,13 (dd, *J*=8,72, 1,64 Hz, 2 H), 7,24 (d, *J*=8,34 Hz, 2 H), 7,69 (d, *J*=8,59 Hz, 1 H), 7,90 (d, *J*=8,08 Hz, 2 H), 8,05 (s, 1 H), 8,08 (s, 1 H), 9,59 (s, 1 H), 10,11 (s, 1 H). ESI-MS: *m/z* 400,2 $(M + H)^+$.

Ejemplo 90: 4–((6-acetamido-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida



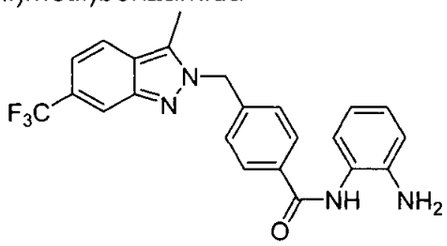
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,06 (s, 3 H), 4,88 (s, 2 H), 5,67 (s, 2 H), 6,51 - 6,65 (m, 1 H), 6,76 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,89 - 7,00 (m, 1 H), 7,06 (dd, *J*=8,84, 1,77 Hz, 1 H), 7,14 (d, *J*=7,33 Hz, 1 H), 7,40 (d, *J*=8,08 Hz, 2 H), 7,63 (d, *J*=8,34 Hz, 1 H), 7,94 (d, *J*=8,08 Hz, 2 H), 8,04 (s, 1 H), 8,42 (s, 1 H), 9,62 (s, 1 H), 9,93 (s, 1 H). ESI-MS: *m/z* 400,2 $(M + H)^+$.

Ejemplo 91: N-(2-aminofenil)-4–((3-metil-7-(trifluorometil)-2H-indazol-2-il)metil)benzamida



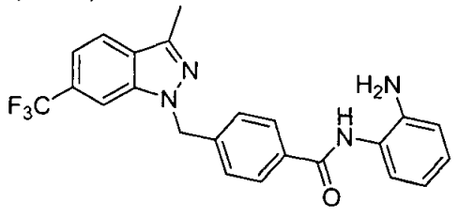
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,66 (s, 3 H), 4,89 (s, 2 H), 5,82 (s, 2 H), 6,58 (t, *J*=7,45 Hz, 1 H), 6,76 (d, *J*=7,83 Hz, 1 H), 6,96 (t, *J*=7,58 Hz, 1 H), 7,14 (ddd, *J*=7,26, 3,92, 3,73 Hz, 2 H), 7,28 (d, *J*=8,08 Hz, 2 H), 7,66 (d, *J*=6,82 Hz, 1 H), 7,94 (d, *J*=8,08 Hz, 2 H), 8,05 (d, *J*=8,34 Hz, 1 H), 9,62 (s, 1H). ESI-MS: *m/z* 425,2 $(M + H)^+$.

Ejemplo 92: N-(2-aminofenil)-4–((3-metil-6-(trifluorometil)-2H-indazol-2-il)metil)benzamida



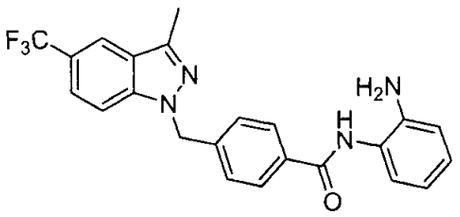
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,67 (s, 3 H), 4,88 (s, 2 H), 5,80 (s, 2 H), 6,58 (t, *J*=7,58 Hz, 1 H), 6,76 (d, *J*=7,83 Hz, 1 H), 6,96 (t, *J*=7,71 Hz, 1 H), 7,14 (d, *J*=7,83 Hz, 1 H), 7,22 (d, *J*=8,84 Hz, 1 H), 7,30 (d, *J*=8,08 Hz, 2 H), 7,92 - 8,02 (m, 4 H), 9,63 (s, 1H). ESI-MS: *m/z* 425,2 $(M + H)^+$.

Ejemplo 93: N-(2-aminofenil)-4–((3-metil-6-(trifluorometil)-1H-indazol-1-il)metil)benzamida



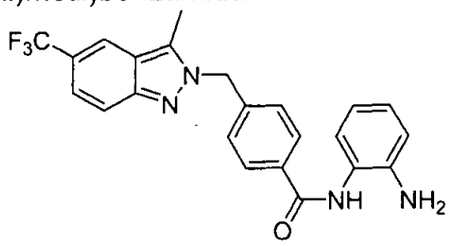
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,55 (s, 3 H), 4,87 (s, 2 H), 5,79 (s, 2 H), 6,57 (t, *J*=7,33 Hz, 1 H), 6,75 (d, *J*=8,08 Hz, 1 H), 6,95 (t, *J*=7,58 Hz, 1 H), 7,13 (d, *J*=7,58 Hz, 1 H), 7,33 (d, *J*=8,08 Hz, 2 H), 7,41 (d, *J*=8,59 Hz, 1 H), 7,90 (d, *J*=7,83 Hz, 2 H), 7,98 (d, *J*=8,34 Hz, 1 H), 8,24 (s, 1 H), 9,58 (s, 1H). ESI-MS: *m/z* 425,2 $(M + H)^+$.

Ejemplo 94: N-(2-aminofenil)-4–((3-metil-5-(trifluorometil)-1H-indazol-1-il)metil)benzamida



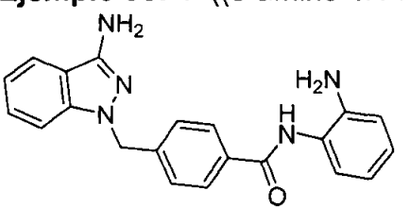
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,57 (s, 3 H), 4,87 (s, 2 H), 5,73 (s, 2 H), 6,57 (t, *J*=7,45 Hz, 1 H), 6,75 (d, *J*=7,83 Hz, 1 H), 6,95 (t, *J*=7,45 Hz, 1 H), 7,13 (d, *J*=7,58 Hz, 1 H), 7,33 (d, *J*=7,83 Hz, 2 H), 7,67 (d, *J*=8,84 Hz, 1 H), 7,90 (d, *J*=8,34 Hz, 3 H), 8,22 (s, 1 H), 9,58 (s, 1H). ESI-MS: *m/z* 425,2 $(M + H)^+$.

Ejemplo 95: N-(2-aminofenil)-4–((3-metil-5-(trifluorometil)-2H-indazol-2-il)metil)benzamida



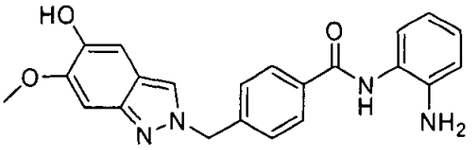
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,70 (s, 3 H), 4,88 (s, 2 H), 5,78 (s, 2 H), 6,58 (t, *J*=7,45 Hz, 1 H), 6,76 (d, *J*=8,08 Hz, 1 H), 6,93 - 6,99 (m, 1 H), 7,14 (d, *J*=7,33 Hz, 1 H), 7,31 (d, *J*=8,08 Hz, 2 H), 7,44 (d, *J*=8,84 Hz, 1 H), 7,75 (d, *J*=9,09 Hz, 1 H), 7,94 (d, *J*=8,08 Hz, 2 H), 8,25 (s, 1 H), 9,63 (s, 1H). ESI-MS: *m/z* 425,2 $(M + H)^+$.

Ejemplo 96: 4–((3-amino-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida



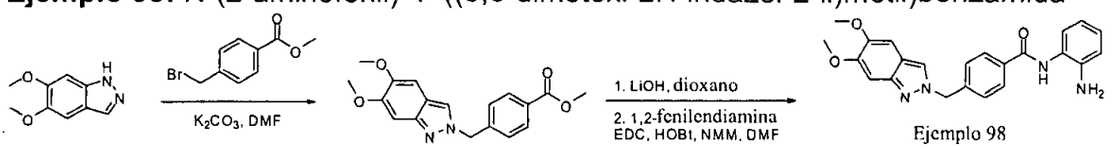
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,87 (s, 2 H), 5,39 (s, 2 H), 5,52 (s, 2 H), 6,57 (t, *J*=7,45 Hz, 1 H), 6,75 (d, *J*=7,83 Hz, 1 H), 6,94 (q, *J*=7,75 Hz, 2 H), 7,13 (d, *J*=7,58 Hz, 1 H), 7,27 (t, *J*=8,21 Hz, 3 H), 7,44 (d, *J*=8,34 Hz, 1 H), 7,70 (d, *J*=7,83 Hz, 1 H), 7,86 (d, *J*=7,83 Hz, 2 H), 9,55 (s, 1 H). ESI-MS: *m/z* 358,4 $(M + H)^+$.

Ejemplo 97: N-(2-aminofenil)-4–((5-hidroxi-6-metoxi-2H-indazol-2-il)metil)benzamida



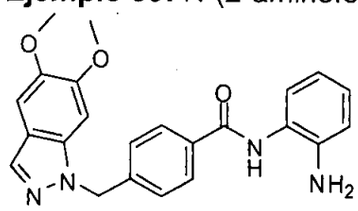
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,81 (s, 2 H) 4,89 (s, 2 H) 5,58 (s, 2 H) 6,59 (t, *J*=7,58 Hz, 1 H) 6,77 (dd, *J*=7,96, 1,39 Hz, 1 H) 6,85 (s, 1 H) 6,91 (s, 1 H) 6,96 (dd, *J*=15,16, 1,52 Hz, 1 H) 7,15 (d, *J*=7,33 Hz, 1 H) 7,36 (d, *J*=8,08 Hz, 2 H) 7,93 (d, *J*=8,08 Hz, 2 H) 8,11 (s, 1 H) 8,82 (s, 1 H) 9,62 (s, 1 H). ESI-MS: *m/z* 389,4 $(M + H)^+$.

Ejemplo 98: N-(2-aminofenil)-4–((5,6-dimetoxi-2H-indazol-2-il)metil)benzamida



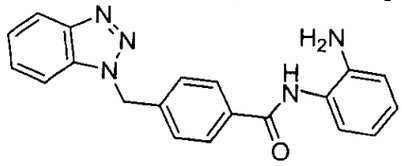
Se preparó 5,6-dimetoxi-1H-indazol de acuerdo con el procedimiento descrito en Dennler *et al.*, "Synthesis de indazoles using polyfosforic acid- I" **Tetrahedron**, **22**(9): 3131-3141 (1966), que se incorpora a la presente por completo a modo de referencia. El compuesto del título luego se preparó usando un procedimiento análogo al descrito en el Esquema 1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,78 (s, 3 H) 3,83 (s, 3 H) 4,88 (br. s., 2 H) 5,69 (s, 2 H) 6,58 (t, *J*=7,45 Hz, 1 H) 6,77 (d, *J*=1,01 Hz, 1 H) 6,96 (dd, *J*=15,16, 1,26 Hz, 1 H) 7,17 (s, 1 H) 7,13 (d, *J*=7,58 Hz, 1 H) 7,27 (s, 1 H) 7,30 (d, *J*=8,34 Hz, 2 H) 7,83 - 7,93 (m, 3 H) 9,59 (s, 1 H). ESI-MS: *m/z* 403,4 $(M + H)^+$.

Ejemplo 99: N-(2-aminofenil)-4–((5,6-dimetoxi-1H-indazol-1-il)metil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,78 (s, 3 H) 3,83 (s, 3 H) 4,88 (br. s., 2 H) 5,69 (s, 2 H) 6,58 (s, 1 H) 6,77 (d, *J*=1,01 Hz, 1 H) 6,95 (d, *J*=7,33 Hz, 1 H) 7,17 (s, 1 H) 7,13 (d, *J*=7,58 Hz, 1 H) 7,27 (s, 1 H) 7,30 (d, *J*=8,34 Hz, 2 H) 7,82 - 7,94 (m, 3 H) 9,59 (s, 1 H). ESI-MS: *m/z* 403,4 $(M + H)^+$.

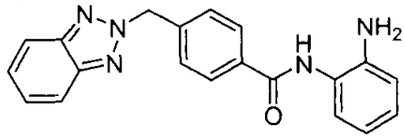
Ejemplo 100: 4–((1*H*-benzo[*d*][1,2,3]triazol-1-il)metil)–N–(2-aminofenil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,88 (s, 2 H), 6,08 (s, 2 H), 6,57 (t, *J*=7,58 Hz, 1 H), 6,74 - 6,78 (m, 1 H), 6,93 - 6,98 (m, 1 H), 7,13 (d, *J*=7,58 Hz, 1 H), 7,39 -

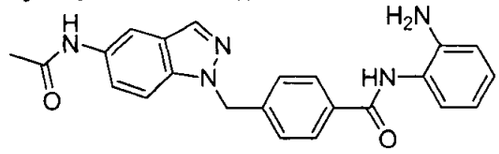
7,46 (m, 3 H), 7,55 (t, *J*=7,71 Hz, 1 H), 7,86 (d, *J*=8,34 Hz, 1 H), 7,94 (d, *J*=8,08 Hz, 2 H), 8,07 (d, *J*=8,34 Hz, 1 H), 9,60 (s, 1 H). ESI-MS: *m/z* 344,4 $(M + H)^+$.

Ejemplo 101: 4–((2*H*-benzo[*d*][1,2,3]triazol-2-il)metil)–N–(2-aminofenil)benzamida



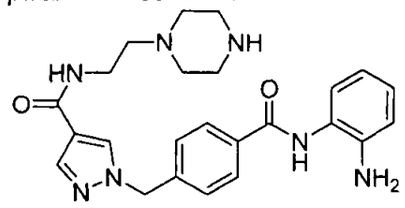
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,88 (s, 2 H), 6,07 (s, 2 H), 6,55 - 6,61 (m, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,93 - 6,99 (m, 1 H), 7,15 (d, *J*=7,58 Hz, 1 H), 7,43 - 7,48 (m, 2 H), 7,50 (d, *J*=8,34 Hz, 2 H), 7,91 - 7,99 (m, 4 H), 9,63 (s, 1 H). ESI-MS: *m/z* 344,4 $(M + H)^+$.

Ejemplo 102: 4–((5-acetamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida



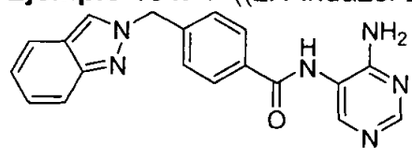
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,05 (s, 3 H), 5,70 (s, 2 H), 6,95 - 7,03 (m, 4 H), 7,06 - 7,13 (m, 1 H), 7,30 - 7,40 (m, 5 H), 7,64 (d, *J*=9,09 Hz, 1 H), 7,75 (d, *J*=8,84 Hz, 2 H), 7,86 (d, *J*=8,08 Hz, 2 H), 8,11 (d, *J*=17,68 Hz, 2 H), 9,96 (s, 1 H), 10,21 (s, 1 H). ESI-MS: *m/z* 477,3 $(M + H)^+$.

Ejemplo 103: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(piperazin-1-il)etil)-1H-pirazol-4–carboxamida



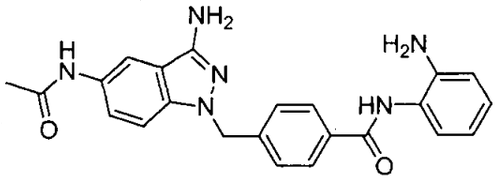
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido bis-trifluoroacético: δ ppm 3,06 (s, 2 H), 3,22 (s, 4 H), 3,30 (s, 4 H), 3,44 - 3,52 (m, 2 H), 5,46 (s, 2 H), 6,79 (t, *J*=7,33 Hz, 1 H), 6,93 (d, *J*=7,07 Hz, 1 H), 7,07 (td, *J*=7,64, 1,39 Hz, 1 H), 7,22 (d, *J*=8,59 Hz, 1 H), 7,38 (d, *J*=8,34 Hz, 2 H), 7,90 (d, *J*=0,51 Hz, 1 H), 7,97 (d, *J*=8,08 Hz, 2 H), 8,29 - 8,32 (m, 1 H), 8,32 - 8,35 (m, 1 H), 9,85 (s, 1 H). ESI-MS: *m/z* 448,4 $(M + H)^+$.

Ejemplo 104: 4–((2*H*-indazol-2-il)metil)–N–(4–aminopirimidin-5-il)benzamida



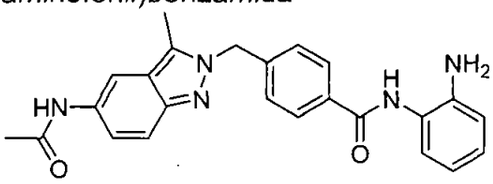
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5,74 (s, 2 H), 6,82 (s, 2 H), 7,00 - 7,08 (m, 1 H), 7,23 (dd, *J*=8,72, 6,69 Hz, 1 H), 7,43 (d, *J*=8,34 Hz, 2 H), 7,59 (d, *J*=8,84 Hz, 1 H), 7,72 (d, *J*=8,34 Hz, 1 H), 7,95 (d, *J*=8,08 Hz, 2 H), 8,15 (s, 1 H), 8,26 (s, 1 H), 8,53 (s, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 345,3 $(M + H)^+$.

Ejemplo 105: 4–((5-acetamido-3-amino-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida



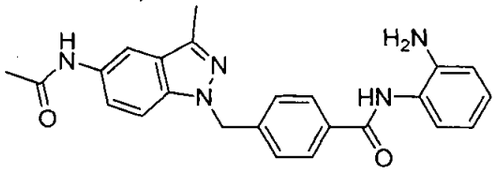
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,03 (s, 3 H), 4,86 (s, 2 H), 5,35 (s, 2 H), 5,43 (s, 2 H), 6,57 (t, *J*=7,45 Hz, 1 H), 6,75 (d, *J*=7,07 Hz, 1 H), 6,92 - 6,98 (m, 1 H), 7,13 (d, *J*=7,33 Hz, 1 H), 7,24 - 7,31 (m, 3 H), 7,35 - 7,41 (m, 1 H), 7,86 (d, *J*=7,83 Hz, 2 H), 7,96 (s, 1 H), 9,55 (s, 1 H), 9,81 (s, 1 H). ESI-MS: *m/z* 415,3 $(M + H)^+$.

Ejemplo 106: 4–((5-acetamido-3-metil-2*H*-indazol-2-il)metil)–N–(2-aminofenil)benzamida



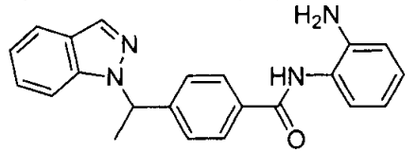
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,05 (s, 3 H), 2,53 (s, 3 H), 4,88 (s, 2 H), 5,68 (s, 2 H), 6,58 (t, *J*=7,45 Hz, 1 H), 6,76 (d, *J*=7,83 Hz, 1 H), 6,93 - 6,98 (m, 1 H), 7,14 (d, *J*=7,83 Hz, 1 H), 7,20 (dd, *J*=9,22, 1,64 Hz, 1 H), 7,27 (d, *J*=8,34 Hz, 2 H), 7,49 (d, *J*=9,09 Hz, 1 H), 7,93 (d, *J*=8,08 Hz, 2 H), 8,05 (s, 1 H), 9,62 (s, 1 H), 9,85 (s, 1 H). ESI-MS: *m/z* 414,3 $(M + H)^+$.

Ejemplo 107: 4–((5-acetamido-3-metil-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida



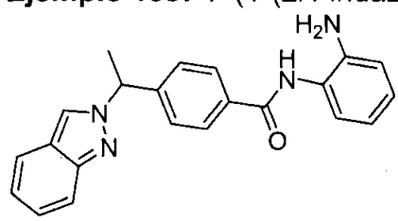
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,04 (s, 3 H), 2,45 (s, 3 H), 4,87 (s, 2 H), 5,61 (s, 2 H), 6,54 - 6,60 (m, 1 H), 6,75 (dd, *J*=7,96, 1,39 Hz, 1 H), 6,92 - 6,98 (m, 1 H), 7,13 (d, *J*=7,33 Hz, 1 H), 7,30 (d, *J*=8,34 Hz, 2 H), 7,38 (dd, *J*=9,09, 1,77 Hz, 1 H), 7,57 (d, *J*=8,84 Hz, 1 H), 7,88 (d, *J*=8,34 Hz, 2 H), 8,04 (d, *J*=1,26 Hz, 1 H), 9,57 (s, 1 H), 9,94 (s, 1 H). ESI-MS: *m/z* 414,3 $(M + H)^+$.

Ejemplo 108: 4–(1-(1*H*-indazol-1-il)etil)–N–(2-aminofenil)benzamida



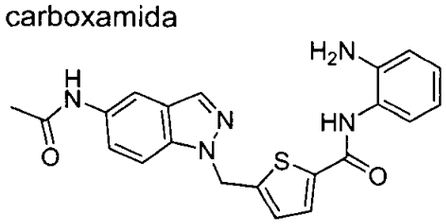
^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 1,97 (d, *J*=7,07 Hz, 3 H), 4,86 (s, 2 H), 6,16 (q, *J*=6,99 Hz, 1 H), 6,57 (t, *J*=7,58 Hz, 1 H), 6,75 (d, *J*=6,82 Hz, 1 H), 6,91 - 6,98 (m, 1 H), 7,13 (t, *J*=7,20 Hz, 2 H), 7,34 (t, *J*=7,58 Hz, 1 H), 7,39 (d, *J*=8,34 Hz, 2 H), 7,66 (d, *J*=8,34 Hz, 1 H), 7,77 (d, *J*=8,08 Hz, 1 H), 7,87 (d, *J*=8,08 Hz, 2 H), 8,17 (s, 1 H), 9,55 (s, 1 H). ESI-MS: *m/z* 357,4 $(M + H)^+$.

Ejemplo 109: 4–(1-(2*H*-indazol-2-il)etil)–N–(2-aminofenil)benzamida



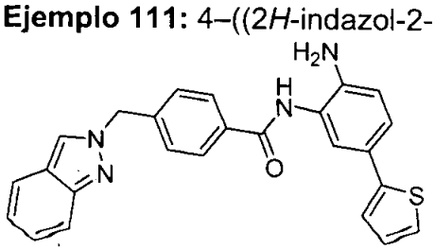
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,99 (d, *J*=7,07 Hz, 3 H), 4,88 (s, 2 H), 6,04 (q, *J*=6,99 Hz, 1 H), 6,57 (t, *J*=7,58 Hz, 1 H), 6,76 (d, *J*=8,08 Hz, 1 H), 6,91 - 6,99 (m, 1 H), 7,01 - 7,06 (m, 1 H), 7,14 (d, *J*=7,58 Hz, 1 H), 7,20 - 7,26 (m, 1 H), 7,44 (d, *J*=8,34 Hz, 2 H), 7,61 (d, *J*=8,84 Hz, 1 H), 7,71 (d, *J*=8,34 Hz, 1 H), 7,92 (d, *J*=8,34 Hz, 2 H), 8,56 (s, 1 H), 9,60 (s, 1 H). ESI-MS: *m/z* 357,4 $(M + H)^+$.

Ejemplo 110: 5-((5-acetamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)tiofen-2-carboxamida



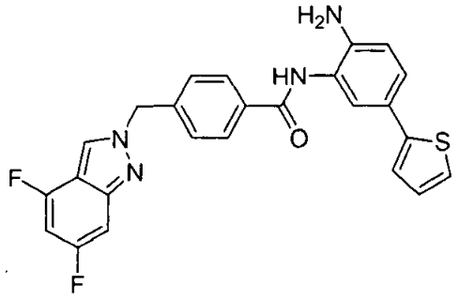
^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 2,05 (s, 3 H), 4,86 (s, 2 H), 5,85 (s, 2 H), 6,52 - 6,58 (m, 1 H), 6,74 (d, *J*=6,82 Hz, 1 H), 6,92 - 6,97 (m, 1 H), 7,02 - 7,07 (m, 1 H), 7,16 (d, *J*=3,54 Hz, 1 H), 7,44 (dd, *J*=9,09, 1,77 Hz, 1 H), 7,71 (d, *J*=9,09 Hz, 1 H), 7,78 (d, *J*=3,03 Hz, 1 H), 8,08 (s, 1 H), 8,13 (d, *J*=1,26 Hz, 1 H), 9,62 (s, 1 H), 9,97 (s, 1 H). ESI-MS: *m/z* 406,3 $(M + H)^+$.

Ejemplo 111: 4–((2*H*-indazol-2-il)metil)–N–(2-amino-5-(tiofen-2-il)fenil)benzamida



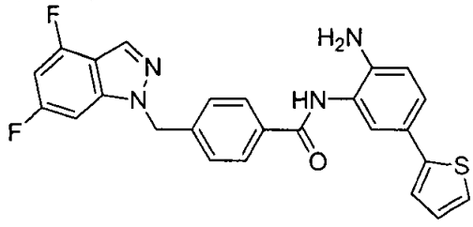
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 5,75 (s, 2 H), 6,98 - 7,09 (m, 3 H), 7,24 (ddd, *J*=8,46, 6,95, 1,26 Hz, 1 H), 7,31 - 7,35 (m, 1 H), 7,39 - 7,47 (m, 4 H), 7,54 (d, *J*=2,02 Hz, 1 H), 7,60 (dd, *J*=8,84, 1,01 Hz, 1 H), 7,73 (d, *J*=8,34 Hz, 1 H), 7,98 (d, *J*=8,34 Hz, 2 H), 8,54 (d, *J*=1,01 Hz, 1 H), 9,96 (s, 1 H). ESI-MS: *m/z* 425,5 $(M + H)^+$.

Ejemplo 112: *N*-(2-amino-5-(tiofen-2-il)fenil)-4–((4,6-difluoro-2*H*-indazol-2-il)metil)benzamida



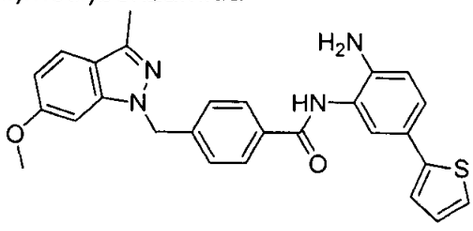
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 5,76 (s, 2 H), 6,93 (s, 1 H), 7,07 (d, *J*=8,59 Hz, 2 H), 7,30 (d, *J*=3,28 Hz, 1 H), 7,35 - 7,42 (m, 4 H), 7,50 (d, *J*=1,77 Hz, 1 H), 7,62 (d, *J*=9,35 Hz, 1 H), 7,95 (d, *J*=8,08 Hz, 2 H), 8,30 (s, 1 H), 9,86 (s, 1 H). ESI-MS: *m/z* 461,3 $(M + H)^+$.

Ejemplo 113: *N*-(2-amino-5-(tiofen-2-il)fenil)-4–((4,6-difluoro-1*H*-indazol-1-il)metil)benzamida



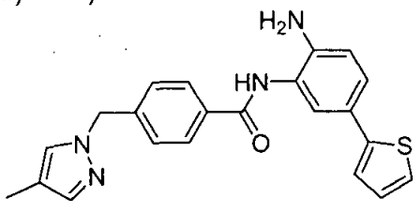
^{1}H NMR (400 MHz, DMSO- d_6) de la sal de ácido trifluoroacético: δ ppm 5,74 (s, 2 H), 6,85 - 6,97 (m, 2 H), 7,04 - 7,07 (m, 1 H), 7,24 - 7,29 (m, 2 H), 7,34 (dd, *J*=8,34, 1,77 Hz, 1 H), 7,38 (d, *J*=5,05 Hz, 1 H), 7,45 - 7,50 (m, 3 H), 7,98 (d, *J*=8,08 Hz, 2 H), 8,84 (s, 1 H), 9,81 (s, 1 H). ESI-MS: *m/z* 461,3 $(M + H)^+$.

Ejemplo 114: *N*-(2-amino-5-(tiofen-2-il)fenil)-4–((6-metoxi-3-metil-1*H*-indazol-1-il)metil)benzamida



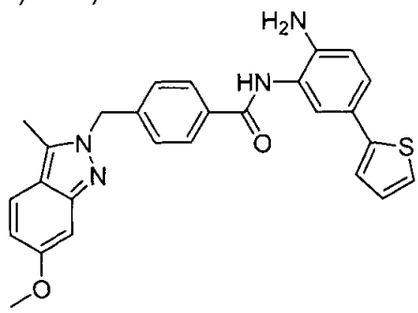
^{1}H NMR (400 MHz, DMSO- d_6) de la sal de ácido trifluoroacético: δ ppm 2,54 (s, 3 H), 3,78 (s, 3 H), 5,64 (s, 2 H), 6,65 (d, *J*=9,09 Hz, 1 H), 6,86 (s, 2 H), 7,05 (s, 1 H), 7,27 (s, 4 H), 7,37 (s, 1 H), 7,48 (s, 1 H), 7,56 (s, 1 H), 7,96 (d, *J*=7,83 Hz, 2 H), 9,78 (s, 1 H). ESI-MS: *m/z* 469,3 $(M + H)^+$.

Ejemplo 115: *N*-(2-amino-5-(tiofen-2-il)fenil)-4–((4–metil-1*H*-pirazol-1-il)metil)benzamida



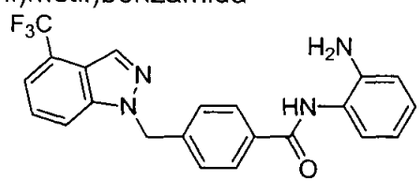
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,02 (s, 3 H), 5,15 (s, 2 H), 5,34 (s, 2 H), 6,80 (d, *J*=8,34 Hz, 1 H), 7,03 - 7,07 (m, 1 H), 7,24 (d, *J*=3,28 Hz, 1 H), 7,27 - 7,33 (m, 4 H), 7,35 (d, *J*=5,05 Hz, 1 H), 7,46 (s, 1 H), 7,60 (s, 1 H), 7,95 (d, *J*=7,83 Hz, 2 H), 9,71 (s, 1 H). ESI-MS: *m/z* 389,3$(M + H)^+$.

Ejemplo 116: *N*-(2-amino-5-(tiofen-2-il)fenil)-4–((6-metoxi-3-metil-2*H*-indazol-2-il)metil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 2,43 (s, 3 H), 3,81 (s, 3 H), 5,61 (s, 2 H), 6,74 (dd, *J*=8,84, 2,02 Hz, 1 H), 7,00 (d, *J*=8,34 Hz, 1 H), 7,08 (dd, *J*=5,05, 3,79 Hz, 1 H), 7,15 (d, *J*=2,02 Hz, 1 H), 7,35 (d, *J*=8,08 Hz, 3 H), 7,40 - 7,45 (m, 2 H), 7,52 - 7,60 (m, 2 H), 7,93 (d, *J*=8,08 Hz, 2 H), 9,94 (s, 1 H). ESI-MS: *m/z* 469,3 $(M + H)^+$.

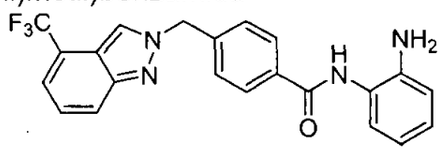
Ejemplo 117: *N*-(2-aminofenil)-4–((4–(trifluorometil)-1*H*-indazol-1-il)metil)benzamida



^{1}H NMR (400 MHz, DMSO- d_6) de la sal de ácido trifluoroacético: δ ppm 5,88 (s, 2 H), 6,95 (t, *J*=7,33 Hz, 1 H), 7,05 (d, *J*=7,33 Hz, 1 H), 7,11 - 7,18 (m, 1 H), 7,27 (d,

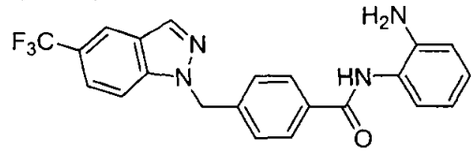
J=7,33 Hz, 1 H), 7,39 (d, *J*=8,34 Hz, 2 H), 7,59 (s, 1 H), 7,60 (d, *J*=2,27 Hz, 1 H), 7,93 (d, *J*=8,08 Hz, 2 H), 8,10 - 8,17 (m, 1 H), 8,27 (s, 1 H), 9,97 (s, 1 H). ESI-MS: *m/z* 411,3 $(M + H)^+$.

Ejemplo 118: *N*-(2-aminofenil)-4–((4–(trifluorometil)-2*H*-indazol-2-il)metil)benzamida



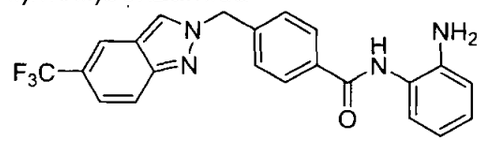
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 5,83 (s, 2 H), 7,11 (t, *J*=7,33 Hz, 1 H), 7,16 - 7,25 (m, 2 H), 7,34 (d, *J*=7,33 Hz, 1 H), 7,38 - 7,44 (m, 1 H), 7,52 (d, *J*=8,08 Hz, 3 H), 7,95 (d, *J*=8,59 Hz, 1 H), 7,99 (d, *J*=8,08 Hz, 2 H), 8,80 (s, 1 H), 10,16 (s, 1 H). ESI-MS: *m/z* 411,3 $(M + H)^+$.

Ejemplo 119: *N*-(2-aminofenil)-4–((5-(trifluorometil)-1*H*-indazol-1-il)metil)benzamida



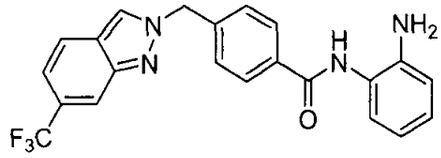
^{1}H NMR (400 MHz, DMSO- d_6) de la sal de ácido trifluoroacético: δ ppm 5,85 (s, 2 H), 6,93 (t, *J*=7,20 Hz, 1 H), 7,03 (d, *J*=7,83 Hz, 1 H), 7,13 (t, *J*=7,07 Hz, 1 H), 7,25 (d, *J*=7,33 Hz, 1 H), 7,36 (d, *J*=8,08 Hz, 2 H), 7,70 (dd, *J*=8,84, 1,52 Hz, 1 H), 7,91 - 7,99 (m, 3 H), 8,28 (s, 1 H), 8,34 (s, 1 H), 9,95 (s, 1 H). ESI-MS: *m/z* 411,3 $(M + H)^+$.

Ejemplo 120: *N*-(2-aminofenil)-4–((5-(trifluorometil)-2*H*-indazol-2-il)metil)benzamida



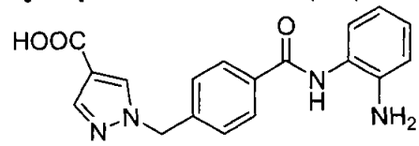
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 5,83 (s, 2 H), 6,98 (t, *J*=7,45 Hz, 1 H), 7,07 (d, *J*=7,83 Hz, 1 H), 7,16 (t, *J*=7,20 Hz, 1 H), 7,29 (d, *J*=7,58 Hz, 1 H), 7,44 - 7,50 (m, 3 H), 7,81 (d, *J*=9,09 Hz, 1 H), 7,98 (d, *J*=8,08 Hz, 2 H), 8,28 (s, 1 H), 8,80 (s, 1 H), 10,03 (s, 1 H). ESI-MS: *m/z* 411,3 $(M + H)^+$.

Ejemplo 121: *N*-(2-aminofenil)-4–((6-(trifluorometil)-2*H*-indazol-2-il)metil)benzamida



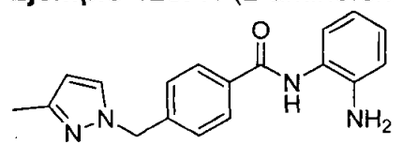
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,90 (s, 2 H), 5,82 (s, 2 H), 6,59 (t, *J*=7,45 Hz, 1 H), 6,77 (d, *J*=7,07 Hz, 1 H), 6,94 - 6,99 (m, 1 H), 7,16 (d, *J*=7,58 Hz, 1 H), 7,45 (d, *J*=8,59 Hz, 3 H), 7,97 (d, *J*=8,34 Hz, 2 H), 8,27 (s, 1 H), 8,74 (s, 1 H), 8,79 (s, 1 H), 9,65 (s, 1 H). ESI-MS: *m/z* 411,3 $(M + H)^+$.

Ejemplo 122: ácido 1-(4–(2-aminofenilcarbamoil)bencil)-1H-pirazol-4–carboxílico



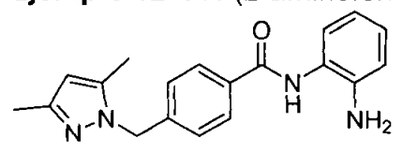
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 5,47 (s, 2 H), 6,93 - 6,99 (m, 1 H), 7,05 (d, *J*=7,33 Hz, 1 H), 7,15 (t, *J*=8,34 Hz, 1 H), 7,28 (d, *J*=7,83 Hz, 1 H), 7,41 (d, *J*=8,34 Hz, 2 H), 7,85 (s, 1 H), 7,97 (d, *J*=8,34 Hz, 2 H), 8,44 (s, 1 H), 10,01 (s, 1 H). ESI-MS: *m/z* 337,3 $(M + H)^+$.

Ejemplo 123: N-(2-aminofenil)-4–((3-metil-1H-pirazol-1-il)metil)benzamida



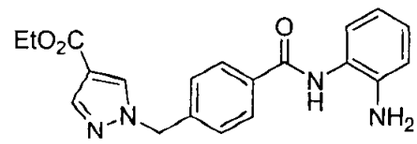
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 2,15 (s, 3 H), 5,33 (s, 2 H), 6,07 (d, *J*=2,27 Hz, 1 H), 7,11 - 7,16 (m, 1 H), 7,18 - 7,26 (m, 2 H), 7,34 (d, *J*=8,34 Hz, 2 H), 7,37 (dd, *J*=7,96, 0,88 Hz, 1 H), 7,74 (d, *J*=2,02 Hz, 1 H), 7,98 (d, *J*=8,34 Hz, 2 H), 10,18 (s, 1 H). ESI-MS: *m/z* 307,4 $(M + H)^+$.

Ejemplo 124: N-(2-aminofenil)-4–((3,5-dimetil-1H-pirazol-1-il)metil)benzamida



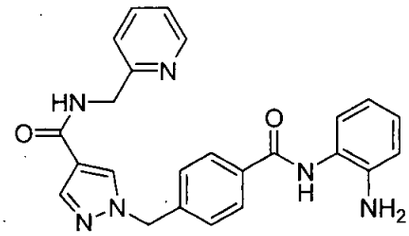
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 2,12 (s, 3 H), 2,17 (s, 3 H), 5,30 (s, 2 H), 5,90 (s, 1 H), 7,10 - 7,15 (m, 1 H), 7,16 - 7,20 (m, 1 H), 7,21 - 7,25 (m, 3 H), 7,35 (dd, *J*=7,83, 1,26 Hz, 1 H), 7,96 (d, *J*=8,34 Hz, 2 H), 10,15 (s, 1 H). ESI-MS: *m/z* 321,4 $(M + H)^+$.

Ejemplo 125: 1-(4–(2-aminofenilcarbamoil)bencil)-1H-pirazol-4–carboxilato de etilo



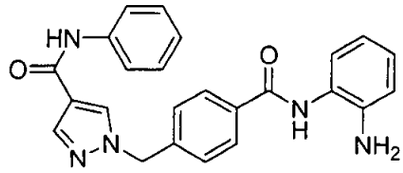
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 1,27 (t, *J*=7,07 Hz, 3 H), 4,22 (q, *J*=7,07 Hz, 2 H), 5,48 (s, 2 H), 6,99 (t, *J*=7,33 Hz, 1 H), 7,05 - 7,11 (m, 1 H), 7,14 - 7,20 (m, 1 H), 7,30 (d, *J*=7,83 Hz, 1 H), 7,41 (d, *J*=8,34 Hz, 2 H), 7,90 (s, 1 H), 7,97 (d, *J*=8,08 Hz, 2 H), 8,53 (s, 1 H), 10,04 (s, 1 H). ESI-MS: *m/z* 365,4 $(M + H)^+$.

Ejemplo 126: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-2-ilmetil)-1H-pirazol-4–carboxamida



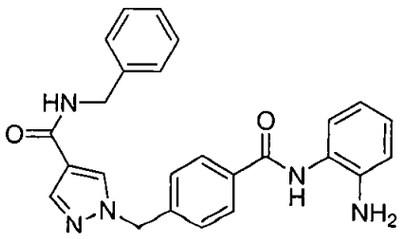
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,49 (d, *J*=6,06 Hz, 2 H), 4,90 (s, 2 H), 5,45 (s, 2 H), 6,59 (td, *J*=7,45, 1,26 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,97 (td, *J*=7,58, 1,52 Hz, 1 H), 7,16 (d, *J*=7,07 Hz, 1 H), 7,25 (ddd, *J*=7,58, 4,80, 1,01 Hz, 1 H), 7,30 (d, *J*=7,83 Hz, 1 H), 7,39 (d, *J*=8,08 Hz, 2 H), 7,75 (td, *J*=7,64, 1,89 Hz, 1 H), 7,94 - 7,98 (m, 3 H), 8,34 (s, 1 H), 8,50 (ddd, *J*=4,93, 1,89, 1,01 Hz, 1 H), 8,75 (t, *J*=5,94 Hz, 1 H), 9,65 (s, 1 H). ESI-MS: *m/z* 427,4 $(M + H)^+$.

Ejemplo 127: 1-(4–(2-aminofenilcarbamoil)bencil)–N–fenil-1H-pirazol-4–carboxamida



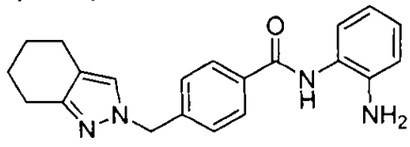
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,90 (s, 2 H), 5,49 (s, 2 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=7,96, 1,39 Hz, 1 H), 6,97 (td, *J*=7,71, 1,52 Hz, 1 H), 7,04 - 7,09 (m, 1 H), 7,16 (d, *J*=7,33 Hz, 1 H), 7,30 - 7,35 (m, 2 H), 7,40 (d, *J*=8,34 Hz, 2 H), 7,70 (dt, *J*=8,65, 1,61 Hz, 2 H), 7,97 (d, *J*=8,08 Hz, 2 H), 8,09 (d, *J*=0,76 Hz, 1 H), 8,49 (s, 1 H), 9,66 (s, 1 H), 9,86 (s, 1 H). ESI-MS: *m/z* 412,4 $(M + H)^+$.

Ejemplo 128: 1-(4–(2-aminofenilcarbamoil)bencil)–N–bencil-1H-pirazol-4–carboxamida



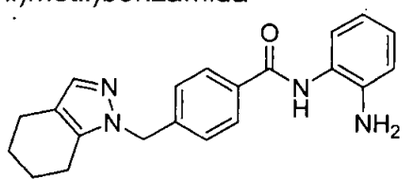
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,41 (d, *J*=6,06 Hz, 2 H), 4,90 (s, 2 H), 5,44 (s, 2 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=7,96, 1,39 Hz, 1 H), 6,97 (td, *J*=7,58, 1,52 Hz, 1 H), 7,15 (d, *J*=7,07 Hz, 1 H), 7,21 - 7,25 (m, 1 H), 7,27 - 7,34 (m, 4 H), 7,38 (d, *J*=8,34 Hz, 2 H), 7,95 (s, 2 H), 7,97 (s, 1 H), 8,32 (s, 1 H), 8,65 (t, *J*=6,06 Hz, 1 H), 9,65 (s, 1 H). ESI-MS: *m/z* 426,4 $(M + H)^+$.

Ejemplo 129: N-(2-aminofenil)-4–((4,5,6,7-tetrahidro-2H-indazol-2-il)metil)benzamida



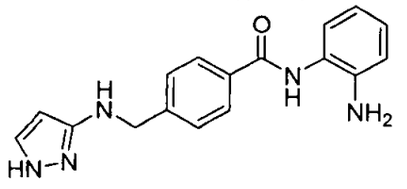
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 1,63 - 1,74 (m, 4 H), 2,45 - 2,49 (m, 4 H), 5,27 (s, 2 H), 6,90 - 6,98 (m, 1 H), 7,04 (d, *J*=8,59 Hz, 1 H), 7,14 (t, *J*=7,83 Hz, 1 H), 7,28 (d, *J*=7,58 Hz, 1 H), 7,36 (d, *J*=8,34 Hz, 2 H), 7,50 (s, 1 H), 7,94 (d, *J*=8,34 Hz, 2 H), 9,96 (s, 1 H). ESI-MS: *m/z* 347,4 $(M + H)^+$.

Ejemplo 130: N-(2-aminofenil)-4–((4,5,6,7-tetrahidro-1H-indazol-1-il)metil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 1,59 - 1,66 (m, 2 H), 1,68 - 1,76 (m, 2 H), 2,44 (t, *J*=5,94 Hz, 2 H), 2,47 - 2,50 (m, 2 H), 5,31 (s, 2 H), 7,04 (t, *J*=7,33 Hz, 1 H), 7,10 - 7,13 (m, 1 H), 7,16 - 7,21 (m, 1 H), 7,23 - 7,27 (m, 3 H), 7,31 (dd, *J*=7,96, 1,14 Hz, 1 H), 7,95 (d, *J*=8,34 Hz, 2 H), 10,07 (s, 1 H). ESI-MS: *m/z* 347,4 $(M + H)^+$.

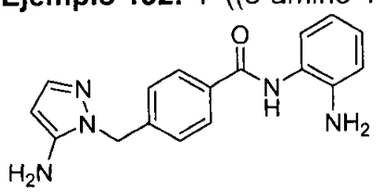
Ejemplo 131: 4–((1H-pirazol-3-ilamino)metil)–N–(2-aminofenil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 4,42 (s, 2 H), 5,74 (d, *J*=2,53 Hz, 1 H), 6,85 (t, *J*=7,45 Hz, 1 H), 6,96 - 7,00 (m, 1 H), 7,10 (td, *J*=7,64, 1,39 Hz, 1 H), 7,23 - 7,27 (m, 1 H), 7,48 (d, *J*=8,34 Hz, 2 H), 7,80 (d,

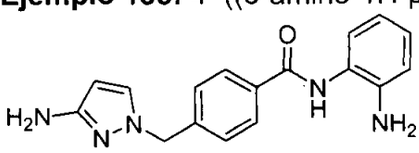
J=2,78 Hz, 1 H), 7,97 (d, *J*=8,34 Hz, 2 H), 9,89 (s, 1 H). ESI-MS: *m/z* 308,4 (M + H)$^+$.

Ejemplo 132: 4–((5-amino-1H-pirazol-1-il)metil)–N–(2-aminofenil)benzamida



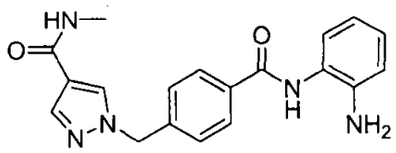
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,89 (s, 2 H), 5,19 (s, 2 H), 5,29 (s, 2 H), 5,31 (d, *J*=2,02 Hz, 1 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,52 Hz, 1 H), 6,96 (td, *J*=7,58, 1,52 Hz, 1 H), 7,10 (d, *J*=2,02 Hz, 1 H), 7,15 (d, *J*=6,82 Hz, 1 H), 7,22 (d, *J*=8,34 Hz, 2 H), 7,90 (d, *J*=8,08 Hz, 2 H), 9,60 (s, 1 H). ESI-MS: *m/z* 308,4 (M + H)$^+$.

Ejemplo 133: 4–((3-amino-1H-pirazol-1-il)metil)–N–(2-aminofenil)benzamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,59 (s, 2 H), 4,89 (s, 2 H), 5,11 (s, 2 H), 5,44 (d, *J*=2,27 Hz, 1 H), 6,59 (td, *J*=7,58, 1,26 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,52 Hz, 1 H), 6,96 (td, *J*=7,58, 1,52 Hz, 1 H), 7,16 (d, *J*=7,83 Hz, 1 H), 7,28 (d, *J*=8,08 Hz, 2 H), 7,48 (d, *J*=2,02 Hz, 1 H), 7,91 (d, *J*=8,08 Hz, 2 H), 9,61 (s, 1 H). ESI-MS: *m/z* 308,4 (M + H)$^+$.

Ejemplo 134: 1-(4–(2-aminofenilcarbamoil)bencil)–N–metil-1H-pirazol-4–carboxamida

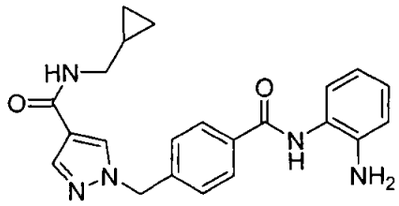


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,70 (d, *J*=4,55 Hz, 3 H), 4,89 (s, 2 H), 5,43 (s, 2 H), 6,59 (td, *J*=7,52, 1,14 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,94 - 6,99 (m, 1 H), 7,15 (d, *J*=7,33 Hz, 1 H), 7,35 (d, *J*=8,34 Hz, 2 H), 7,86 (s, 1 H), 7,95 (d, *J*=8,08 Hz, 2 H), 8,05 (q, *J*=4,55 Hz, 1 H), 8,25 (s, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 350,3 (M + H)$^+$.

Ejemplo 135: 1-(4–(2-aminofenilcarbamoil)bencil)–N–etil-1H-pirazol-4–carboxamida

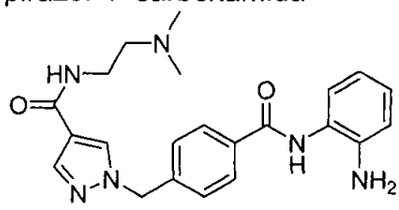
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,48 (m, 2 H), 0,65 (m, 2 H), 2,70 - 2,77 (m, *J*=7,31, 7,31, 3,92, 3,74, 3,74 Hz, 1 H), 4,90 (s, 2 H), 5,42 (s, 2 H), 6,56 - 6,62 (m, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,94 - 6,99 (m, 1 H), 7,15 (d, *J*=7,33 Hz, 1 H), 7,35 (d, *J*=8,08 Hz, 2 H), 7,87 (s, 1 H), 7,95 (d, *J*=8,08 Hz, 2 H), 8,08 (d, *J*=3,79 Hz, 1 H), 8,25 (s, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 376,3 $(M + H)^+$.

Ejemplo 139: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(ciclopropilmetil)-1H-pirazol-4–carboxamida



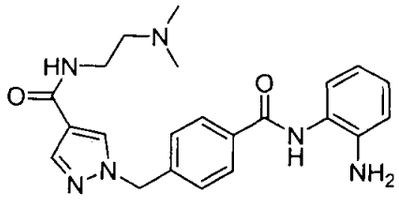
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,17 - 0,21 (m, 2 H), 0,39 - 0,44 (m, 2 H), 0,91 - 1,01 (m, 1 H), 3,07 (t, *J*=6,32 Hz, 2 H), 4,90 (s, 2 H), 5,44 (s, 2 H), 6,59 (t, *J*=7,45 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,01 Hz, 1 H), 6,94 - 6,99 (m, 1 H), 7,15 (d, *J*=7,58 Hz, 1 H), 7,37 (d, *J*=8,08 Hz, 2 H), 7,90 (s, 1 H), 7,96 (d, *J*=8,08 Hz, 2 H), 8,17 (t, *J*=5,68 Hz, 1 H), 8,28 (s, 1 H), 9,65 (s, 1 H). ESI-MS: *m/z* 390,4 $(M + H)^+$.

Ejemplo 140: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(dimetilamino)etil)-1H-pirazol-4–carboxamida



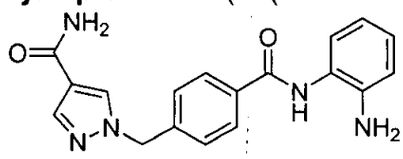
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido bis-trifluoroacético: δ ppm 2,52 - 2,55 (m, 2 H), 2,83 (d, *J*=4,80 Hz, 6 H), 3,17 - 3,23 (m, 2 H), 5,46 (s, 2 H), 6,61 - 6,68 (m, 1 H), 6,82 (d, *J*=7,33 Hz, 1 H), 6,97 - 7,03 (m, 1 H), 7,16 (d, *J*=8,59 Hz, 1 H), 7,38 (d, *J*=7,83 Hz, 2 H), 7,90 (s, 1 H), 7,96 (d, *J*=8,34 Hz, 2 H), 8,30 (s, 1 H), 8,34 (t, *J*=6,06 Hz, 1 H), 9,70 (s, 1 H). ESI-MS: *m/z* 407,4 $(M + H)^+$.

Ejemplo 141: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(dimetilamino)etil)-1H-pirazol-4–carboxamida



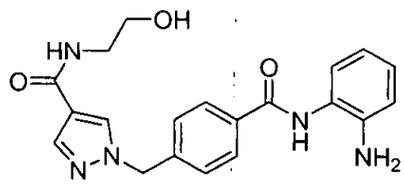
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,23 (s, 6 H), 2,47 - 2,49 (m, 2 H), 3,27 - 3,33 (m, 2 H), 4,89 (s, 2 H), 5,44 (s, 2 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,52 Hz, 1 H), 6,94 - 6,99 (m, 1 H), 7,15 (d, *J*=8,34 Hz, 1 H), 7,36 (d, *J*=8,34 Hz, 2 H), 7,88 (s, 1 H), 7,95 (d, *J*=8,34 Hz, 2 H), 8,04 (t, *J*=5,81 Hz, 1 H), 8,27 (s, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 407,4 $(M + H)^+$.

Ejemplo 142: 1-(4–(2-aminofenilcarbamoil)bencil)-1H-pirazol-4–carboxamida



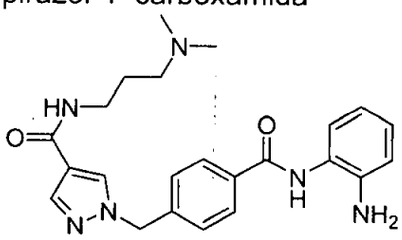
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,90 (s, 2 H), 5,43 (s, 2 H), 6,56 - 6,62 (m, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,94 - 6,99 (m, 1 H), 7,03 (s, 1 H), 7,15 (d, *J*=7,33 Hz, 1 H), 7,36 (d, *J*=8,08 Hz, 2 H), 7,58 (s, 1 H), 7,88 (s, 1 H), 7,96 (d, *J*=8,34 Hz, 2 H), 8,26 (s, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 336,3 $(M + H)^+$.

Ejemplo 143: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-hidroxietil)-1H-pirazol-4–carboxamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,24 (q, *J*=5,98 Hz, 2 H), 3,45 (q, *J*=6,15 Hz, 2 H), 4,69 - 4,72 (m, 1 H), 4,89 (s, 2 H), 5,43 (s, 2 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,52 Hz, 1 H), 6,97 (td, *J*=7,71, 1,52 Hz, 1 H), 7,15 (d, *J*=7,58 Hz, 1 H), 7,36 (d, *J*=8,34 Hz, 2 H), 7,90 (d, *J*=0,51 Hz, 1 H), 7,95 (d, *J*=8,34 Hz, 2 H), 8,09 (t, *J*=5,68 Hz, 1 H), 8,28 (d, *J*=0,76 Hz, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 380,3 $(M + H)^+$.

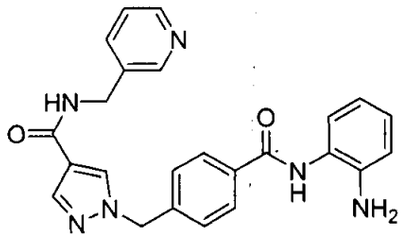
Ejemplo 144: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-(dimetilamino)propil)-1H-pirazol-4–carboxamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,59 (qd, *J*=7,07, 6,82 Hz, 2 H), 2,12 (s, 6 H), 2,23 (t, *J*=7,20 Hz, 2 H), 3,16 - 3,22 (m, 2 H), 4,89 (s, 2 H), 5,43 (s, 2 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,52 Hz, 1 H), 6,97 (td, *J*=7,58, 1,52 Hz, 1

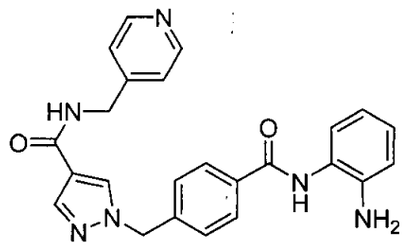
H), 7,15 (d, *J*=7,33 Hz, 1 H), 7,36 (d, *J*=8,08 Hz, 2 H), 7,87 (d, *J*=0,76 Hz, 1 H), 7,95 (d, *J*=8,34 Hz, 2 H), 8,10 (t, *J*=5,68 Hz, 1 H), 8,25 (d, *J*=0,51 Hz, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 421,4 $(M + H)^+$.

Ejemplo 145: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-3-ilmetil)-1H-pirazol-4–carboxamida



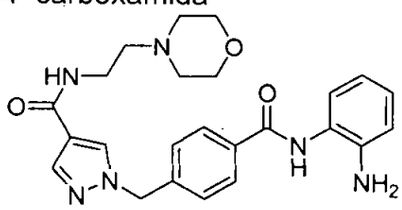
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,42 (d, *J*=5,81 Hz, 2 H), 4,89 (s, 2 H), 5,44 (s, 2 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=7,96, 1,39 Hz, 1 H), 6,97 (td, *J*=7,58, 1,52 Hz, 1 H), 7,15 (d, *J*=7,33 Hz, 1 H), 7,33 - 7,36 (m, 1 H), 7,36 - 7,39 (m, 2 H), 7,69 (dt, *J*=7,83, 2,02 Hz, 1 H), 7,93 (d, *J*=0,51 Hz, 1 H), 7,95 (d, *J*=8,08 Hz, 2 H), 8,32 (d, *J*=0,51 Hz, 1 H), 8,45 (dd, *J*=4,80, 1,77 Hz, 1 H), 8,52 (d, *J*=1,52 Hz, 1 H), 8,70 (t, *J*=5,94 Hz, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 427,3 $(M + H)^+$.

Ejemplo 146: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-4–ilmetil)-1H-pirazol-4–carboxamida



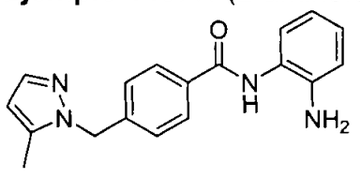
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4,43 (d, *J*=6,06 Hz, 2 H), 4,90 (s, 2 H), 5,46 (s, 2 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=7,96, 1,39 Hz, 1 H), 6,94 - 6,99 (m, 1 H), 7,15 (d, *J*=7,33 Hz, 1 H), 7,26 - 7,29 (m, 2 H), 7,39 (d, *J*=8,34 Hz, 2 H), 7,93 - 7,98 (m, 3 H), 8,34 (s, 1 H), 8,48 - 8,50 (m, 2 H), 8,75 (t, *J*=6,06 Hz, 1 H), 9,65 (s, 1 H). ESI-MS: *m/z* 427,3 $(M + H)^+$.

Ejemplo 147: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-morfolinoetil)-1H-pirazol-4–carboxamida



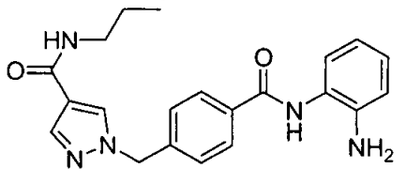
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido bis-trifluoroacético: δ ppm 3,07 - 3,19 (m, 2 H), 3,26 (t, *J*=6,19 Hz, 2 H), 3,49 - 3,59 (m, 4 H), 3,59 - 3,71 (m, 2 H), 4,00 (d, *J*=13,64 Hz, 2 H), 5,46 (s, 2 H), 6,79 (t, *J*=7,20 Hz, 1 H), 6,93 (d, *J*=7,07 Hz, 1 H), 7,05 - 7,10 (m, 1 H), 7,22 (d, *J*=7,07 Hz, 1 H), 7,39 (d, *J*=8,34 Hz, 2 H), 7,91 (d, *J*=0,51 Hz, 1 H), 7,97 (d, *J*=8,34 Hz, 2 H), 8,32 (d, *J*=0,51 Hz, 1 H), 8,42 (t, *J*=5,68 Hz, 1 H), 9,85 (s, 1 H). ESI-MS: *m/z* 449,4 $(M + H)^+$.

Ejemplo 148: N-(2-aminofenil)-4–((5-metil-1H-pirazol-1-il)metil)benzamida



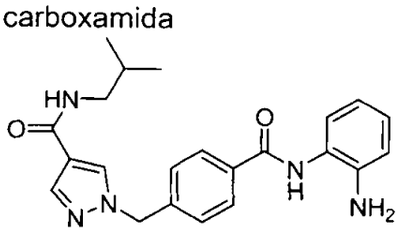
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido trifluoroacético: δ ppm 2,22 (s, 3 H), 5,40 (s, 2 H), 6,11 (dd, *J*=2,15, 1,14 Hz, 1 H), 7,05 (t, *J*=7,58 Hz, 1 H), 7,11 - 7,15 (m, 1 H), 7,19 (d, *J*=7,33 Hz, 1 H), 7,22 (d, *J*=8,08 Hz, 2 H), 7,32 (d, *J*=7,83 Hz, 1 H), 7,39 (d, *J*=1,77 Hz, 1 H), 7,96 (d, *J*=8,08 Hz, 2 H), 10,09 (s, 1 H). ESI-MS: *m/z* 307,3 $(M + H)^+$.

Ejemplo 149: 1-(4–(2-aminofenilcarbamoil)bencil)–N–propil-1H-pirazol-4–carboxamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,86 (t, *J*=7,33 Hz, 3 H), 1,43 - 1,52 (m, *J*=7,23, 7,23, 7,23, 7,23, 7,23 Hz, 2 H), 3,11 - 3,17 (m, 2 H), 4,90 (s, 2 H), 5,43 (s, 2 H), 6,59 (td, *J*=7,45, 1,26 Hz, 1 H), 6,77 (dd, *J*=7,96, 1,39 Hz, 1 H), 6,97 (td, *J*=7,71, 1,52 Hz, 1 H), 7,15 (d, *J*=7,83 Hz, 1 H), 7,36 (d, *J*=8,34 Hz, 2 H), 7,89 (d, *J*=0,51 Hz, 1 H), 7,96 (d, *J*=8,08 Hz, 2 H), 8,06 (t, *J*=5,68 Hz, 1 H), 8,26 (s, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 378,3 $(M + H)^+$.

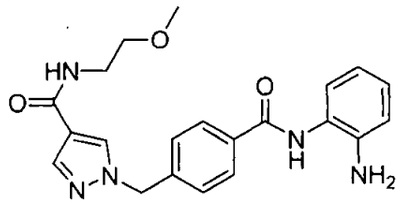
Ejemplo 150: 1-(4–(2-aminofenilcarbamoil)bencil)–N–isobutil-1H-pirazol-4–carboxamida



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,86 (d, *J*=6,57 Hz, 6 H), 1,76 (tt, *J*=13,52, 6,82 Hz, 1 H), 2,98 - 3,02 (m, 2 H), 4,90 (s, 2 H), 5,43 (s, 2 H), 6,59 (td, *J*=7,58,

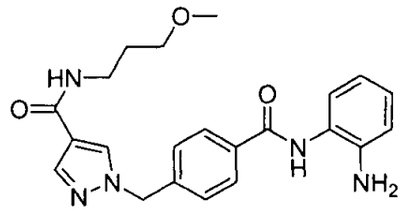
1,26 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,97 (td, *J*=7,58, 1,52 Hz, 1 H), 7,15 (d, *J*=7,58 Hz, 1 H), 7,37 (d, *J*=8,34 Hz, 2 H), 7,91 (d, *J*=0,51 Hz, 1 H), 7,96 (d, *J*=8,08 Hz, 2 H), 8,06 (t, *J*=5,94 Hz, 1 H), 8,27 (s, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 392,4 $(M + H)^+$.

Ejemplo 151: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-metoxietil)-1H-pirazol-4–carboxamida



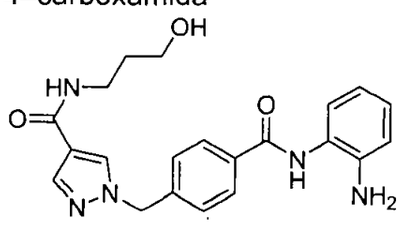
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3,25 (s, 3 H), 3,33 - 3,36 (m, 2 H), 3,38 - 3,42 (m, 2 H), 4,89 (s, 2 H), 5,43 (s, 2 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,97 (td, *J*=7,64, 1,39 Hz, 1 H), 7,15 (d, *J*=7,07 Hz, 1 H), 7,36 (d, *J*=8,34 Hz, 2 H), 7,90 (d, *J*=0,51 Hz, 1 H), 7,95 (d, *J*=8,08 Hz, 2 H), 8,16 (t, *J*=5,43 Hz, 1 H), 8,28 (d, *J*=0,51 Hz, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 394,3 $(M + H)^+$.

Ejemplo 152: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-metoxipropil)-1H-pirazol-4–carboxamida



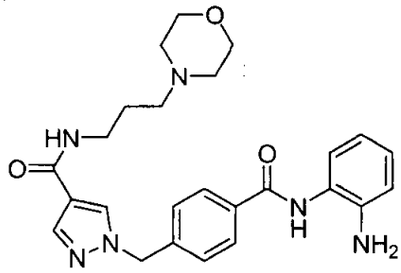
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,66 - 1,73 (m, 2 H), 3,18 - 3,22 (m, 1 H), 3,22 (s, 4 H), 3,33 (t, *J*=3,16 Hz, 2 H), 4,89 (s, 2 H), 5,43 (s, 2 H), 6,59 (td, *J*=7,58, 1,26 Hz, 1 H), 6,77 (dd, *J*=7,96, 1,39 Hz, 1 H), 6,97 (td, *J*=7,58, 1,52 Hz, 1 H), 7,15 (d, *J*=7,33 Hz, 1 H), 7,36 (d, *J*=8,34 Hz, 2 H), 7,88 (d, *J*=0,76 Hz, 1 H), 7,95 (d, *J*=8,08 Hz, 2 H), 8,08 (t, *J*=5,68 Hz, 1 H), 8,26 (d, *J*=0,76 Hz, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 408,4 $(M + H)^+$.

Ejemplo 153: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-hidroxipropil)-1H-pirazol-4–carboxamida



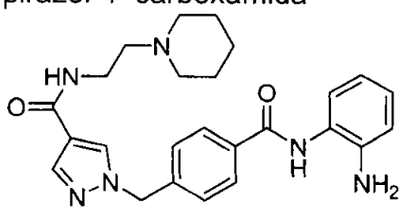
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,62 (qd, *J*=6,74, 6,57 Hz, 2 H), 3,23 (q, *J*=6,65 Hz, 2 H), 3,40 - 3,46 (m, 2 H), 4,46 (t, *J*=5,31 Hz, 1 H), 4,90 (s, 2 H), 5,43 (s, 2 H), 6,59 (td, *J*=7,52, 1,39 Hz, 1 H), 6,77 (dd, *J*=8,08, 1,26 Hz, 1 H), 6,97 (td, *J*=7,58, 1,52 Hz, 1 H), 7,15 (d, *J*=7,07 Hz, 1 H), 7,36 (d, *J*=8,08 Hz, 2 H), 7,89 (d, *J*=0,51 Hz, 1 H), 7,96 (d, *J*=8,08 Hz, 2 H), 8,07 (t, *J*=5,68 Hz, 1 H), 8,26 (d, *J*=0,51 Hz, 1 H), 9,64 (s, 1 H). ESI-MS: *m/z* 394,3 $(M + H)^+$.

Ejemplo 154: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-morfolinopropil)-1H-pirazol-4–carboxamida



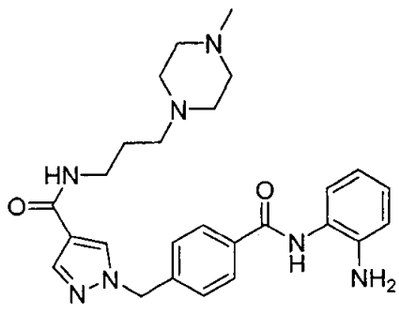
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido bis-trifluoroacético: δ ppm 1,83 - 1,91 (m, 2 H), 3,01 - 3,10 (m, 2 H), 3,10 - 3,17 (m, 2 H), 3,26 (q, *J*=6,32 Hz, 2 H), 3,43 (d, *J*=11,87 Hz, 2 H), 3,64 (t, *J*=11,87 Hz, 2 H), 3,97 (d, *J*=11,87 Hz, 2 H), 5,46 (s, 2 H), 6,93 (t, *J*=7,07 Hz, 1 H), 7,04 (dd, *J*=8,08, 1,26 Hz, 1 H), 7,11 - 7,17 (m, 1 H), 7,28 (d, *J*=8,84 Hz, 1 H), 7,39 (d, *J*=8,34 Hz, 2 H), 7,91 (s, 1 H), 7,98 (d, *J*=8,08 Hz, 2 H), 8,29 - 8,35 (m, 2 H), 10,00 (s, 1 H). ESI-MS: *m/z* 463,4 $(M + H)^+$.

Ejemplo 155: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(piperidin-1-il)etil)-1H-pirazol-4–carboxamida



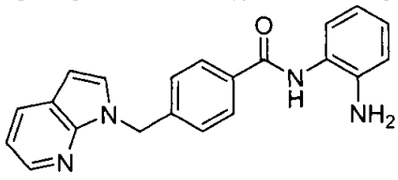
1H NMR (400 MHz, DMSO-d_6) de la sal de ácido bis-trifluoroacético: δ ppm 1,32 - 1,43 (m, 1 H), 1,60 - 1,71 (m, 3 H), 1,81 (d, *J*=14,40 Hz, 2 H), 2,87 - 2,97 (m, 2 H), 3,18 (d, *J*=5,31 Hz, 2 H), 3,49 - 3,59 (m, 4 H), 5,47 (s, 2 H), 6,94 (t, *J*=6,95 Hz, 1 H), 7,05 - 7,08 (m, 1 H), 7,15 (td, *J*=7,64, 1,39 Hz, 1 H), 7,30 (d, *J*=6,82 Hz, 1 H), 7,40 (d, *J*=8,34 Hz, 2 H), 7,92 (d, *J*=0,76 Hz, 1 H), 7,99 (d, *J*=8,08 Hz, 2 H), 10,02 (s, 1 H). ESI-MS: *m/z* 447,4 $(M + H)^+$.

Ejemplo 156: 1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-(4–metilpiperazin-1-il)propil)-1H-pirazol-4–carboxamida



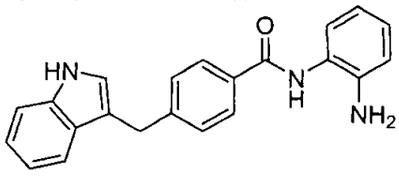
^{1}H NMR (400 MHz, DMSO-d_6) de la sal de ácido bis-trifluoroacético: δ ppm 1,80 - 1,88 (m, 2 H), 2,84 (s, 3 H), 3,06 - 3,13 (m, 2 H), 3,26-3,60 (m, 10 H), 5,45 (s, 2 H), 6,91 (t, *J*=6,95 Hz, 1 H), 7,03 (dd, *J*=8,08, 1,26 Hz, 1 H), 7,13 (td, *J*=7,58, 1,52 Hz, 1 H), 7,27 (d, *J*=8,84 Hz, 1 H), 7,39 (d, *J*=8,34 Hz, 2 H), 7,91 (d, *J*=0,76 Hz, 1 H), 7,98 (d, *J*=8,34 Hz, 2 H), 8,30 (d, *J*=0,76 Hz, 1 H), 9,98 (s, 1 H). ESI-MS: *m/z* 476,4 $(M + H)^+$.

Ejemplo 157: 4–((1*H*-Pirrolo[2,3-b]piridin-1-il)metil)–N–(2-aminofenil)benzamida



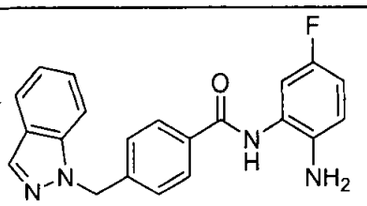
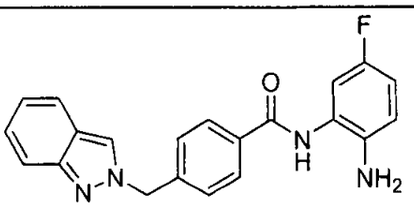
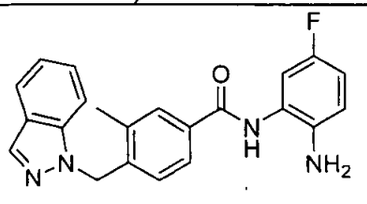
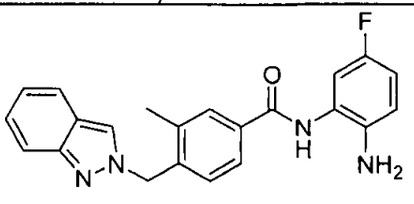
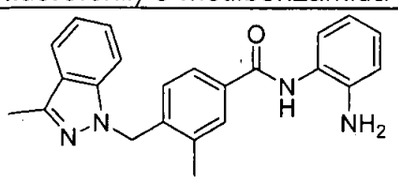
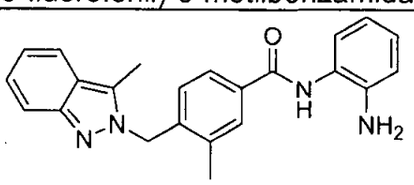
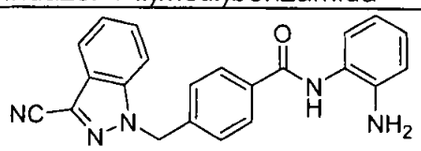
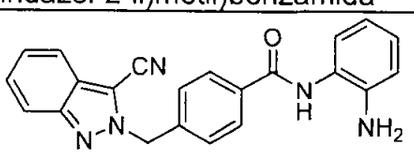
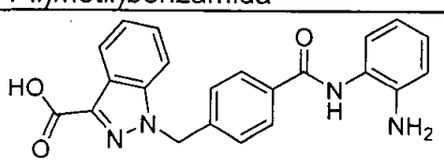
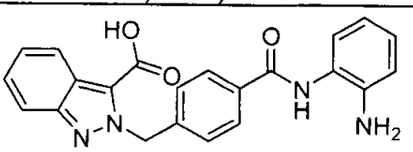
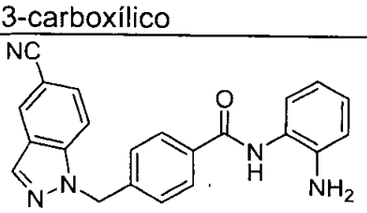
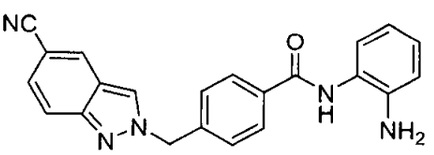
^{1}H NMR (400 MHz, DMSO-D6) de la sal de ácido trifluoroacético: δ ppm 6,03 (s, 2 H) 6,67 (s, 1 H) 6,83 (s, 1 H) 6,91 - 7,02 (m, 2 H) 7,12 (d, *J*=7,33 Hz, 1 H) 7,31 - 7,40 (m, 2 H) 7,45 (d, *J*=8,34 Hz, 1 H) 7,58 - 7,70 (m, 1 H) 7,87 - 7,99 (m, 2 H) 8,65 - 8,80 (m, 2 H) 9,76 (s, 1 H)ESI-MS: *m/z* 343,4 $(M + H)^+$.

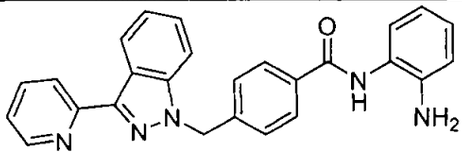
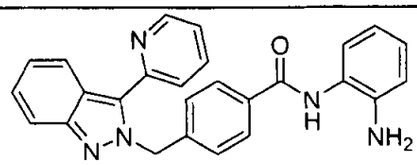
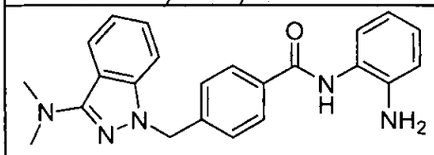
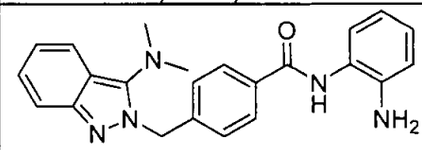
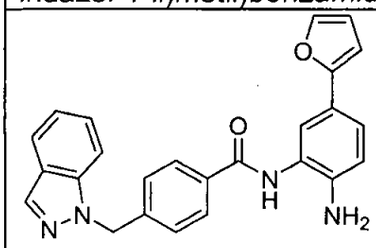
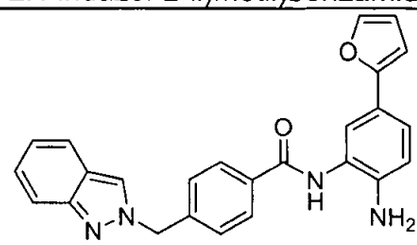
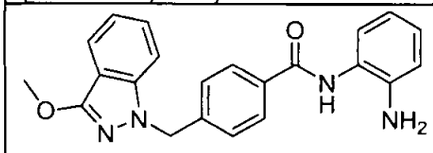
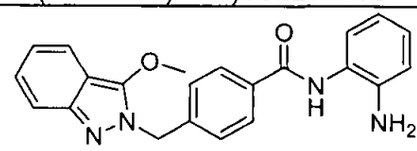
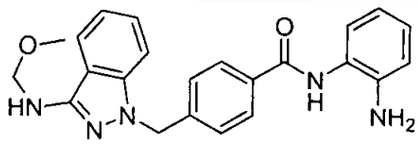
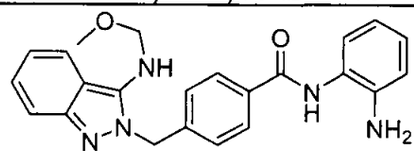
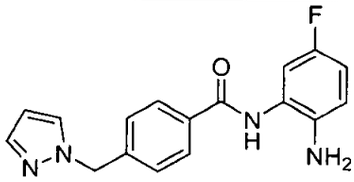
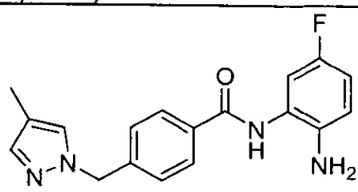
Ejemplo 158: 4–((1*H*-Indol-3-il)metil)–N–(2-aminofenil)benzamida

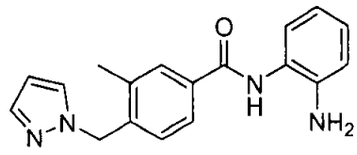
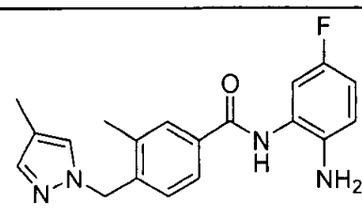
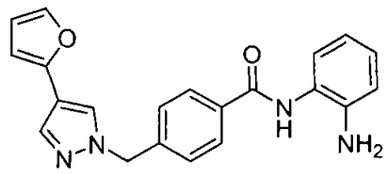
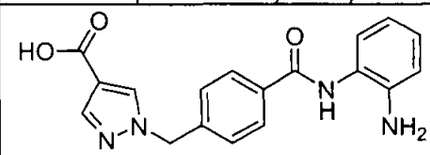
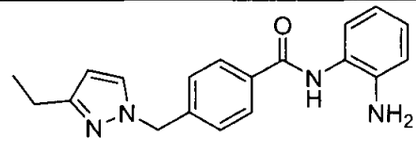
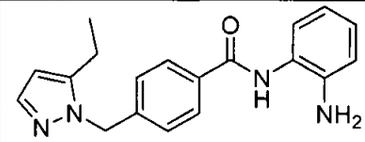
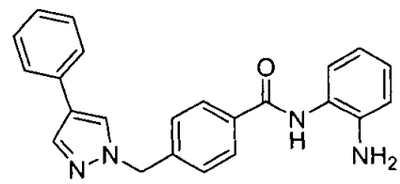
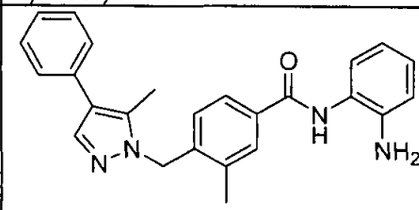
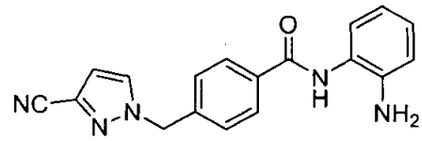
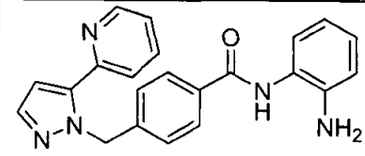
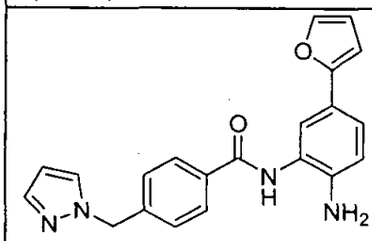
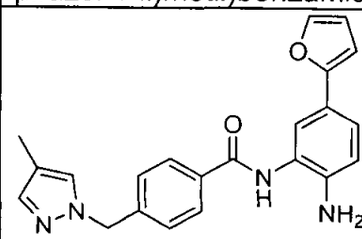


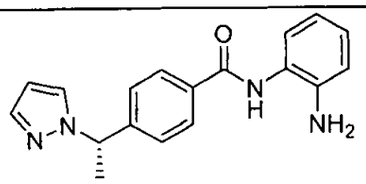
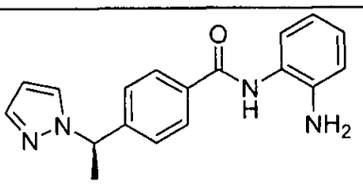
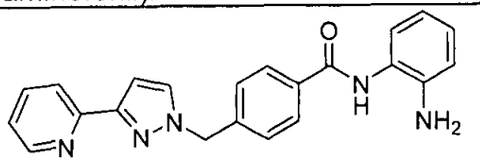
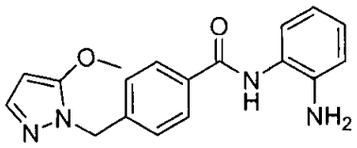
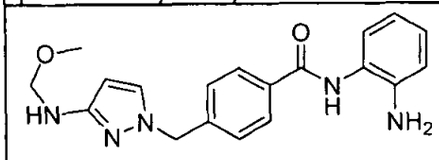
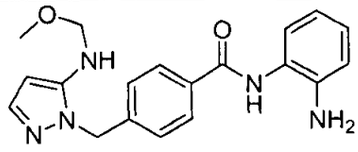
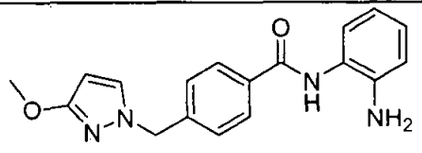
^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4,10 (s, 2 H) 4,84 (s, 2 H) 6,53 - 6,60 (m, 1 H) 6,74 (d, *J*=7,83 Hz, 1 H) 6,88 - 6,97 (m, 2 H) 7,00 - 7,07 (m, 2 H) 7,11 (s, 1 H) 7,19 (d, *J*=2,27 Hz, 1 H) 7,32 (d, *J*=8,08 Hz, 1 H) 7,36 - 7,42 (m, 2 H) 7,85 (d, *J*=8,08 Hz, 2 H) 9,54 (s, 1 H) 10,87 (s, 1 H)ESI-MS: *m/z* 342,4 $(M + H)^+$.

Además de los ejemplos que se han descrito, el siguiente grupo de compuestos no limitativo se puede preparar utilizando los esquemas de reacción descritos y sus variaciones, con la selección apropiada de sustituyentes:

	
4–((1H-indazol-1-il)metil)–N–(2-amino-5-fluorofenil)benzamida	4–((2H-indazol-2-il)metil)–N–(2-amino-5-fluorofenil)benzamida
	
4–((1H-indazol-1-il)metil)–N–(2-amino-5-fluorofenil)-3-metilbenzamida	4–((2H-indazol-2-il)metil)–N–(2-amino-5-fluorofenil)-3-metilbenzamida
	
N-(2-aminofenil)-3-metil-4–((3-metil-1H-indazol-1-il)metil)benzamida	N-(2-aminofenil)-3-metil-4–((3-metil-2H-indazol-2-il)metil)benzamida
	
N-(2-aminofenil)-4–((3-ciano-1H-indazol-1-il)metil)benzamida	N-(2-aminofenil)-4–((3-ciano-2H-indazol-2-il)metil)benzamida
	
ácido 1-(4–((2-aminofenil)carbamoil)bencil)-1H-indazole-3-carboxílico	ácido 2-(4–((2-aminofenil)carbamoil)bencil)-2H-indazole-3-carboxílico
	
N-(2-aminofenil)-4–((5-ciano-1H-indazol-1-il)metil)benzamida	N-(2-aminofenil)-4–((5-ciano-2H-indazol-2-il)metil)benzamida

 N-(2-aminofenil)-4–((3-(piridin-2-il)-1H-indazol-1-il)metil)benzamida	 N-(2-aminofenil)-4–((3-(piridin-2-il)-2H-indazol-2-il)metil)benzamida
 N-(2-aminofenil)-4–((3-(dimetilamino)-1H-indazol-1-il)metil)benzamida	 N-(2-aminofenil)-4–((3-(dimetilamino)-2H-indazol-2-il)metil)benzamida
 4–((1H-indazol-1-il)metil)–N–(2-amino-5-(furan-2-il)fenil)benzamida	 4–((2H-indazol-2-il)metil)–N–(2-amino-5-(furan-2-il)fenil)benzamida
 N-(2-aminofenil)-4–((3-metoxi-1H-indazol-1-il)metil)benzamida	 N-(2-aminofenil)-4–((3-metoxi-2H-indazol-2-il)metil)benzamida
 N-(2-aminofenil)-4–((3-(metoximetilamino)-1H-indazol-1-il)metil)benzamida	 N-(2-aminofenil)-4–((3-(metoximetilamino)-2H-indazol-2-il)metil)benzamida
 4–((1H-pirazol-1-il)metil)–N–(2-amino-5-fluorofenil)benzamida	 N-(2-amino-5-fluorofenil)-4–((4–metil-1H-pirazol-1-il)metil)benzamida

 4–((1H-pirazol-1-il)metil)–N–(2-aminofenil)-3-metilbenzamida	 N-(2-amino-5-fluorofenil)-3-metil-4–((4–metil-1H-pirazol-1-il)metil)benzamida
 N-(2-aminofenil)-4–((4–(furan-2-il)-1H-pirazol-1-il)metil)benzamida	 ácido 1-(4–((2-aminofenil)carbamoil)bencil)-1H-pirazol-4–carboxílico
 N-(2-aminofenil)-4–((3-etil-1H-pirazol-1-il)metil)benzamida	 N-(2-aminofenil)-4–((5-etil-1H-pirazol-1-il)metil)benzamida
 N-(2-aminofenil)-4–((4–fenil-1H-pirazol-1-il)metil)benzamida	 N-(2-aminofenil)-3-metil-4–((5-metil-4–fenil-1H-pirazol-1-il)metil)benzamida
 N-(2-aminofenil)-4–((3-ciano-1H-pirazol-1-il)metil)benzamida	 N-(2-aminofenil)-4–((5-(piridin-2-il)-1H-pirazol-1-il)metil)benzamida
 4–((1H-pirazol-1-il)metil)–N–(2-amino-5-(furan-2-il)fenil)benzamida	 N-(2-amino-5-(furan-2-il)fenil)-4–((4–metil-1H-pirazol-1-il)metil)benzamida

 (S)-4–(1-(1H-pirazol-1-il)etil)–N–(2-aminofenil)benzamida	 (R)-4–(1-(1H-pirazol-1-il)etil)–N–(2-aminofenil)benzamida
 N-(2-aminofenil)-4–((3-(piridin-2-il)-1H-pirazol-1-il)metil)benzamida	 N-(2-aminofenil)-4–((5-metoxi-1H-pirazol-1-il)metil)benzamida
 N-(2-aminofenil)-4–((3-(metoximetilamino)-1H-pirazol-1-il)metil)benzamida	 N-(2-aminofenil)-4–((5-(metoximetilamino)-1H-pirazol-1-il)metil)benzamida
 N-(2-aminofenil)-4–((3-metoxi-1H-pirazol-1-il)metil)benzamida	

Pruebas biológicas

La actividad de los compuestos como inhibidores de HDAC puede ser evaluada *in vitro*, *in vivo* o en una línea celular. Además, los compuestos acordes con la presente invención pueden ser examinados por su actividad contra una o más HDAC. A continuación se proveen ensayos para la actividad contra HDAC1, HDAC2, HDAC6 y HDAC8.

Las HDAC1, HDAC2, HDAC6 y HDAC8 se pueden obtener de la siguiente manera.

Para HDAC1, el ADN que codifica los residuos 1-482 de la secuencia de longitud completa de la enzima humana se puede amplificar por PCR y clonar en los sitios BamHI/XbaI del pFastbac (Invitrogen), que incorpora una marca Flag por ambos extremos N- y C-terminales. La SEQ ID Nº: 1 corresponde a los residuos 1-482 con la marca Flag N-y C-terminal y la SEQ ID Nº: 2 es la secuencia de ADN que se usó para codificar la SEQ ID Nº: 1.

Para HDAC2, el ADN que codifica los residuos 1-488 de la secuencia de longitud completa de la enzima humana se puede amplificar por PCR y clonar en los sitios BamHI/SmaI del pFastbac (Invitrogen), que incorpora una marca de 6-histidina en el extremo C-terminal. La SEQ ID Nº: 3 corresponde a los residuos 1-488 con la marca de 6-histidina C-terminal y la SEQ ID Nº: 4 es la secuencia de ADN que se usó para codificar la SEQ ID Nº: 3.

Para HDAC6, el ADN que codifica los residuos 73-845 de la enzima humana se puede amplificar por PCR y clonar en el sitio SmaI del pFastbac (Invitrogen), que incorpora una marca 6xhistidina en el extremo C-terminal. La SEQ ID Nº: 5 corresponde a los residuos 73-845 con la marca de 6-histidina C-terminal y la SEQ ID Nº: 6 es la secuencia de ADN que se usó para codificar la SEQ ID Nº: 5.

Para HDAC8, el ADN que codifica los residuos 1-377 correspondientes a toda la secuencia de la enzima humana se puede amplificar por PCR y clonar en los sitios BamHI/SmaI del pFastbac (Invitrogen), que incorpora una marca de 6-histidina en el extremo N-terminal. La SEQ ID Nº: 7 corresponde a los residuos 1-377 con la marca de 6-histidina N-terminal y la SEQ ID Nº: 8 es la secuencia de ADN que se usó para codificar la SEQ ID Nº: 7.

El baculovirus recombinante que incorpora las construcciones de HDAC se pueden generar por transposición usando el sistema Bac-to-Bac (Invitrogen). Se pueden obtener soluciones madre virales de título alto por infección de células Sf9 de *Spodoptera frugiperda*; la expresión de la proteína recombinante se puede efectuar por infección de células Sf9 de *Spodoptera frugiperda* o Hi5 de *Trichoplusia ni* (Invitrogen) en biorreactores Wave de 10 l (Wave Biotech).

La proteína recombinante puede aislarse de los extractos celulares por pasaje sobre una resina ProBond (Invitrogen) o un gel de afinidad M2 anti-Flag (Sigma) para HDAC1. Luego, la HDAC1 parcialmente purificada puede ser purificada adicionalmente por cromatografía líquida de alta presión con una columna Mono Q. Los extractos parcialmente purificados de HDAC distintas de HDAC1 y HDAC6 pueden ser purificadas aún más por cromatografía líquida de alta presión sobre una resina para filtración sobre gel BioSep S3000. La pureza de las proteínas HDAC puede determinarse sobre un gel SDS-PAGE desnaturalizante. Las HDAC purificadas se puede concentrar luego hasta una concentración final de 0,6 mg/ml para HDAC1, 10 mg/ml para HDAC2, 0,3 mg/ml para HDAC6 y 3 mg/ml para

HDAC8. Las proteínas se pueden guardar a –78 °C en una solución amortiguadora que contiene TRIS-HCl 25 mM pH 7,6, NaCl 150 mM, EDTA 0,1mM y TCEP 0,25 mM o a –20 °C en presencia de glicerol (concentración final de glicerol al 50%). Como alternativa, la proteína HDAC6 se puede guardar a –78 °C en una solución amortiguadora que contiene TRIS-HCl 25 mM pH 7,2, NaCl 250mM y glicerol 5%.

Se debe tener en cuenta que existe una gran variedad de otros sistemas de expresión y huéspedes que también son adecuados para la expresión de HDAC, como comprenderán fácilmente los especialistas en la técnica.

Las propiedades inhibidoras de los compuestos con relación a HDAC1, HDAC2, HDAC6 y HDAC8 pueden determinarse usando un formato de placas blancas o negras de 384 cavidades bajo las siguientes condiciones de reacción: Tris 25 mM pH 8,0, NaCl 100 mM, KCl 50 mM, EDTA 0,1 mM, Brij35 0,01%, TCEP 0,1 mM, tBoc-Lys(Ac)-AMC 50 µM, DMSO 2%. El producto de reacción puede determinarse cuantitativamente por la intensidad de fluorescencia usando un lector de placas para Fluorescence (Molecular Devices Gemini) con una longitud de onda de excitación a 370 nm y de emisión a 480 nm (para las placas blancas) o 465 nm (para las placas negras).

La reacción de ensayo se puede iniciar de la siguiente manera: se agregaron 5 µl de tBoc-Lys(Ac)AMC 150 µM a cada cavidad de la placa, seguido de la adición de 5 µl de inhibidor (diluciones en serie al medio para 11 datos para cada inhibidor) que contiene DMSO 6%. Se pueden agregar 5 µl de solución de HDAC1, HDAC2, HDAC6 o HDAC8 para iniciar la reacción (las concentraciones finales de enzima fueron de 2,5 nM para HDAC1, 1 nM para HDAC2, 2,5 nM para HDAC6 y 10 nM para HDAC8). La mezcla de reacción se puede incubar luego a temperatura ambiente durante 60 minutos y detener y revelar por adición de 5 µl de fenantrolina 10 mM y tripsina 4 mg/ml (concentración final de fenantrolina es de 2,5 mM y de tripsina es de 1 mg/ml). Las intensidades de fluorescencia de las mezclas de reacción resultantes se pueden medir luego de 30 minutos de incubación a temperatura ambiente.

Los valores de IC_{50} se pueden calcular por ajuste no lineal de la curva de las concentraciones de compuesto y las intensidades de fluorescencia a la ecuación IC_{50} estándar. Como referencias para este ensayo, el ácido suberanilhidroxámico

(SAHA) mostró un valor de IC_{50} de 63 nM para HDAC1, 69 nM para HDAC2, 108 nM para HDAC6 y 242 nM para HDAC8. Los valores de IC_{50} para los compuestos seleccionados de la presente invención se muestran en la Tabla 4.

TABLA 4: IC_{50} de ejemplos de compuestos seleccionados contra HDAC2

EJEMPLO	IC_{50}
1.	≤50 nM
2.	50-100 nM
3.	≤50 nM
4.	≤50 nM
5.	≤50 nM
6.	≤50 nM
7.	≤50 nM
8.	≤50 nM
9.	50-100 nM
10.	≤50 nM
11.	≤50 nM
12.	≤50 nM
13.	≤50 nM
14.	≤50 nM
15.	≤50 nM
16.	≤50 nM
17.	≤50 nM
18.	≤50 nM
19.	100-500 nM
20.	≤50 nM
21.	≤50 nM
22.	≤50 nM
23.	≤50 nM
24.	100-500 nM
25.	100-500 nM
26.	≤50 nM
27.	≤50 nM

EJEMPLO	IC_{50}
28.	50-100 nM
29.	50-100 nM
30.	50-100 nM
31.	≥500 nM
32.	≤50 nM
33.	≥500 nM
34.	100-500 nM
35.	50-100 nM
36.	50-100 nM
37.	50-100 nM
38.	≤50 nM
39.	≥500 nM
40.	100-500 nM
41.	50-100 nM
42.	≤50 nM
43.	≤50 nM
44.	50-100 nM
45.	50-100 nM
46.	50-100 nM
47.	50-100 nM
48.	50-100 nM
49.	≤50 nM
50.	50-100 nM
51.	50-100 nM
52.	50-100 nM
53.	50-100 nM
54.	100-500 nM
55.	50-100 nM
56.	50-100 nM
57.	50-100 nM
58.	50-100 nM

EJEMPLO	IC_{50}
59.	≤50 nM
60.	50-100 nM
61.	≤50 nM
62.	≤50 nM
63.	50-100 nM
64.	50-100 nM
65.	100-500 nM
66.	≤50 nM
67.	≤50 nM
68.	50-100 nM
69.	50-100 nM
70.	100-500 nM
71.	50-100 nM
72.	50-100 nM
73.	100-500 nM
74.	≤50 nM
75.	100-500 nM
76.	50-100 nM
77.	50-100 nM
78.	≤50 nM
79.	≤50 nM
80.	50-100 nM
81.	50-100 nM
82.	50-100 nM
83.	≤50 nM
84.	100-500 nM
85.	≤50 nM
86.	≤50 nM
87.	50-100 nM
88.	50-100 nM
89.	≤50 nM

EJEMPLO	IC_{50}
90.	≤50 nM
91.	50-100 nM
92.	50-100 nM
93.	50-100 nM
94.	50-100 nM
95.	≤50 nM
96.	50-100 nM
97.	50-100 nM
98.	≤50 nM
99.	≤50 nM
100.	50-100 nM
101.	50-100 nM
102.	≥500 nM
103.	≤50 nM
104.	≥500 nM
105.	50-100 nM
106.	≤50 nM
107.	50-100 nM
108.	50-100 nM
109.	50-100 nM
110.	50-100 nM
111.	≤50 nM
112.	100-500 nM
113.	100-500 nM
114.	50-100 nM
115.	≤50 nM
116.	50-100 nM
117.	50-100 nM
118.	50-100 nM
119.	50-100 nM
120.	50-100 nM

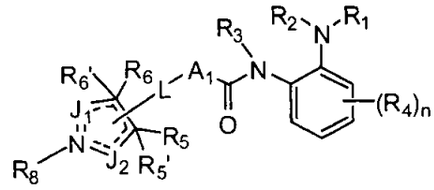
EJEMPLO	IC_{50}
121.	≤50 nM
122.	≥500 nM
123.	100-500 nM
124.	100-500 nM
125.	50-100 nM
126.	≤50 nM
127.	≤50 nM
128.	≤50 nM
129.	50-100 nM
130.	100-500 nM
131.	≥500 nM
132.	≥500 nM
133.	100-500 nM
134.	50-100 nM
135.	50-100 nM
136.	100-500 nM
137.	≤50 nM
138.	50-100 nM
139.	50-100 nM
140.	50-100 nM
141.	50-100 nM
142.	50-100 nM
143.	50-100 nM
144.	≤50 nM
145.	≤50 nM
146.	≤50 nM
147.	50-100 nM
148.	100-500 nM
149.	≤50 nM
150.	≤50 nM
151.	50-100 nM

EJEMPLO	IC_{50}
152.	≤50 nM
153.	≤50 nM
154.	≤50 nM
155.	≤50 nM
156.	50-100 nM
157.	100-500 nM
158.	50-100 nM

Los especialistas en la técnica comprenderán que es posible efectuar diversas modificaciones y variaciones en los compuestos, composiciones, conjuntos de elementos y métodos de la presente invención sin apartarse del espíritu o alcance de la invención. Por consiguiente, se pretende que la presente invención abarque las modificaciones y variaciones de esta invención siempre y cuando se encuentren dentro del alcance de las reivindicaciones adjuntas y los equivalentes de las mismas.

REIVINDICACIONES:

1. Un compuesto CARACTERIZADO PORQUE comprende:



en donde:

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

J_1 se selecciona del grupo formado por $-CR_7R_7'$- y $-NR_{19}$-;

J_2 se selecciona del grupo formado por $-CR_{20}R_{20}'$ y $-NR_{10}$-;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino

(C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

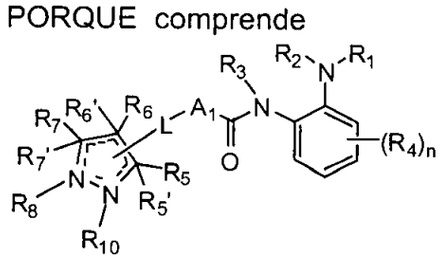
cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se pueden tomar juntos para formar un anillo sustituido o no

sustituido, con la salvedad de que R_5, R_6, R_7 y R_{20}, cada uno en forma independiente están ausentes cuando el C al cual están unidos está unido a L, y R_5', R_6', R_7' y R_{20}', cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

R_8, R_{10} y R_{19} se selecciona cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}', R_{10} y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}', y R_{19}, se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{19} y cualquiera de R_5, R_5', R_6, R_6', R_{20}, y R_{20}', se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8, R_{10} y R_{19} cada uno en forma independiente están ausentes cuando el N al cual están unidos está unido a L, y R_8, R_{10} y R_{19} cada uno en forma independiente están ausentes cuando el N al cual están unidos forma parte de un doble enlace.

2. El compuesto de acuerdo con la reivindicación 1 CARACTERIZADO PORQUE comprende



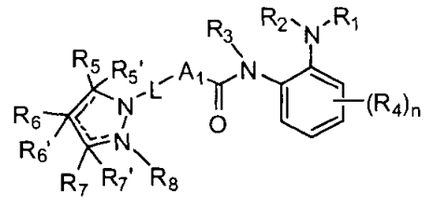
en donde:

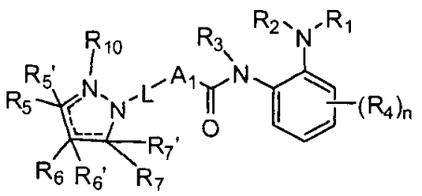
R_5, R_5', R_6, R_6', R_7 y R_7' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5, R_6 y R_7 cada uno en forma independiente están ausentes cuando el C al cual están unidos está unido a L, y R_5', R_6' y R_7' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

R_8 y R_{10} se selecciona cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7' y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la

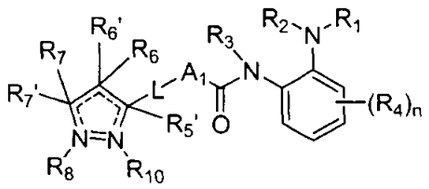
salvedad de que R_8 y R_{10} cada uno en forma independiente están ausentes cuando el N al cual están unidos está unido a L, y R_8 y R_{10} cada uno en forma independiente están ausentes cuando el N al cual están unidos forma parte de un doble enlace.

3. El compuesto de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:





and



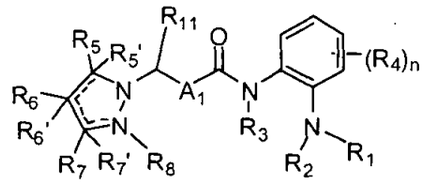
en donde:

R_5, R_5', R_6, R_6', R_7 y R_7' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоaril(C_{1-5})alquilo, hetero(C_{8-12})biciclоaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})biciclоalquilo, hetero(C_{3-12})biciclоalquilo, arilo, heteroarilo, (C_{9-12})biciclоarilo y hetero(C_{4-12})biciclоarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5', R_6' y R_7' cada uno en forma independiente están

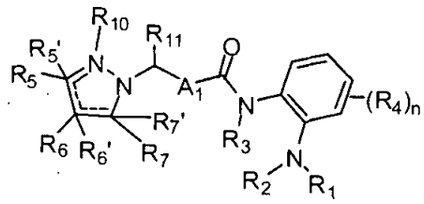
ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

R_8 y R_{10} se selecciona cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7' y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6', R_7 y R_7' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 y R_{10} cada uno en forma independiente están ausentes cuando el N al cual están unidos forma parte de un doble enlace.

4. El compuesto de acuerdo con la reivindicación 3, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



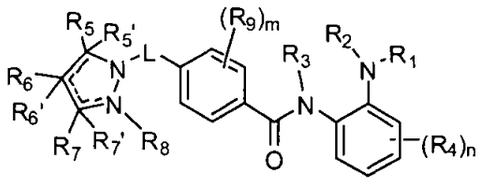
y



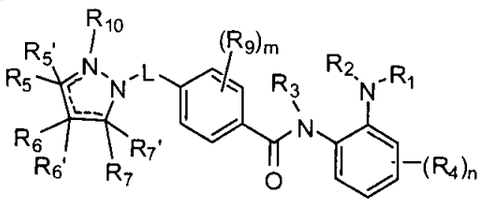
en donde:

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido.

5. El compuesto de acuerdo con la reivindicación 3, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



y



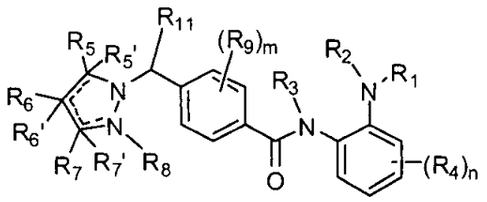
en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

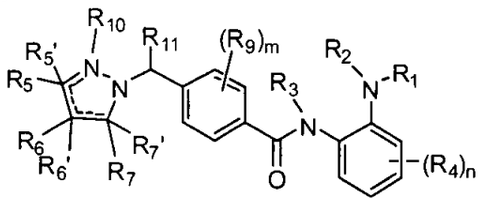
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo,

hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_3, R_5, R_5', R_7, R_7', R_8 y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

6. El compuesto de acuerdo con la reivindicación 3, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



y



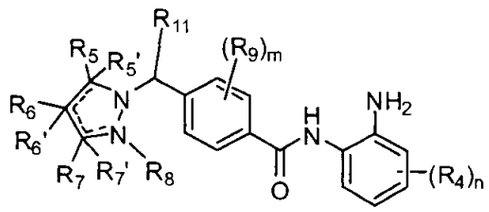
en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

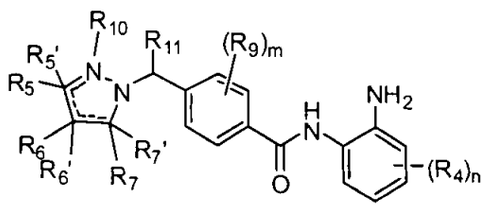
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_3, R_5, R_5', R_7, R_7', R_8 y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

7. El compuesto de acuerdo con la reivindicación 3, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



and



en donde:

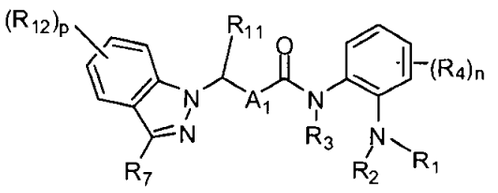
m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo,

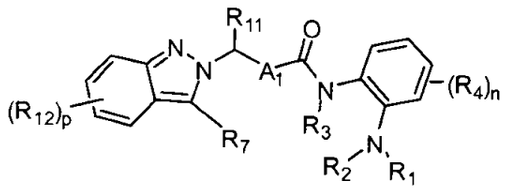
hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_5, R_5', R_7, R_7', R_8 y R_{10} se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

8. El compuesto de acuerdo con la reivindicación 3, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



y



en donde:

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

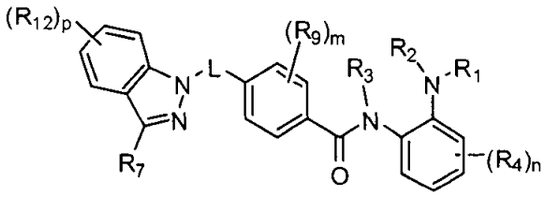
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоaril(C_{1-5})alquilo, hetero(C_{8-12})biciclоaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})biciclоalquilo, hetero(C_{3-12})biciclоalquilo, arilo, heteroarilo, (C_{9-12})biciclоarilo y hetero(C_{4-12})biciclоarilo, cada uno sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоaril(C_{1-5})alquilo, hetero(C_{8-12})biciclоaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})biciclоalquilo, hetero(C_{3-12})biciclоalquilo, arilo, heteroarilo, (C_{9-12})biciclоarilo y hetero(C_{4-12})biciclоarilo, cada uno sustituido o no sustituido, o R_{11} y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

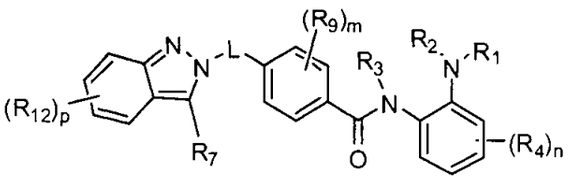
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo,

aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

9. El compuesto de acuerdo con la reivindicación 3, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



y



en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

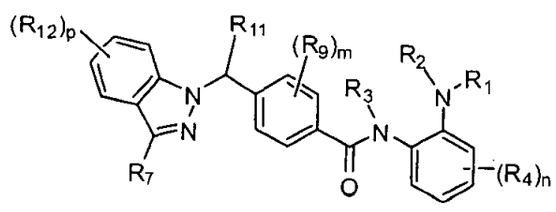
p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

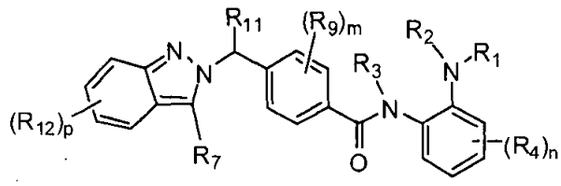
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9, a un R_9 y R_3 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

10. El compuesto de acuerdo con la reivindicación 3, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



y



en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

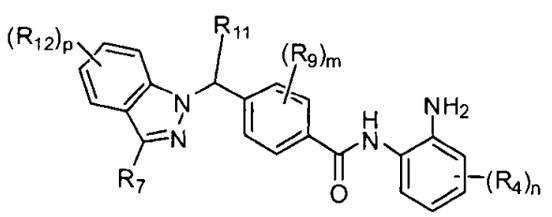
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y R_3 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

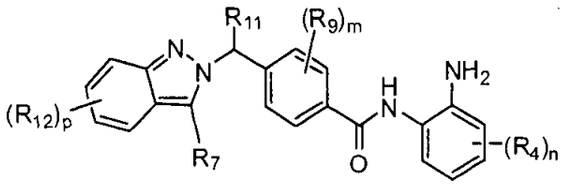
R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

11. El compuesto de acuerdo con la reivindicación 3, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



and



en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

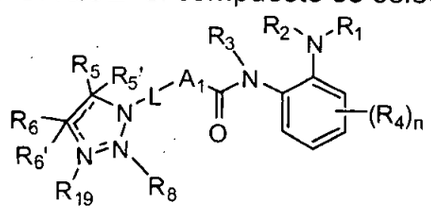
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

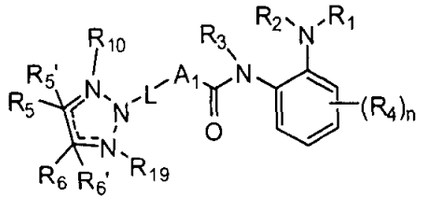
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_7 o R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

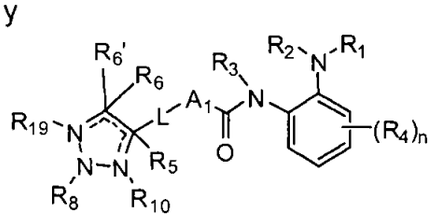
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

12. El compuesto de acuerdo con la reivindicación 1, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:





y



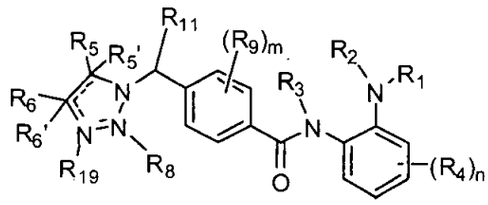
en donde:

R_5, R_5', R_6 y R_6' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6 y R_6' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5' y R_6' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

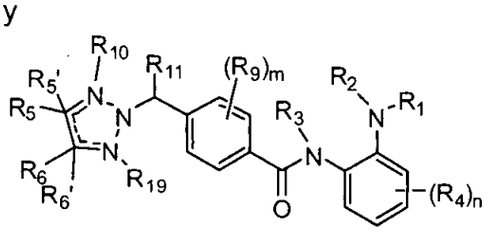
R_8, R_{10} y R_{19}, se selecciona cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_{10} y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{10} y cualquiera de R_5, R_5', R_6, R_6' y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido, o R_{19} y cualquiera de R_5, R_5', R_6 y R_6' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8, R_{10} y R_{19} cada uno en forma independiente están ausentes cuando el N al cual están unidos forma parte de un doble enlace.

13. El compuesto de acuerdo con la reivindicación 12, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



y



en donde:

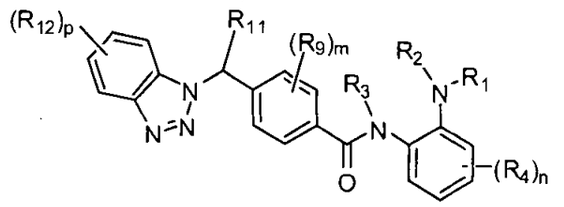
m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo,

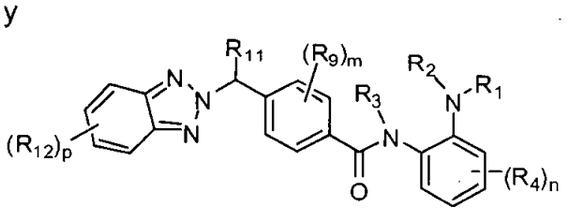
hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_3, R_5, R_5', R_8, R_{10} y R_{19} se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

14. El compuesto de acuerdo con la reivindicación 12, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



y



en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

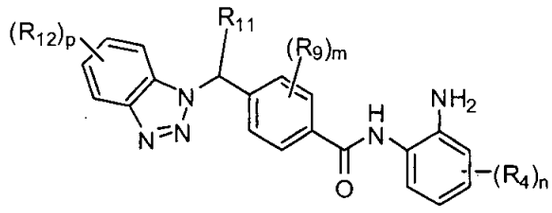
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y R_3 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

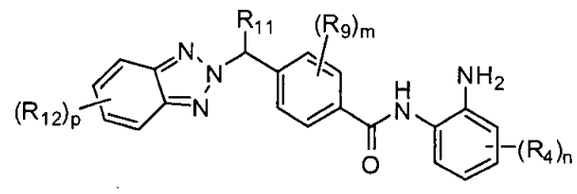
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo,

aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_{11} se pueden tomar juntos para formar a sustituido o no sustituido.

15. El compuesto de acuerdo con la reivindicación 12, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:



y



en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

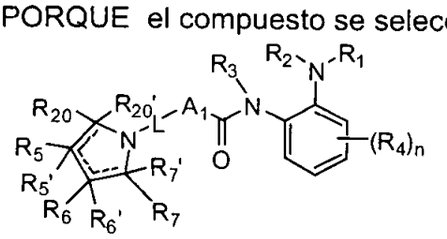
p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

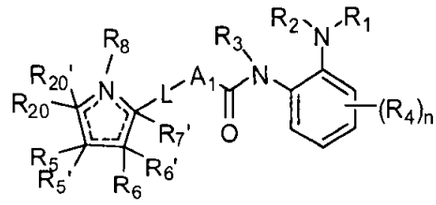
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxilo, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

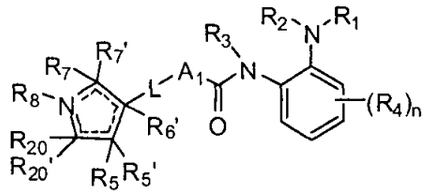
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxilo, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamida, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

16. El compuesto de acuerdo con la reivindicación 1, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:





y



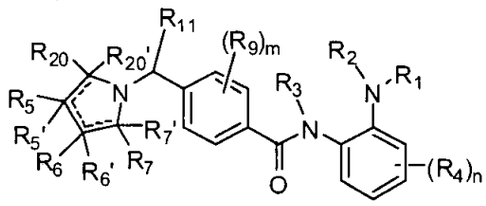
en donde:

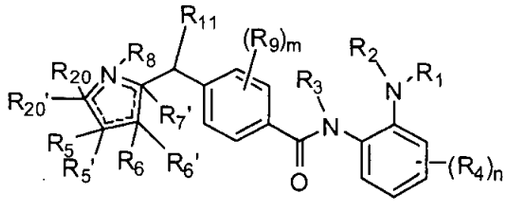
R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_5', R_6', R_7' y R_{20}' cada uno en forma independiente están ausentes cuando el C al cual están unidos forma parte de un doble enlace; y

R_8 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo,

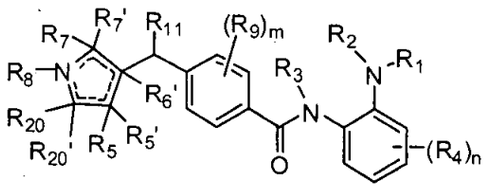
hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_8 y cualquiera de R_5, R_5', R_6, R_6', R_7, R_7', R_{20} y R_{20}' se pueden tomar juntos para formar un anillo sustituido o no sustituido, con la salvedad de que R_8 está ausente cuando el N al cual está unido forma parte de un doble enlace.

17. El compuesto de acuerdo con la reivindicación 16, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:





y



en donde:

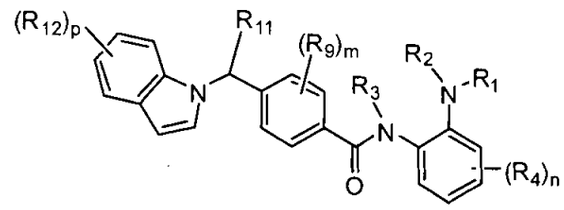
m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

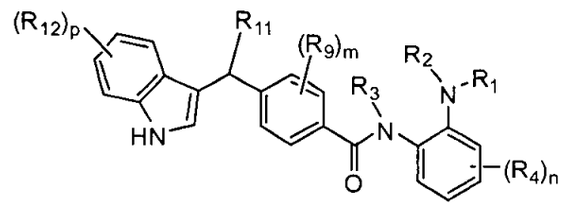
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo,

hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y cualquiera de R_3, R_5, R_5', R_6, R_6', R_7, R_7', R_{20}, R_{20}' y R_8 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

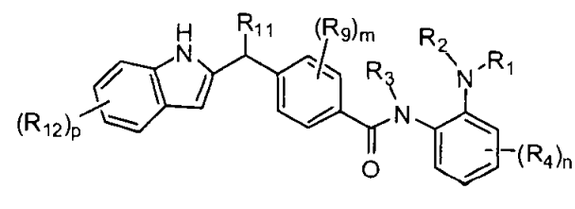
R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo; sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

18. El compuesto de acuerdo con la reivindicación 16, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:





y



en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

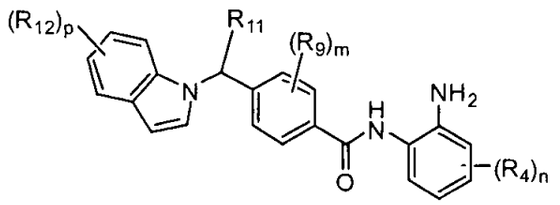
cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 a un R_9 y R_3 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

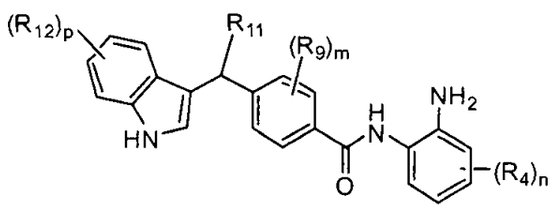
R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo,

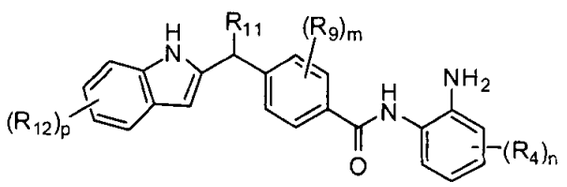
carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

19. El compuesto de acuerdo con la reivindicación 16, CARACTERIZADO PORQUE el compuesto se selecciona del grupo formado por:





y



en donde:

m se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

cada R_9 se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo,

hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o cualesquier dos R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_{11} se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{11} y R_9 se pueden tomar juntos para formar un anillo sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

20. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-6, 8-10, 12-14 y 16-18, en CARACTERIZADO PORQUE R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquil y imino(C_{1-3})alquilo, cada uno sustituido o no sustituido.

21. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-6, 8-10, 12-14 y 16-18, CARACTERIZADO PORQUE R_1 es hidrógeno o un sustituyente convertible in vivo en hidrógeno.

22. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-6, 8-10, 12-14 y 16-18, CARACTERIZADO PORQUE R_2 es hidrógeno o un sustituyente convertible in vivo en hidrógeno.

23. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-6, 8-10, 12-14 y 16-18, CARACTERIZADO PORQUE R_3 es hidrógeno o un sustituyente convertible in vivo en hidrógeno.

24. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-19, CARACTERIZADO PORQUE R_4 se selecciona del grupo formado por hidrógeno, halo, arilo y heteroarilo, cada uno sustituido o no sustituido.

25. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-19, CARACTERIZADO PORQUE R_4 se selecciona del grupo formado por fenilo, oxazolilo, tiazolilo, morfolinilo y tiomorfolinilo, cada uno sustituido o no sustituido.

26. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-13 y 16-17, CARACTERIZADO PORQUE R_5, R_6, R_7 y R_{20} se seleccionan cada uno en forma independiente del grupo formado por carbonilo, oxo, amino, (C_{1-10})alquilamino, amido, carboxamido, ciano, alcoxi, (C_{1-10})alquilo, arilo, y heteroarilo, cada uno sustituido o no sustituido.

27. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-7, 12-13 y 16-17, CARACTERIZADO PORQUE R_5 y R_6 se toman juntos para formar un anillo sustituido o no sustituido.

28. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-7, 12-13 y 16-17, CARACTERIZADO PORQUE R_5 y R_6 se toman juntos para formar un

anillo seleccionado del grupo formado por arilo y heteroarilo, cada uno sustituido o no sustituido.

29. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-7, 12-13 y 16-17, CARACTERIZADO PORQUE el anillo formado por R_5 y R_6 está sustituido con un sustituyente seleccionado del grupo formado por halo, alcoxi, amino(C_{1-10})alcoxi, amino(C_{1-10})alquilamino, amino(C_{1-10})alquilsulfanilo, amido, carboxamido, halo(C_{1-10})alquilo, arilo y heteroarilo, cada uno sustituido o no sustituido.

30. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-7, 12-13 y 16-17, CARACTERIZADO PORQUE el anillo formado por R_5 y R_6 está sustituido con un sustituyente seleccionado del grupo formado por tiofenilo, piridinilo, furanilo y pirimidinilo, cada uno sustituido o no sustituido.

31. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-7, 12-13 y 16-17, CARACTERIZADO PORQUE el anillo formado por R_5 y R_6 está sustituido con $-O-CH_2CH_2-NR_{13}R_{14}$, en donde R_{13} y R_{14} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero (C_{8-12})bicicloarilo (C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{13} y R_{14} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

32. El compuesto according cualquiera de las reivindicaciones 1-7, 12-13 y 16-17, CARACTERIZADO PORQUE el anillo formado por R_5 y R_6 está sustituido con $-NH-CH_2CH_2-NR_{13}R_{14}$, en donde R_{13} y R_{14} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo,

aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero (C_{8-12})bicicloarilo (C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{13} y R_{14} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

33. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-7, 12-13 y 16-17, CARACTERIZADO PORQUE el anillo formado por R_5 y R_6 está sustituido con $-S-CH_2CH_2-NR_{13}R_{14}$, en donde R_{13} y R_{14} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero (C_{8-12})bicicloarilo (C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{13} y R_{14} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

34. El compuesto de acuerdo con cualquiera de las reivindicaciones 31-33, CARACTERIZADO PORQUE R_{13} y R_{14} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, y heteroarilo, cada uno sustituido o no sustituido.

35. El compuesto de acuerdo con cualquiera de las reivindicaciones 31-33, CARACTERIZADO PORQUE R_{13} y R_{14} se toman juntos para formar un anillo seleccionado del grupo formado por morfolinilo, pirrolidinilo, piperazinilo y tiomorfolinilo, cada uno sustituido o no sustituido.

36. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-7, 12-13, y 16-17, CARACTERIZADO PORQUE R_8, R_{10} y R_{19} se seleccionan cada uno en forma independiente del grupo formado por hidrógeno y (C#1-#1#0)alquilo sustituido o no sustituido.

37. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-3, 5, 9, 12 y 16 CARACTERIZADO PORQUE L es un ligador que provee una separación de 1-5 átomos entre los dos átomos del anillos a los cuales L está unido.

38. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-3, 5, 9, 12 y 16, CARACTERIZADO PORQUE L es un ligador que provee una separación de 1-3 átomos entre los dos átomos del anillos a los cuales L está unido.

39. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-3, 5, 9, 12 y 16, CARACTERIZADO PORQUE L es un alquileno sustituido o no sustituido.

40. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-3, 5, 9, 12 y 16, CARACTERIZADO PORQUE L es $-CH_2-$.

41. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-3, 5, 9, 12 y 16, CARACTERIZADO PORQUE L se selecciona del grupo formado por $-NR_{15}-$; $-NR_{15}-CH_2-$; $-O-CH_2-$; $-S-CH_2-$; $-CH_2-NR_{15}-$; $-CH_2-O-$ y $-CH_2-S-$, en donde R_{15} se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido.

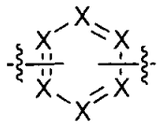
42. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4, 8, 12 y 16, CARACTERIZADO PORQUE A_1 se selecciona del grupo formado por arilo y heteroarilo, cada uno sustituido o no sustituido.

43. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4, 8, 12 y 16, en donde A_1 es un fenileno sustituido o no sustituido.

44. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4, 8, 12 y 16, CARACTERIZADO PORQUE A_1 es un 1,4–fenileno sustituido o no sustituido.

45. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4, 8, 12 y 16, CARACTERIZADO PORQUE A_1 se selecciona del grupo formado por a tiofendiilo, furandiilo, pirroldiilo, tiazoldiilo, oxazoldiilo, imidazoldiilo y piridindiilo, cada uno sustituido o no sustituido.

46. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4, 8, 12 y 16, CARACTERIZADO PORQUE A_1 comprende:



en donde:

cada X se selecciona en forma independiente del grupo formado por CR_{16} y N; y

cada R_{16} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{16} está ausente cuando el C al cual está unido también está unido a L o al carbonilo adyacente a A_1.

47. El compuesto de acuerdo con la reivindicación 11, CARACTERIZADO PORQUE m es 0, R_{11} es hidrógeno, y R_{12} se selecciona del grupo formado por hidroxilo, alcoxi, halo, amido, carboxamido, y (C_{1-10})alquilamido, cada uno sustituido o no sustituido.

48. El compuesto de acuerdo con la reivindicación 47, CARACTERIZADO PORQUE n es 0, p es 2, y R_{12} se selecciona del grupo formado por hidroxilo, alcoxi, y halo.

49. El compuesto de acuerdo con la reivindicación 48, CARACTERIZADO PORQUE R_7 es hidrógeno, y R_{12} es alcoxi.

50. Un compuesto CARACTERIZADO PORQUE es seleccionado del grupo formado por:

4–((1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((2*H*-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-2*H*-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((5-nitro-1H-indazol-1-il)metil)benzamida;

4–((5-benzamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((5-amino-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((5-nitro-2*H*-indazol-2-il)metil)benzamida;

4–((5-amino-2*H*-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((5-benzamido-2*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

2-(4–((2-aminofenil)carbamoil)bencil)-2*H*-indazol-5-ilcarbamato de 2-Metoxietilo;

2-(4–((2-aminofenil)carbamoil)bencil)-2*H*-indazol-5-ilcarbamato de Metilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de 2-Metoxietilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de Metilo

1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de Bencilo;

2-(4–((2-aminofenil)carbamoil)bencil)-2*H*-indazol-5-ilcarbamato de Bencilo;

N-(4–Amino-bifenil-3-il)-4–(5-nitro-indazol-2-ilmetil)-benzamida;

N-(2-(4–((2-Aminofenil)carbamoil)bencil)-2*H*-indazol-5-il)morfolin-4–carboxamida;

5-((2*H*-Indazol-2-il)metil)–N–(2-aminofenil)tiofen-2-carboxamida;

N-(2-Aminofenil)-5-((5-nitro-2*H*-indazol-2-il)metil)tiofen-2-carboxamida;

N-(1-(4–((2-Aminofenil)carbamoil)bencil)-1*H*-indazol-5-il)morfolin-4–carboxamida;

1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de 2-Morfolinoetilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de Piridin-3-ilmetilo;

5-((1*H*-Indazol-1-il)metil)–N–(2-aminofenil)tiofen-2-carboxamida;

4–((2*H*-Pirazolo[3,4–b]piridin-2-il)metil)–N–(2-aminofenil)benzamida;

N-(4–Amino-bifenil-3-il)-4–pirazolo[3,4–*b*]□piridin-2-ilmetil-benzamida;

N-(4–Amino-bifenil-3-il)-4–indazol-2-ilmetil-benzamida;

N-(2-Aminofenil)-4–((3-metil-1*H*-indazol-1-il)metil)benzamida;

N-(2-Aminofenil)-4–((3-metil-2*H*-indazol-2-il)metil)benzamida;

4–((1H-indazol-3-ilamino)metil)–N–(2-aminofenil)benzamida;

4–((1H-pirazol-1-il)metil)–N–(2-aminofenil)benzamida;

N-(2-(4–((2-Aminofenil)carbamoil)bencil)-2*H*-indazol-5-il)morfolin-4–carboxamida;

3-(4–((2H-indazol-2-il)metil)benzamido)-4–aminobenzoato de Metilo;

N-(2-aminofenil)-4–((4–metil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-fluoro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-fluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-fluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-fluoro-2H-indazol-2-il)metil)benzamida;

4–(1-(1H-indazol-1-il)propan-2-il)–N–(2-aminofenil)benzamida;

4–(2-(1H-indazol-1-il)etil)–N–(2-aminofenil)benzamida;

4–(2-(2H-indazol-2-il)etil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((4–cloro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–cloro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4,6-difluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4,6-difluoro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((7-fluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((7-fluoro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fluoro-2H-indazol-2-il)metil)benzamida;

(R)-4–(1-(2H-indazol-2-il)etil)–N–(2-aminofenil)benzamida;

(S)-4–(1-(2H-indazol-2-il)etil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((7-fluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((7-fluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-difluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-difluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-cloro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-cloro-2H-indazol-2-il)metil)benzamida;

4–((3-amino-5-(trifluorometil)-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((3-amino-5-(trifluorometil)-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((3-oxo-2,3-dihidro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-oxo-1H-indazol-2(3H)-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-fluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-fluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5-fluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-fluoro-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-etil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-etil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-hidroxi-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-hidroxi-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-fenil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-fenil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5-metoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3,5-dimetil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3,5-dimetil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((7-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((7-metoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–metoxi-1H-indazol-1-il)metil)benzamida;

4–((6-acetamido-3-metil-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-3-metil-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((3-amino-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((3-metil-7-(trifluorometil)-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metil-6-(trifluorometil)-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metil-6-(trifluorometil)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metil-5-(trifluorometil)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metil-5-(trifluorometil)-2H-indazol-2-il)metil)benzamida;

4–((3-amino-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((5-hidroxi-6-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-dimetoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-dimetoxi-1H-indazol-1-il)metil)benzamida;

4–((1*H*-benzo[*d*][1,2,3]triazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((2*H*-benzo[*d*][1,2,3]triazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(piperazin-1-il)etil)-1H-pirazol-4–carboxamida;

4–((2*H*-indazol-2-il)metil)–N–(4–aminopirimidin-5-il)benzamida;

4–((5-acetamido-3-amino-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-3-metil-2*H*-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-3-metil-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–(1-(1*H*-indazol-1-il)etil)–N–(2-aminofenil)benzamida;

4–(1-(2*H*-indazol-2-il)etil)–N–(2-aminofenil)benzamida;

5-((5-acetamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)tiofen-2-carboxamida;

4–((2*H*-indazol-2-il)metil)–N–(2-amino-5-(tiofen-2-il)fenil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4,6-difluoro-2*H*-indazol-2-il)metil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4,6-difluoro-1*H*-indazol-1-il)metil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((6-metoxi-3-metil-1*H*-indazol-1-il)metil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4–metil-1*H*-pirazol-1-il)metil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((6-metoxi-3-metil-2*H*-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–(trifluorometil)-1*H*-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–(trifluorometil)-2*H*-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5-(trifluorometil)-1*H*-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-(trifluorometil)-2*H*-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-(trifluorometil)-2*H*-indazol-2-il)metil)benzamida;

ácido 1-(4–(2-aminofenilcarbamoil)bencil)-1H-pirazol-4–carboxílico;

N-(2-aminofenil)-4–((3-metil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3,5-dimetil-1H-pirazol-1-il)metil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)-1H-pirazol-4–carboxilato de etilo;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-2-ilmetil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–fenil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–bencil-1H-pirazol-4–carboxamida;

N-(2-aminofenil)-4–((4,5,6,7-tetrahidro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4,5,6,7-tetrahidro-1H-indazol-1-il)metil)benzamida;

4–((1H-pirazol-3-ilamino)metil)–N–(2-aminofenil)benzamida;

4–((5-amino-1H-pirazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((3-amino-1H-pirazol-1-il)metil)–N–(2-aminofenil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–metil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–etil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)-N,N-dimetil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–isopropil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–ciclopropil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(ciclopropilmetil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(dimetilamino)etil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-hidroxietil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-(dimetilamino)propil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-3-ilmetil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-4–ilmetil)-1H-pirazol-4–carboxamida.;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-morfolinoetil)-1H-pirazol-4–carboxamida;

N-(2-aminofenil)-4–((5-metil-1H-pirazol-1-il)metil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–propil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–isobutil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-metoxietil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-metoxipropil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-hidroxipropil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-morfolinopropil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(piperidin-1-il)etil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-(4–metilpiperazin-1-il)propil)-1H-pirazol-4–carboxamida;

4–((1*H*-Pirrolo[2,3-b]piridin-1-il)metil)–N–(2-aminofenil)benzamida;

4–((1*H*-Indol-3-il)metil)–N–(2-aminofenil)benzamida;

4–((1H-indazol-1-il)metil)–N–(2-amino-5-fluorofenil)benzamida;

4–((2H-indazol-2-il)metil)–N–(2-amino-5-fluorofenil)benzamida;

4–((1H-indazol-1-il)metil)–N–(2-amino-5-fluorofenil)-3-metilbenzamida;

4–((2H-indazol-2-il)metil)–N–(2-amino-5-fluorofenil)-3-metilbenzamida;

N-(2-aminofenil)-3-metil-4–((3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-3-metil-4–((3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-ciano-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-ciano-2H-indazol-2-il)metil)benzamida;

Ácido 1-(4–((2-aminofenil)carbamoil)bencil)-1H-indazole-3-carboxílico;

Ácido 2-(4–((2-aminofenil)carbamoil)bencil)-2H-indazole-3-carboxílico;

N-(2-aminofenil)-4–((5-ciano-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-ciano-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(piridin-2-il)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(piridin-2-il)-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(dimetilamino)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(dimetilamino)-2H-indazol-2-il)metil)benzamida;

4–((1H-indazol-1-il)metil)–N–(2-amino-5-(furan-2-il)fenil)benzamida;

4–((2H-indazol-2-il)metil)–N–(2-amino-5-(furan-2-il)fenil)benzamida;

N-(2-aminofenil)-4–((3-metoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(metoximetilamino)-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(metoximetilamino)-2H-indazol-2-il)metil)benzamida;

4–((1H-pirazol-1-il)metil)–N–(2-amino-5-fluorofenil)benzamida;

N-(2-amino-5-fluorofenil)-4–((4–metil-1H-pirazol-1-il)metil)benzamida;

4–((1H-pirazol-1-il)metil)–N–(2-aminofenil)-3-metilbenzamida;

N-(2-amino-5-fluorofenil)-3-metil-4–((4–metil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–(furan-2-il)-1H-pirazol-1-il)metil)benzamida;

Ácido 1-(4–((2-aminofenil)carbamoil)bencil)-1H-pirazol-4–carboxílico;

N-(2-aminofenil)-4–((3-etil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-etil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fenil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-3-metil-4–((5-metil-4–fenil-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-ciano-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-(piridin-2-il)-1H-pirazol-1-il)metil)benzamida;

4–((1H-pirazol-1-il)metil)–N–(2-amino-5-(furan-2-il)fenil)benzamida;

N-(2-amino-5-(furan-2-il)fenil)-4–((4–metil-1H-pirazol-1-il)metil)benzamida;

(S)-4–(1-(1H-pirazol-1-il)etil)–N–(2-aminofenil)benzamida;

(R)-4–(1-(1H-pirazol-1-il)etil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((3-(piridin-2-il)-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-metoxi-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((3-(metoximetilamino)-1H-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-(metoximetilamino)-1H-pirazol-1-il)metil)benzamida; y

N-(2-aminofenil)-4–((3-metoxi-1H-pirazol-1-il)metil)benzamida.

51. Un compuesto CARACTERIZADO PORQUE es seleccionado del grupo formado por:

4–((1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((5-acetamido-2*H*-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((5-nitro-1H-indazol-1-il)metil)benzamida;

4–((5-benzamido-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((5-amino-1*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((5-nitro-2*H*-indazol-2-il)metil)benzamida;

4–((5-benzamido-2*H*-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

2-(4–((2-aminofenil)carbamoil)bencil)-2H-indazol-5-ilcarbamato de 2-Metoxietilo;

2-(4–((2-aminofenil)carbamoil)bencil)-2*H*-indazol-5-ilcarbamato de Metilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de 2-Metoxietilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1H-indazol-5-ilcarbamato de Metilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de Bencilo;

2-(4–((2-aminofenil)carbamoil)bencil)-2*H*-indazol-5-ilcarbamato de Bencilo;

N-(4–Amino-bifenil-3-il)-4–(5-nitro-indazol-2-ilmetil)-benzamida;

N-(2-(4–((2-Aminofenil)carbamoil)bencil)-2*H*-indazol-5-il)morfolin-4–carboxamida;

N-(2-Aminofenil)-5-((5-nitro-2*H*-indazol-2-il)metil)tiofen-2-carboxamida;

N-(1-(4–((2-Aminofenil)carbamoil)bencil)-1H-indazol-5-il)morfolin-4–carboxamida;

1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de 2-Morfolinoetilo;

1-(4–((2-aminofenil)carbamoil)bencil)-1*H*-indazol-5-ilcarbamato de Piridin-3-ilmetilo;

N-(4–Amino-bifenil-3-il)-4–pirazolo[3,4–*b*]piridin-2-ilmetil-benzamida;

N-(4–Amino-bifenil-3-il)-4–indazol-2-ilmetil-benzamida;

N-(2-aminofenil)-4–((5-fluoro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–cloro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4–cloro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–fluoro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((3-cloro-2H-indazol-2-il)metil)benzamida;

4–((3-amino-5-(trifluorometil)-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-metoxi-3-metil-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((6-hidroxi-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-metoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5-metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–metoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((4–metoxi-1H-indazol-1-il)metil)benzamida;

4–((6-acetamido-3-metil-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

N-(2-aminofenil)-4–((3-metil-5-(trifluorometil)-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-dimetoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-dimetoxi-1H-indazol-1-il)metil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(piperazin-1-il)etil)-1H-pirazol-4–carboxamida;

4–((2*H*-indazol-2-il)metil)–N–(2-amino-5-(tiofen-2-il)fenil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4–metil-1*H*-pirazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((6-(trifluorometil)-2*H*-indazol-2-il)metil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-2-ilmetil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–fenil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–bencil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–isopropil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-(dimetilamino)propil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-3-ilmetil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(piridin-4–ilmetil)-1H-pirazol-4–carboxamida.;

1-(4–(2-aminofenilcarbamoil)bencil)–N–propil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–isobutil-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-metoxipropil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-hidroxipropil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(3-morfolinopropil)-1H-pirazol-4–carboxamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–(2-(piperidin-1-il)etil)-1H-pirazol-4–carboxamida;

52. Un compuesto CARACTERIZADO PORQUE es seleccionado del grupo formado por:

N-(2-aminofenil)-4–((4,6-difluoro-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((4,6-difluoro-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-difluoro-3-metil-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-difluoro-3-metil-2H-indazol-2-il)metil)benzamida;

4–((3-amino-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-1H-indazol-1-il)metil)–N–(2-aminofenil)benzamida;

4–((6-acetamido-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4,6-difluoro-2*H*-indazol-2-il)metil)benzamida;

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4,6-difluoro-1*H*-indazol-1-il)metil)benzamida;

1-(4–(2-aminofenilcarbamoil)bencil)–N–etil-1H-pirazol-4–carboxamida;

N-(2-aminofenil)-4–((5,6-dimetoxi-1H-indazol-1-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-dimetoxi-2H-indazol-2-il)metil)benzamida; y

N-(2-aminofenil)-4–((5-hidroxi-6-metoxi-2H-indazol-2-il)metil)benzamida.

53. Un compuesto CARACTERIZADO PORQUE es seleccionado del grupo formado por:

1-(4–(2-aminofenilcarbamoil)bencil)–N–etil-1H-pirazol-4–carboxamida;

N-(2-aminofenil)-4–((5,6-dimetoxi-2H-indazol-2-il)metil)benzamida;

4–((6-acetamido-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida; y

4–((3-amino-2H-indazol-2-il)metil)–N–(2-aminofenil)benzamida.

54. Un compuesto CARACTERIZADO PORQUE es seleccionado del grupo formado por:

N-(2-aminofenil)-4–((5-hidroxi-6-metoxi-2H-indazol-2-il)metil)benzamida.

N-(2-aminofenil)-4–((5,6-dimetoxi-2H-indazol-2-il)metil)benzamida;

N-(2-aminofenil)-4–((5,6-difluoro-3-metil-2H-indazol-2-il)metil)benzamida; y

N-(2-amino-5-(tiofen-2-il)fenil)-4–((4,6-difluoro-2*H*-indazol-2-il)metil)benzamida.

55. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-54, CARACTERIZADO PORQUE el compuesto está en la forma de una sal aceptable para uso farmacéutico.

56. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-55, CARACTERIZADO PORQUE el compuesto está presente en una mezcla de estereoisómeros.

57. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-55, CARACTERIZADO PORQUE el compuesto comprende un solo estereoisómero.

58. Una composición farmacéutica CARACTERIZADA PORQUE comprende como ingrediente activo un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57.

59. La composición farmacéutica de acuerdo con la reivindicación 58, CARACTERIZADA PORQUE la composición es una formulación específica adapatada para la administración oral.

60. La composición farmacéutica de acuerdo con la reivindicación 58, CARACTERIZADA PORQUE la composición es una formulación lìquida adapatada para la administración oral.

61. La composición farmacéutica de acuerdo con la reivindicación 58, CARACTERIZADA PORQUE la composición es una tableta.

62. La composición farmacéutica de acuerdo con la reivindicación 58, CARACTERIZADA PORQUE la composición es una formulación liquida adaptada para administración parenteral.

63. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57, CARACTERIZADA PORQUE la composición está adaptada para la administración por una vía seleccionada del grupo formado por vía oral, parenteral, intraperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposomal, por inhalación, vaginal, intraocular, por administración local, subcutánea, intraadiposa, intraarticular o intratecal.

64. Un conjunto de elementos (kit) CARACTERIZADO PORQUE comprende:

un compuesto de cualquiera de las reivindicaciones 1-57; e

instrucciones que comprenden una o más formas de información seleccionadas del grupo formado por indicar un estado de enfermedad para el cual el compuesto se puede administrar, información de almacenamiento del compuesto, información de dosificación e instrucciones sobre la manera de administrar el compuesto.

65. El conjunto de elementos de la reivindicación 64, CARACTERIZADO PORQUE el conjunto de elementos comprende el compuesto en una forma de dosificación múltiple.

66. Un artículo manufacturado CARACTERIZADO PORQUE comprende:

un compuesto de cualquiera de las reivindicaciones 1-57; y

materiales de envase.

67. El artículo manufacturado de la reivindicación 65, CARACTERIZADO PORQUE el material de envase comprende un recipiente para albergar el compuesto.

68. El artículo manufacturado de la reivindicación 67, CARACTERIZADO PORQUE el recipiente comprende una etiqueta que indica uno o más del siguiente grupo: un estado de enfermedad para el cual el compuesto se puede administrar, información de almacenamiento, información de dosificación y/o instrucciones sobre la manera de administrar el compuesto.

69. El artículo manufacturado de la reivindicación 65, CARACTERIZADO PORQUE el artículo manufacturado comprende el compuesto en una forma de dosificación múltiple.

70. Un método terapéutico CARACTERIZADO PORQUE comprende:

administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57 a un sujeto.

71. Un método de inhibir histona deacetilasa CARACTERIZADO PORQUE comprende:

poner en contacto histona deacetilasa con un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57.

72. Un método de inhibir histona deacetilasa CARACTERIZADO PORQUE comprende:

causar que un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57 se encuentre presente en un sujeto con el fin de inhibir histona deacetilasa *in vivo*.

73. Un método de inhibir histona deacetilasa CARACTERIZADO PORQUE comprende:

administrar a un sujeto un primer compuesto que se convierte *in vivo* en un segundo compuesto en donde el segundo compuesto inhibe histona deacetilasa *in vivo*, siendo el segundo compuesto un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57.

74. Un método de tratar un estado de enfermedad para el cual la histona deacetilasa posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, CARACTERIZADO PORQUE comprende:

causar que un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57 se encuentre presente en un sujeto en una cantidad eficaz para uso terapéutico del estado de enfermedad.

75. Un método de tratar un estado de enfermedad para el cual la histona deacetilasa posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, CARACTERIZADO PORQUE comprende:

administrar a un sujeto un primer compuesto que se convierte *in vivo* en un segundo compuesto de acuerdo con cualquiera de las reivindicaciones 1-57 en donde el segundo compuesto está presente en un sujeto en una cantidad eficaz para uso terapéutico del estado de enfermedad.

76. Un método de tratar un estado de enfermedad para el cual la histona deacetilasa posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad CARACTERIZADO PORQUE comprende:

administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57, en donde el compuesto está presente en el sujeto en una cantidad eficaz para uso terapéutico del estado de enfermedad.

77. El método de acuerdo con cualquiera de las reivindicaciones 71-76, CARACTERIZADO PORQUE la histona deacetilasa es una HDAC2.

78. El método de acuerdo con cualquiera de las reivindicaciones 71-76, CARACTERIZADO PORQUE la histona deacetilasa es una HDAC8.

79. Un método para tratar cáncer CARACTERIZADO PORQUE comprende:

administrar una composición de acuerdo con cualquiera de las reivindicaciones 1-57 a un mamífero que lo necesita.

80. El método de la reivindicación 79, CARACTERIZADO PORQUE el cáncer se selecciona del grupo formado por carcinoma de células escamosas, astrocitoma, sarcoma de Kaposi, glioblastoma, cáncer de pulmón de células no pequeñas, cáncer de vejiga, cáncer de cabeza y cuello, melanoma, cáncer de ovario, cáncer de próstata, cáncer de mama, cáncer de pulmón de células pequeñas, glioma, cáncer colorrectal, cáncer genitourinario y cáncer gastrointestinal.

81. Un método para tratar inflamación, sindrome del intestino irritable, psoriasis, o rechazo de transplantes CARACTERIZADO PORQUE comprende administrar

un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57 a un mamífero que lo necesita.

82. Un método para tratar artritis CARACTERIZADO PORQUE comprende administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57 a un mamífero que lo necesita.

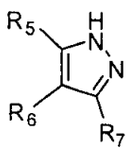
83. Un método para tratar enfermedades oftálmicas degenerativas CARACTERIZADO PORQUE comprende administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57 a un mamífero que lo necesita.

84. Un método para tratar esclerosis múltiple, esclerosis amiotrófica lateral, neoplasma de tiroides o Mal de Alzheimer CARACTERIZADO PORQUE comprende administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57 a un mamífero que lo necesita.

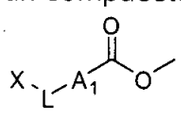
85. Un método para tratar enfermedades hiperproliferativas de la piel o trastornos cutáneos inflamatorios CARACTERIZADO PORQUE comprende administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1-57 a un mamífero que lo necesita.

86. Un proceso CARACTERIZADO PORQUE comprende:

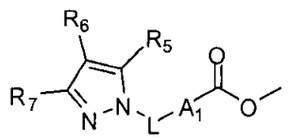
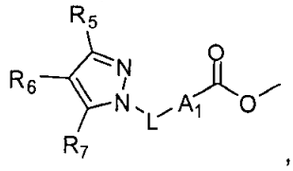
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula seleccionada del grupo formado por

 y  ,

en donde

X es un grupo saliente;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

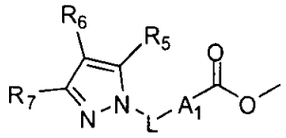
arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido; y

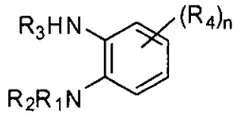
R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

87. Un proceso CARACTERIZADO PORQUE comprende:

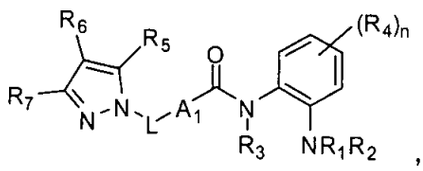
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula



,

en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

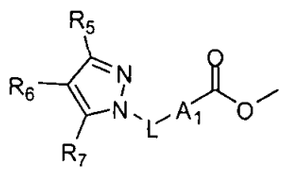
cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo,

imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

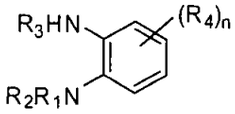
R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

88. Un proceso CARACTERIZADO PORQUE comprende:

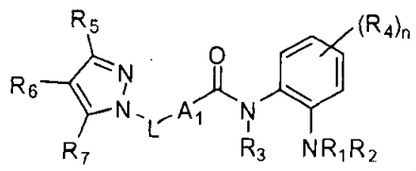
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

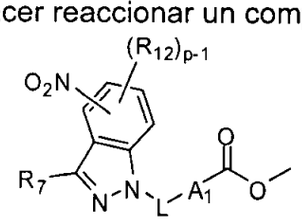
R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

89. Un proceso CARACTERIZADO PORQUE comprende:

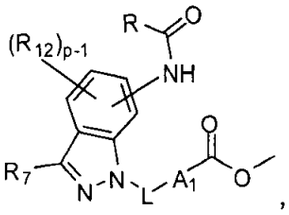
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula

R-C(O)-X

bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

X es un grupo saliente;

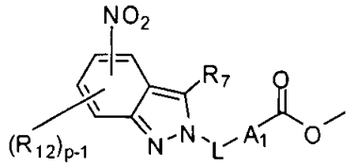
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

90. Un proceso CARACTERIZADO PORQUE comprende:

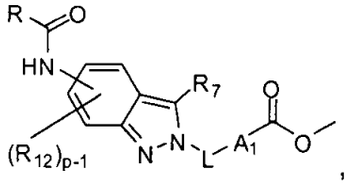
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula

R-C(O)-X

bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

X es un grupo saliente;

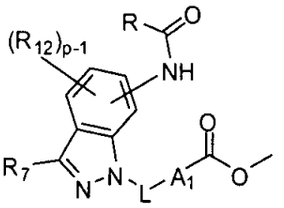
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido,

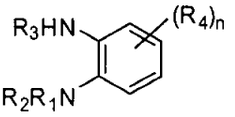
imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

91. Un proceso CARACTERIZADO PORQUE comprende:

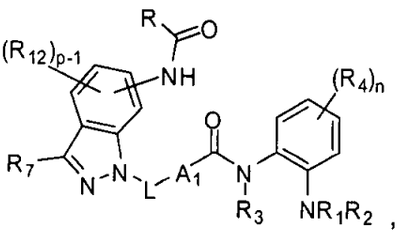
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo,

hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

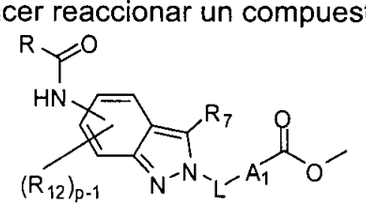
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo,

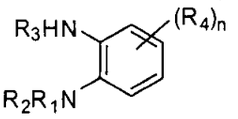
sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

92. Un proceso CARACTERIZADO PORQUE comprende:

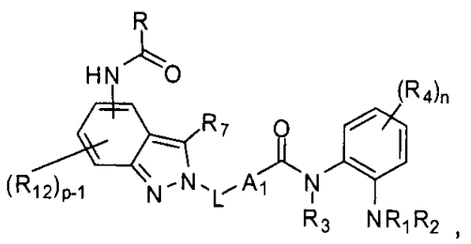
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula



bajo condiciones que forman un producto de reacción que comprende una fórmula



en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino,

sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

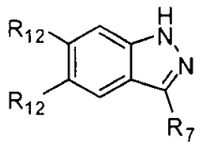
R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo,

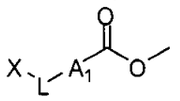
hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

93. Un proceso CARACTERIZADO PORQUE comprende:

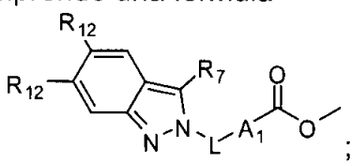
hacer reaccionar un compuesto que comprende la fórmula



con un compuesto que comprende la fórmula

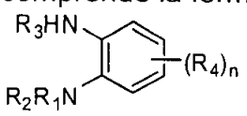


bajo condiciones que forman un primer producto de reacción que comprende una fórmula

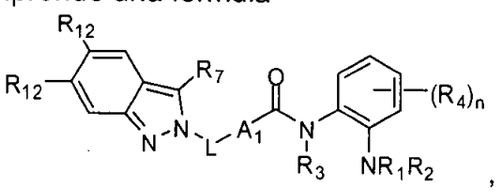


; y

hacer reaccionar el primer producto de reacción con un compuesto que comprende la fórmula



bajo condiciones que forman un segundo producto de reacción que comprende una fórmula



,

en donde

n se selecciona del grupo formado por 0, 1, 2, 3 y 4;

X es un grupo saliente;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_1 y R_2 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_1 y R_2 se pueden tomar juntos para formar un anillo sustituido o no sustituido;

R_3 se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

cada R_4 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo,

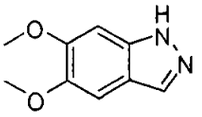
heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

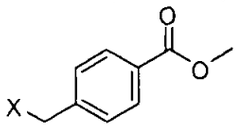
cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

94. El proceso de acuerdo con la reivindicación 93 CARACTERIZADO PORQUE comprende:

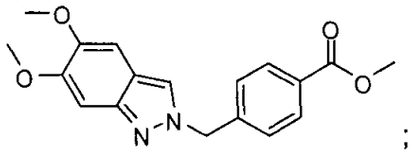
hacer reaccionar un compuesto que comprende la fórmula



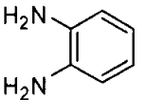
con un compuesto que comprende la fórmula



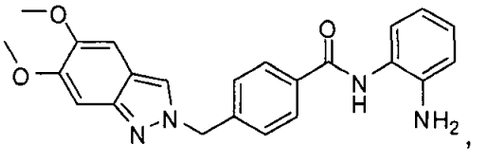
bajo condiciones que forman un primer producto de reacción que comprende una fórmula


; y

hacer reaccionar el primer producto de reacción con un compuesto que comprende la fórmula



bajo condiciones que forman un segundo producto de reacción que comprende una fórmula


,

en donde

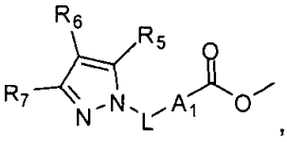
X es un grupo saliente.

95. El proceso de acuerdo con cualquiera de las reivindicaciones 86, 89, 90, 93 y 94 CARACTERIZADO PORQUE X es halo.

96. El proceso de acuerdo con la reivindicación 95 CARACTERIZADO PORQUE X es bromo.

97. El proceso de acuerdo con la reivindicación 95 CARACTERIZADO PORQUE X es cloro.

98. Un compuesto CARACTERIZADO PORQUE comprende:


,

en donde

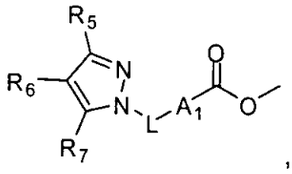
A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo,

arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido; y

R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

99. Un compuesto CARACTERIZADO PORQUE comprende:



en donde

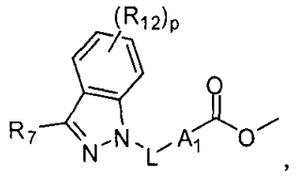
A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido; y

R_5, R_6 y R_7 se seleccionan cada uno en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo,

sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o dos cualquiera de R_5, R_6 y R_7 se pueden tomar juntos para formar un anillo sustituido o no sustituido.

100. Un compuesto CARACTERIZADO PORQUE comprende:



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

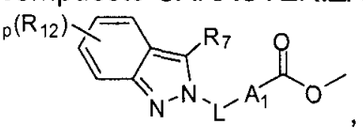
A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

101. Un compuesto CARACTERIZADO PORQUE comprende:



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

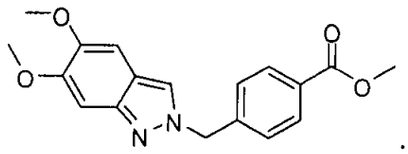
L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo,

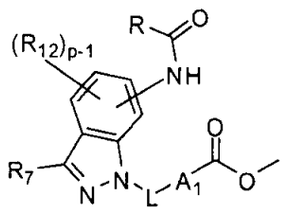
hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

102. El compuesto de acuerdo con la reivindicación 101 CARACTERIZADO PORQUE comprende:



103. Un compuesto CARACTERIZADO PORQUE comprende:



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

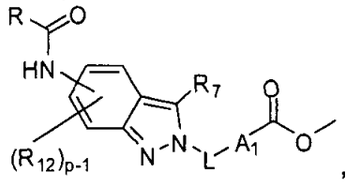
R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo,

hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

104. Un compuesto CARACTERIZADO PORQUE comprende:



en donde

p se selecciona del grupo formado por 0, 1, 2, 3 y 4;

A_1 se selecciona del grupo formado por (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

L es un ligador que provee una separación de 0-6 átomos entre los dos átomos del anillos a los cuales L está unido;

R se selecciona del grupo formado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido;

R_7 se selecciona del grupo formado por hidrógeno, halo, nitro, ciano, oxo, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino

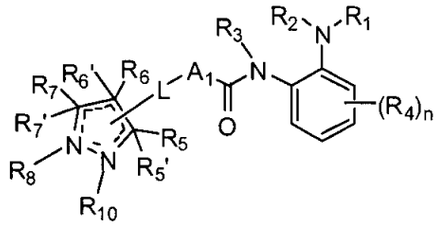
(C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido; y

cada R_{12} se selecciona en forma independiente del grupo formado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, (C_{1-10})alquilamino, amido, carboxamido, sulfonamido, imino, sulfonilo, sulfinilo, (C_{1-10})alquilo, halo(C_{1-10})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, amino (C_{1-10})alquilo, imino(C_{1-3})alquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloaril(C_{1-5})alquilo, hetero(C_{8-12})bicicloaril(C_{1-5})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, (C_{9-12})bicicloalquilo, hetero(C_{3-12})bicicloalquilo, arilo, heteroarilo, (C_{9-12})bicicloarilo y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido, o R_{12} y R_7 o R_{11} se pueden tomar juntos para formar un anillo sustituido o no sustituido.

INHIBIDORES DE HISTONA DEACETILASA

RESUMEN

Compuestos, composiciones farmacéuticas, conjuntos de elementos (*kits*) para usar con HDAC que comprenden un compuesto seleccionado del grupo formado por:



donde los sustituyentes son los definidos en la memoria descriptiva.

FIGURA 1

Secuencia de aminoácidos para los residuos 1-482 de HDAC1 y una marca flag en los extremos N- y C- terminales

[SEQ. I.D. No. 1]

MDYKDDDDKMAQTQGTRRKVCYYYDGDVGNYYYGQGHPMKPHRIRMTHNLLLNYGLYRKM
EIYRPHKANAEEMTKYHSDDYIKFLRSIRPDNMSEYSKQMQRFNVGEDCPVFDGLFEFCQ
LSTGGSVASAVKLNKQQTDIAVNWAGGLHHAKKSEASGFCYVNDIVLAILELLKYHQRVL
YIDIDIHHGDGVEEAFYTTDRVMTVSFHKYGEYFPGTGDLRDIGAGKGKYYAVNYPLRDG
IDDESYEAIFKPVMSKVMEMFQPSAVVLQCGSDSLSGDRLGCFNLTIKGHAKCVEFVKSF
NLPMLMLGGGGYTIRNVARCWTYETAVALDTEIPNELPYNDYFEYFGPDFKLHISPSNMT
NQNTNEYLEKIKQRLFENLRMLPHAPGVQMQAIPEDAIPEESGDEDEDDPDKRISICSSD
KRIACEEEFSDSEEEGEGGRKNSSNFKKAKRVKTEDEKEKDPEEKKEVTEEEKTKEEKPE
AKGVKEEVKLADYKDDDDK

FIGURA 2

Secuencia de ADN usada para codificar los residuos 1-482 de HDAC1 y una marca Flag en los extremos N- y C- terminales

[SEQ. I.D. No. 2]

ATGGACTACAAAGACGACGACGACAAAATGGCGCAGACGCAGGGCACCCGGAGGAAAGTC
TGTTACTACTACGACGGGGATGTTGGAAATTACTATTATGGACAAGGCCACCCAATGAAG
CCTCACCGAATCCGCATGACTCATAATTTGCTGCTCAACTATGGTCTCTACCGAAAAATG
GAAATCTATCGCCCTCACAAAGCCAATGCTGAGGAGATGACCAAGTACCACAGCGATGAC
TACATTAAATTCTTGCGCTCCATCCGTCCAGATAACATGTCGGAGTACAGCAAGCAGATG
CAGAGATTCAACGTTGGTGAGGACTGTCCAGTATTCGATGGCCTGTTTGAGTTCTGTCAG
TTGTCTACTGGTGGTTCTGTGGCAAGTGCTGTGAAACTTAATAAGCAGCAGACGGACATC
GCTGTGAATTGGGCTGGGGGCCTGCACCATGCAAAGAAGTCCGAGGCATCTGGCTTCTGT
TACGTCAATGATATCGTCTTGGCCATCCTGGAACTGCTAAAGTATCACCAGAGGGTGCTG
TACATTGACATTGATATTCACCATGGTGACGGCGTGGAAGAGGCCTTCTACACCACGGAC
CGGGTCATGACTGTGTCCTTTCATAAGTATGGAGAGTACTTCCCAGGAACTGGGGACCTA
CGGGATATCGGGGCTGGCAAAGGCAAGTATTATGCTGTTAACTACCCGCTCCGAGACGGG
ATTGATGACGAGTCCTATGAGGCCATTTTCAAGCCGGTCATGTCCAAAGTAATGGAGATG
TTCCAGCCTAGTGCGGTGGTCTTACAGTGTGGCTCAGACTCCCTATCTGGGGATCGGTTA
GGTTGCTTCAATCTAACTATCAAAGGACACGCCAAGTGTGTGGAATTTGTCAAGAGCTTT
AACCTGCCTATGCTGATGCTGGGAGGCGGTGGTTACACCATTCGTAACGTTGCCCGGTGC
TGGACATATGAGACAGCTGTGGCCCTGGATACGGAGATCCCTAATGAGCTTCCATACAAT
GACTACTTTGAATACTTTGGACCAGATTTCAAGCTCCACATCAGTCCTTCCAATATGACT
AACCAGAACACGAATGAGTACCTGGAGAAGATCAAACAGCGACTGTTTGAGAACCTTAGA
ATGCTGCCGCACGCACCTGGGGTCCAAATGCAGGCGATTCCTGAGGACGCCATCCCTGAG
GAGAGTGGCGATGAGGACGAAGACGACCCTGACAAGCGCATCTCGATCTGCTCCTCTGAC
AAACGAATTGCCTGTGAGGAAGAGTTCTCCGATTCTGAAGAGGAGGGAGAGGGGGGCCGC
AAGAACTCTTCCAACTTCAAAAAAGCCAAGAGAGTCAAAACAGAGGATGAAAAAGAGAAA
GACCCAGAGGAGAAGAAAGAAGTCACCGAAGAGGAGAAAACCAAGGAGGAGAAGCCAGAA
GCCAAAGGGGTCAAGGAGGAGGTCAAGTTGGCCGACTACAAAGACGACGACGACAAATGA

FIGURA 3

Secuencia de aminoácidos para los residuos 1-488 de HDAC2 y una marca de 6-histidina en el extremo C-terminal

[SEQ. I.D. No. 3]

MGSMAYSQGGGKKKVCYYYDGDIGNYYYGQGHPMKPHRIRMTHNLLLNYGLYRKMEIYRP
HKATAEEMTKYHSDEYIKFLRSIRPDNMSEYSKQMQRFNVGEDCPVFDGLFEFCQLSTGG
SVAGAVKLNRQQTDMAVNWAGGLHHAKKSEASGFCYVNDIVLAILELLKYHQRVLYIDID
IHHGDGVEEAFYTTDRVMTVSFHKYGEYFPGTGDLRDIGAGKGKYYAVNFPMRDGIDDES
YGQIFKPIISKVMEMYQPSAVVLQCGADSLSGDRLGCFNLTVKGHAKCVEVVKTFNLPLL
MLGGGGYTIRNVARCWTYETAVALDCEIPNELPYNDYFEYFGPDFKLHISPSNMTNQNTP
EYMEKIKQRLFENLRMLPHAPGVQMQAIPEDAVHEDSGDEDGEDPDKRISIRASDKRIAC
DEEFSDSEDEGEGGRRNVADHKKGAKKARIEEDKKETEDKKTDVKEEDKSKDNSGEKTDT
KGTKSEQLSNPGHHHHHH

FIGURA 4

ADN usado para codificar los residuos 1-488 de HDAC2 y una marca de 6-histidina en el extremo C-terminal.

[SEQ. I.D. No. 4]

ATGGGATCCATGGCGTACAGTCAAGGAGGCGGCAAAAAAAAAGTCTGCTACTACTACGAC
GGTGATATTGGAAATTATTATTATGGACAGGGTCATCCCATGAAGCCTCATAGAATCCGC
ATGACCCATAACTTGCTGTTAAATTATGGCTTATACAGAAAAATGGAAATATATAGGCCC
CATAAAGCCACTGCCGAAGAAATGACAAAATATCACAGTGATGAGTATATCAAATTTCTA
CGGTCAATAAGACCAGATAACATGTCTGAGTATAGTAAGCAGATGCAGAGATTTAATGTT
GGAGAAGATTGTCCAGTGTTTGATGGACTCTTTGAGTTTTGTCAGCTCTCAACTGGCGGT
TCAGTTGCTGGAGCTGTGAAGTTAAACCGACAACAGACTGATATGGCTGTTAATTGGGCT
GGAGGATTACATCATGCTAAGAAATCAGAAGCATCAGGATTCTGTTACGTTAATGATATT
GTGCTTGCCATCCTTGAATTACTAAAGTATCATCAGAGAGTCTTATATATTGATATAGAT
ATTCATCATGGTGATGGTGTTGAAGAAGCTTTTTATACAACAGATCGTGTAATGACGGTA
TCATTCCATAAATATGGGGAATACTTTCCTGGCACAGGAGACTTGAGGGATATTGGTGCT
GGAAAAGGCAAATACTATGCTGTCAATTTTCCAATGAGAGATGGTATAGATGATGAGTCA
TATGGGCAGATATTTAAGCCTATTATCTCAAAGGTGATGGAGATGTATCAACCTAGTGCT
GTGGTATTACAGTGTGGTGCAGACTCATTATCTGGTGATAGACTGGGTTGTTTCAATCTA
ACAGTCAAAGGTCATGCTAAATGTGTAGAAGTTGTAAAAACTTTTAACTTACCATTACTG
ATGCTTGGAGGAGGTGGCTACACAATCCGTAATGTTGCTCGATGTTGGACATATGAGACT
GCAGTTGCCCTTGATTGTGAGATTCCCAATGAGTTGCCATATAATGATTACTTTGAGTAT
TTTGGACCAGACTTCAAACTGCATATTAGTCCTTCAAACATGACAAACCAGAACACTCCA
GAATATATGGAAAAGATAAAACAGCGTTTGTTTGAAAATTTGCGCATGTTACCTCATGCA
CCTGGTGTCCAGATGCAAGCTATTCCAGAAGATGCTGTTCATGAAGACAGTGGAGATGAA
GATGGAGAAGATCCAGACAAGAGAATTTCTATTCGAGCATCAGACAAGCGGATAGCTTGT
GATGAAGAATTCTCAGATTCTGAGGATGAAGGAGAAGGAGGTCGAAGAAATGTGGCTGAT
CATAAGAAAGGAGCAAAGAAAGCTAGAATTGAAGAAGATAAGAAAGAAACAGAGGACAAA
AAAACAGACGTTAAGGAAGAAGATAAATCCAAGGACAACAGTGGTGAAAAAACAGATACC
AAAGGAACCAAATCAGAACAGCTCAGCAACCCCGGGCATCACCATCACCATCACTAA

FIGURA 5

Secuencia de aminoácidos para los residuos 73-845 de HDAC6 y una marca de 6-histidina en el extremo C-terminal

[SEQ. I.D. No. 5]

MPGMDLNLEAEALAGTGLVLDEQLNEFHCLWDDSFPEGPERLHAIKEQLIQEGLLDRCVS
FQARFAEKEELMLVHSLEYIDLMETTQYMNEGELRVLADTYDSVYLHPNSYSCACLASGS
VLRLVDAVLGAEIRNGMAIIRPPGHHAQHSLMDGYCMFNHVAVAARYAQQKHRIRRVLIV
DWDVHHGQGTQFTFDQDPSVLYFSIHRYEQGRFWPHLKASNWSTTGFGQGQGYTINVPWN
QVGMRDADYIAAFLHVLLPVALEFQPQLVLVAAGFDALQGDPKGEMAATPAGFAQLTHLL
MGLAGGKLILSLEGGYNLRALAEGVSASLHTLLGDPCPMLESPGAPCRSAQASVSCALEA
LEPFWEVLVRSTETVERDNMEEDNVEESEEEGPWEPPVLPILTWPVLQSRTGLVYDQNMM
NHCNLWDSHHPEVPQRILRIMCRLEELGLAGRCLTLTPRPATEAELLTCHSAEYVGHLRA
TEKMKTRELHRESSNFDSIYICPSTFACAQLATGAACRLVEAVLSGEVLNGAAVVRPPGH
HAEQDAACGFCFFNSVAVAARHAQTISGHALRILIVDWDVHHGNGTQHMFEDDPSVLYVS
LHRYDHGTFFPMGDEGASSQIGRAAGTGFTVNVAWNGPRMGDADYLAAWHRLVLPIAYEF
NPELVLVSAGFDAARGDPLGGCQVSPEGYAHLTHLLMGLASGRIILILEGGYNLTSISES
MAACTRSLLGDPPPLLTLPRPPLSGALASITETIQVHRRYWRSLRVMKVEDREGPGHHHH
HH

FIGURA 6

Secuencia de ADN usada para codificar los residuos 73-845 de HDAC6 y una marca de 6-histidina en el extremo C-terminal

[SEQ. I.D. No. 6]

ATGCCCGGGATGGATCTGAACCTTGAGGCTGAAGCACTGGCTGGCACTGGCTTGGTGTTG
GATGAGCAGTTAAATGAATTCCATTGCCTCTGGGATGACAGCTTCCCGGAAGGCCCTGAG
CGGCTCCATGCCATCAAGGAGCAACTGATCCAGGAGGGCCTCCTAGATCGCTGCGTGTCC
TTTCAGGCCCGGTTTGCTGAAAAGGAAGAGCTGATGTTGGTTCACAGCCTAGAATATATT
GATCTGATGGAAACAACCCAGTACATGAATGAGGGAGAACTCCGTGTCCTAGCAGACACC
TACGACTCAGTTTATCTGCATCCGAACTCATACTCCTGTGCCTGCCTGGCCTCAGGCTCT
GTCCTCAGGCTGGTGGATGCGGTCCTGGGGGCTGAGATCCGGAATGGCATGGCCATCATT
AGGCCTCCTGGACATCACGCCCAGCACAGTCTTATGGATGGCTATTGCATGTTCAACCAC
GTGGCTGTGGCAGCCCGCTATGCTCAACAGAAACACCGCATCCGGAGGGTCCTTATCGTA
GATTGGGATGTGCACCACGGTCAAGGAACACAGTTCACCTTCGACCAGGACCCCAGTGTC
CTCTATTTCTCCATCCACCGCTACGAGCAGGGTAGGTTCTGGCCCCACCTGAAGGCCTCT
AACTGGTCCACCACAGGTTTCGGCCAAGGCCAAGGATATACCATCAATGTGCCTTGGAAC
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GCCCTCGAGTTCCAGCCTCAGCTGGTCCTGGTGGCTGCTGGATTTGATGCCCTGCAAGGG
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GAGGAGGACAATGTAGAGGAGAGCGAGGAGGAAGGACCCTGGGAGCCCCCTGTGCTCCCA
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AATCACTGCAACTTGTGGGACAGCCACCACCCTGAGGTACCCCAGCGCATCTTGCGGATC
ATGTGCCGTCTGGAGGAGCTGGGCCTTGCCGGGCGCTGCCTCACCCTGACACCGCGCCCT
GCCACAGAGGCTGAGCTGCTCACCTGTCACAGTGCTGAGTACGTGGGTCATCTCCGGGCC
ACAGAGAAAATGAAAACCCGGGAGCTGCACCGTGAGAGTTCCAACTTTGACTCCATCTAT
ATCTGCCCCAGTACCTTCGCCTGTGCACAGCTTGCCACTGGCGCTGCCTGCCGCCTGGTG
GAGGCTGTGCTCTCAGGAGAGGTTCTGAATGGTGCTGCTGTGGTGCGTCCCCCAGGACAC
CACGCAGAGCAGGATGCAGCTTGCGGTTTTTGCTTTTTCAACTCTGTGGCTGTGGCTGCT
CGCCATGCCCAGACTATCAGTGGGCATGCCCTACGGATCCTGATTGTGGATTGGGATGTC
CACCACGGTAATGGAACTCAGCACATGTTTGAGGATGACCCCAGTGTGCTATATGTGTCC
CTGCACCGCTATGATCATGGCACCTTCTTCCCCATGGGGGATGAGGGTGCCAGCAGCCAG
ATCGGCCGGGCTGCGGGCACAGGCTTCACCGTCAACGTGGCATGGAACGGGCCCCGCATG
GGTGATGCTGACTACCTAGCTGCCTGGCATCGCCTGGTGCTTCCCATTGCCTACGAGTTT
AACCCAGAACTGGTGCTGGTCTCAGCTGGCTTTGATGCTGCACGGGGGGATCCGCTGGGG
GGCTGCCAGGTGTCACCTGAGGGTTATGCCCACCTCACCCACCTGCTGATGGGCCTTGCC
AGTGGCCGCATTATCCTTATCCTAGAGGGTGGCTATAACCTGACATCCATCTCAGAGTCC
ATGGCTGCCTGCACTCGCTCCCTCCTTGGAGACCCACCACCCCTGCTGACCCTGCCACGG
CCCCCACTATCAGGGGCCCTGGCCTCAATCACTGAGACCATCCAAGTCCATCGCAGATAC
TGGCGCAGCTTACGGGTCATGAAGGTAGAAGACAGAGAAGGACCCGGGCATCACCATCAC
CATCACTAA

FIGURA 7

Secuencia de aminoácidos para los residuos 1-377 de HDAC8 y una marca de 6-histidina en el extremo N-terminal

[SEQ. I.D. No. 7]

MHHHHHHPMEEPEEPADSGQSLVPVYIYSPEYVSMCDSLAKIPKRASMVHSLIEAYALHK
QMRIVKPKVASMEEMAAFHTDAYLQHLQKVSQEGDDDHPDSIEYGLGYDCPATEGIFDYA
AAIGGATITAAQCLIDGMCKVAINWSGGWHHAKKDEASGFCYLNDAVLGILRLRRKFERI
LYVDLDLHHGDGVEDAFSFTSKVMTVSLHKFSPGFFPGTGDVSDVGLGKGRYYSVNVPIQ
DGIQDEKYYQICESVLKEVYQAFNPKAVVLQLGADTIAGDPMCSFNMTPVGIGKCLKYIL
QWQLATLILGGGGYNLANTARCWTYLTGVILGKTLSSEIPDHEFFTAYGPDYVLEITPSC
RPDRNEPHRIQQILNYIKGNLKHVV

FIGURA 8

Secuencia de ADN usada para codificar los residuos 1-377 de HDAC8 y una marca de 6-histidina en el extremo N-terminal

[SEQ. I.D. No. 8]

ATGCACCATCACCATCACCATCCCATGGAGGAGCCGGAGGAACCGGCGGACAGTGGGCAG
TCGCTGGTCCCGGTTTATATCTATAGTCCCGAGTATGTCAGTATGTGTGACTCCCTGGCC
AAGATCCCCAAACGGGCCAGTATGGTGCATTCTTTGATTGAAGCATATGCACTGCATAAG
CAGATGAGGATAGTTAAGCCTAAAGTGGCCTCCATGGAGGAGATGGCCGCCTTCCACACT
GATGCTTATCTGCAGCATCTCCAGAAGGTCAGCCAAGAGGGCGATGATGATCATCCGGAC
TCCATAGAATATGGGCTAGGTTATGACTGCCCAGCCACTGAAGGGATATTTGACTATGCA
GCAGCTATAGGAGGGGCTACGATCACAGCTGCCCAATGCCTGATTGACGGAATGTGCAAA
GTAGCAATTAACTGGTCTGGAGGGTGGCATCATGCAAAGAAAGATGAAGCATCTGGTTTT
TGTTATCTCAATGATGCTGTCCTGGGAATATTACGATTGCGACGGAAATTTGAGCGTATT
CTCTACGTGGATTTGGATCTGCACCATGGAGATGGTGTAGAAGACGCATTCAGTTTCACC
TCCAAAGTCATGACCGTGTCCCTGCACAAATTCTCCCCAGGATTTTTCCCAGGAACAGGT
GACGTGTCTGATGTTGGCCTAGGGAAGGGACGGTACTACAGTGTAAATGTGCCCATTCAG
GATGGCATACAAGATGAAAAATATTACCAGATCTGTGAAAGTGTACTAAAGGAAGTATAC
CAAGCCTTTAATCCCAAAGCAGTGGTCTTACAGCTGGGAGCTGACACAATAGCTGGGGAT
CCCATGTGCTCCTTTAACATGACTCCAGTGGGAATTGGCAAGTGTCTTAAGTACATCCTT
CAATGGCAGTTGGCAACACTCATTTTGGGAGGAGGAGGCTATAACCTTGCCAACACGGCT
CGATGCTGGACATACTTGACCGGGGTCATCCTAGGGAAAACACTATCCTCTGAGATCCCA
GATCATGAGTTTTTCACAGCATATGGTCCTGATTATGTGCTGGAAATCACGCCAAGCTGC
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CTGAAGCATGTGGTCTAG

LISTADO DE SECUENCIAS

<110> Takeda San Diego, Inc.

<120> INHIBIDORES DE HISTONA DEACETILASA

<130> HDAC-5015-AR

<150> 60/699,139
<151> 2005-07-14

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<170> PatentIn version 3.3

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<223> Secuencia de aminoácidos para los residuos 1-482 de HDAC1 y una marca flag en los extremos N- y C- terminales

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1 5 10 15

Arg Arg Lys Val Cys Tyr Tyr Tyr Asp Gly Asp Val Gly Asn Tyr Tyr
20 25 30

Tyr Gly Gln Gly His Pro Met Lys Pro His Arg Ile Arg Met Thr His
35 40 45

Asn Leu Leu Leu Asn Tyr Gly Leu Tyr Arg Lys Met Glu Ile Tyr Arg
50 55 60

Pro His Lys Ala Asn Ala Glu Glu Met Thr Lys Tyr His Ser Asp Asp
65 70 75 80

Tyr Ile Lys Phe Leu Arg Ser Ile Arg Pro Asp Asn Met Ser Glu Tyr
85 90 95

Ser Lys Gln Met Gln Arg Phe Asn Val Gly Glu Asp Cys Pro Val Phe
100 105 110

Asp Gly Leu Phe Glu Phe Cys Gln Leu Ser Thr Gly Gly Ser Val Ala
115 120 125

Ser Ala Val Lys Leu Asn Lys Gln Gln Thr Asp Ile Ala Val Asn Trp
130 135 140

Ala Gly Gly Leu His His Ala Lys Lys Ser Glu Ala Ser Gly Phe Cys
145 150 155 160

Tyr Val Asn Asp Ile Val Leu Ala Ile Leu Glu Leu Leu Lys Tyr His
165 170 175

Gln Arg Val Leu Tyr Ile Asp Ile Asp Ile His His Gly Asp Gly Val
180 185 190

Glu Glu Ala Phe Tyr Thr Thr Asp Arg Val Met Thr Val Ser Phe His
195 200 205

Lys Tyr Gly Glu Tyr Phe Pro Gly Thr Gly Asp Leu Arg Asp Ile Gly
210 215 220

Ala Gly Lys Gly Lys Tyr Tyr Ala Val Asn Tyr Pro Leu Arg Asp Gly
225 230 235 240

Ile Asp Asp Glu Ser Tyr Glu Ala Ile Phe Lys Pro Val Met Ser Lys
245 250 255

Val Met Glu Met Phe Gln Pro Ser Ala Val Val Leu Gln Cys Gly Ser
260 265 270

Asp Ser Leu Ser Gly Asp Arg Leu Gly Cys Phe Asn Leu Thr Ile Lys
275 280 285

Gly His Ala Lys Cys Val Glu Phe Val Lys Ser Phe Asn Leu Pro Met
290 295 300

Leu Met Leu Gly Gly Gly Gly Tyr Thr Ile Arg Asn Val Ala Arg Cys
305 310 315 320

Trp Thr Tyr Glu Thr Ala Val Ala Leu Asp Thr Glu Ile Pro Asn Glu
325 330 335

Leu Pro Tyr Asn Asp Tyr Phe Glu Tyr Phe Gly Pro Asp Phe Lys Leu
340 345 350

His Ile Ser Pro Ser Asn Met Thr Asn Gln Asn Thr Asn Glu Tyr Leu
355 360 365

Glu Lys Ile Lys Gln Arg Leu Phe Glu Asn Leu Arg Met Leu Pro His
370 375 380

Ala Pro Gly Val Gln Met Gln Ala Ile Pro Glu Asp Ala Ile Pro Glu
385 390 395 400

Glu Ser Gly Asp Glu Asp Glu Asp Asp Pro Asp Lys Arg Ile Ser Ile
405 410 415

Cys Ser Ser Asp Lys Arg Ile Ala Cys Glu Glu Glu Phe Ser Asp Ser
420 425 430

Glu Glu Glu Gly Glu Gly Gly Arg Lys Asn Ser Ser Asn Phe Lys Lys
435 440 445

Ala Lys Arg Val Lys Thr Glu Asp Glu Lys Glu Lys Asp Pro Glu Glu
450 455 460

Lys Lys Glu Val Thr Glu Glu Glu Lys Thr Lys Glu Glu Lys Pro Glu
465 470 475 480

Ala Lys Gly Val Lys Glu Glu Val Lys Leu Ala Asp Tyr Lys Asp Asp
485 490 495

Asp Asp Lys

<210> 2
<211> 1500
<212> ADN
<213> Secuencia Artificial

<220>
<223> Secuencia de ADN usada para codificar los residuos 1-482 de HDAC1 y una marca Flag en los extremos N- y C- terminales

<400> 2
atggactaca aagacgacga cgacaaaatg gcgcagacgc agggcacccg gaggaaagtc 60

tgttactact acgacgggga tgttggaaat tactattatg gacaaggcca cccaatgaag 120

cctcaccgaa tccgcatgac tcataatttg ctgctcaact atggtctcta ccgaaaaatg 180

gaaatctatc gccctcacaa agccaatgct gaggagatga ccaagtacca cagcgatgac 240

tacattaaat tcttgcgctc catccgtcca gataacatgt cggagtacag caagcagatg 300

cagagattca acgttggtga ggactgtcca gtattcgatg gcctgtttga gttctgtcag 360

ttgtctactg gtggttctgt ggcaagtgct gtgaaactta ataagcagca gacggacatc 420

gctgtgaatt gggctggggg cctgcaccat gcaaagaagt ccgaggcatc tggcttctgt 480

tacgtcaatg atatcgtctt ggccatcctg gaactgctaa agtatcacca gagggtgctg 540

tacattgaca ttgatattca ccatggtgac ggcgtggaag aggccttcta caccacggac 600

cgggtcatga ctgtgtcctt tcataagtat ggagagtact tcccaggaac tggggaccta 660

cgggatatcg gggctggcaa aggcaagtat tatgctgtta actacccgct ccgagacggg 720

attgatgacg agtcctatga ggccattttc aagccggtca tgtccaaagt aatggagatg 780

ttccagccta gtgcggtggt cttacagtgt ggctcagact ccctatctgg ggatcggtta 840

ggttgcttca atctaactat caaaggacac gccaagtgtg tggaatttgt caagagcttt 900

aacctgccta tgctgatgct gggaggcggt ggttacacca ttcgtaacgt tgcccggtgc 960

tggacatatg agacagctgt ggccctggat acggagatcc ctaatgagct tccatacaat 1020

gactactttg aatactttgg accagatttc aagctccaca tcagtccttc caatatgact 1080

aaccagaaca cgaatgagta cctggagaag atcaaacagc gactgtttga gaaccttaga 1140

atgctgccgc acgcacctgg ggtccaaatg caggcgattc ctgaggacgc catccctgag 1200

gagagtggcg atgaggacga agacgaccct gacaagcgca tctcgatctg ctcctctgac 1260

aaacgaattg cctgtgagga agagttctcc gattctgaag aggagggaga ggggggccgc 1320

aagaactctt ccaacttcaa aaaagccaag agagtcaaaa cagaggatga aaaagagaaa 1380

gacccagagg agaagaaaga agtcaccgaa gaggagaaaa ccaaggagga gaagccagaa 1440

gccaaagggg tcaaggagga ggtcaagttg gccgactaca aagacgacga cgacaaatga 1500

<210> 3
<211> 498
<212> PRT
<213> Secuencia Artificial

<220>
<223> Secuencia de aminoácidos para los residuos 1-488 de HDAC2 y una marca de 6-histidina en el extremo C-terminal

<400> 3

Met Gly Ser Met Ala Tyr Ser Gln Gly Gly Gly Lys Lys Lys Val Cys

1 5 10 15

Tyr Tyr Tyr Asp Gly Asp Ile Gly Asn Tyr Tyr Tyr Gly Gln Gly His
20 25 30

Pro Met Lys Pro His Arg Ile Arg Met Thr His Asn Leu Leu Leu Asn
35 40 45

Tyr Gly Leu Tyr Arg Lys Met Glu Ile Tyr Arg Pro His Lys Ala Thr
50 55 60

Ala Glu Glu Met Thr Lys Tyr His Ser Asp Glu Tyr Ile Lys Phe Leu
65 70 75 80

Arg Ser Ile Arg Pro Asp Asn Met Ser Glu Tyr Ser Lys Gln Met Gln
85 90 95

Arg Phe Asn Val Gly Glu Asp Cys Pro Val Phe Asp Gly Leu Phe Glu
100 105 110

Phe Cys Gln Leu Ser Thr Gly Gly Ser Val Ala Gly Ala Val Lys Leu
115 120 125

Asn Arg Gln Gln Thr Asp Met Ala Val Asn Trp Ala Gly Gly Leu His
130 135 140

His Ala Lys Lys Ser Glu Ala Ser Gly Phe Cys Tyr Val Asn Asp Ile
145 150 155 160

Val Leu Ala Ile Leu Glu Leu Leu Lys Tyr His Gln Arg Val Leu Tyr
165 170 175

Ile Asp Ile Asp Ile His His Gly Asp Gly Val Glu Glu Ala Phe Tyr
180 185 190

Thr Thr Asp Arg Val Met Thr Val Ser Phe His Lys Tyr Gly Glu Tyr
195 200 205

Phe Pro Gly Thr Gly Asp Leu Arg Asp Ile Gly Ala Gly Lys Gly Lys
210 215 220

Tyr Tyr Ala Val Asn Phe Pro Met Arg Asp Gly Ile Asp Asp Glu Ser
225 230 235 240

Tyr Gly Gln Ile Phe Lys Pro Ile Ile Ser Lys Val Met Glu Met Tyr
245 250 255

Gln Pro Ser Ala Val Val Leu Gln Cys Gly Ala Asp Ser Leu Ser Gly
260 265 270

Asp Arg Leu Gly Cys Phe Asn Leu Thr Val Lys Gly His Ala Lys Cys
275 280 285

Val Glu Val Val Lys Thr Phe Asn Leu Pro Leu Leu Met Leu Gly Gly
290 295 300

Gly Gly Tyr Thr Ile Arg Asn Val Ala Arg Cys Trp Thr Tyr Glu Thr
305 310 315 320

Ala Val Ala Leu Asp Cys Glu Ile Pro Asn Glu Leu Pro Tyr Asn Asp
325 330 335

Tyr Phe Glu Tyr Phe Gly Pro Asp Phe Lys Leu His Ile Ser Pro Ser
340 345 350

Asn Met Thr Asn Gln Asn Thr Pro Glu Tyr Met Glu Lys Ile Lys Gln
355 360 365

Arg Leu Phe Glu Asn Leu Arg Met Leu Pro His Ala Pro Gly Val Gln
370 375 380

Met Gln Ala Ile Pro Glu Asp Ala Val His Glu Asp Ser Gly Asp Glu
385 390 395 400

Asp Gly Glu Asp Pro Asp Lys Arg Ile Ser Ile Arg Ala Ser Asp Lys
405 410 415

Arg Ile Ala Cys Asp Glu Glu Phe Ser Asp Ser Glu Asp Glu Gly Glu
420 425 430

Gly Gly Arg Arg Asn Val Ala Asp His Lys Lys Gly Ala Lys Lys Ala
435 440 445

Arg Ile Glu Glu Asp Lys Lys Glu Thr Glu Asp Lys Lys Thr Asp Val
450 455 460

Lys Glu Glu Asp Lys Ser Lys Asp Asn Ser Gly Glu Lys Thr Asp Thr
465 470 475 480

Lys Gly Thr Lys Ser Glu Gln Leu Ser Asn Pro Gly His His His His
485 490 495

His His

<210> 4
<211> 1497
<212> ADN
<213> Secuencia Artificial

<220>
<223> ADN usado para codificar los residuos 1-488 de HDAC2 y una marca de 6-histidina en el extremo C-terminal.

<400> 4
atgggatcca tggcgtacag tcaaggaggc ggcaaaaaaa aagtctgcta ctactacgac 60

ggtgatattg gaaattatta ttatggacag ggtcatccca tgaagcctca tagaatccgc 120

atgacccata acttgctgtt aaattatggc ttatacagaa aaatggaaat atataggccc 180

cataaagcca ctgccgaaga aatgacaaaa tatcacagtg atgagtatat caaatttcta 240

cggtcaataa gaccagataa catgtctgag tatagtaagc agatgcagag atttaatgtt 300

ggagaagatt gtccagtgtt tgatggactc tttgagtttt gtcagctctc aactggcggt 360

tcagttgctg gagctgtgaa gttaaaccga caacagactg atatggctgt taattgggct 420

ggaggattac atcatgctaa gaaatcagaa gcatcaggat tctgttacgt taatgatatt 480

gtgcttgcca tccttgaatt actaaagtat catcagagag tcttatatat tgatatagat 540

attcatcatg gtgatggtgt tgaagaagct ttttatacaa cagatcgtgt aatgacggta 600

tcattccata aatatgggga atactttcct ggcacaggag acttgaggga tattggtgct 660

ggaaaaggca aatactatgc tgtcaatttt ccaatgagag atggtataga tgatgagtca 720

tatgggcaga tatttaagcc tattatctca aaggtgatgg agatgtatca acctagtgct 780

gtggtattac agtgtggtgc agactcatta tctggtgata gactgggttg tttcaatcta 840

acagtcaaag gtcatgctaa atgtgtagaa gttgtaaaaa ctttttaactt accattactg 900

atgcttggag gaggtggcta cacaatccgt aatgttgctc gatgttggac atatgagact 960

gcagttgccc ttgattgtga gattcccaat gagttgccat ataatgatta ctttgagtat 1020

tttggaccag acttcaaact gcatattagt ccttcaaaca tgacaaacca gaacactcca 1080

gaatatatgg aaaagataaa acagcgtttg tttgaaaatt tgcgcatgtt acctcatgca 1140

cctggtgtcc agatgcaagc tattccagaa gatgctgttc atgaagacag tggagatgaa 1200

gatggagaag atccagacaa gagaatttct attcgagcat cagacaagcg gatagcttgt 1260

gatgaagaat tctcagattc tgaggatgaa ggagaaggag gtcgaagaaa tgtggctgat 1320

cataagaaag gagcaaagaa agctagaatt gaagaagata agaaagaaac agaggacaaa 1380

aaaacagacg ttaaggaaga agataaatcc aaggacaaca gtggtgaaaa aacagatacc 1440

aaaggaacca aatcagaaca gctcagcaac cccgggcatc accatcacca tcactaa 1497

<210> 5
<211> 782
<212> PRT
<213> Secuencia Artificial

<220>
<223> Secuencia de aminoácidos para los residuos 73-845 de HDAC6 y una marca de 6-histidina en el extremo C-terminal

<400> 5

Met Pro Gly Met Asp Leu Asn Leu Glu Ala Glu Ala Leu Ala Gly Thr
1 5 10 15

Gly Leu Val Leu Asp Glu Gln Leu Asn Glu Phe His Cys Leu Trp Asp
20 25 30

Asp Ser Phe Pro Glu Gly Pro Glu Arg Leu His Ala Ile Lys Glu Gln
35 40 45

Leu Ile Gln Glu Gly Leu Leu Asp Arg Cys Val Ser Phe Gln Ala Arg
50 55 60

Phe Ala Glu Lys Glu Glu Leu Met Leu Val His Ser Leu Glu Tyr Ile
65 70 75 80

Asp Leu Met Glu Thr Thr Gln Tyr Met Asn Glu Gly Glu Leu Arg Val
85 90 95

Leu Ala Asp Thr Tyr Asp Ser Val Tyr Leu His Pro Asn Ser Tyr Ser
100 105 110

Cys Ala Cys Leu Ala Ser Gly Ser Val Leu Arg Leu Val Asp Ala Val

115 120 125

Leu Gly Ala Glu Ile Arg Asn Gly Met Ala Ile Ile Arg Pro Pro Gly
130 135 140

His His Ala Gln His Ser Leu Met Asp Gly Tyr Cys Met Phe Asn His
145 150 155 160

Val Ala Val Ala Ala Arg Tyr Ala Gln Gln Lys His Arg Ile Arg Arg
165 170 175

Val Leu Ile Val Asp Trp Asp Val His His Gly Gln Gly Thr Gln Phe
180 185 190

Thr Phe Asp Gln Asp Pro Ser Val Leu Tyr Phe Ser Ile His Arg Tyr
195 200 205

Glu Gln Gly Arg Phe Trp Pro His Leu Lys Ala Ser Asn Trp Ser Thr
210 215 220

Thr Gly Phe Gly Gln Gly Gln Gly Tyr Thr Ile Asn Val Pro Trp Asn
225 230 235 240

Gln Val Gly Met Arg Asp Ala Asp Tyr Ile Ala Ala Phe Leu His Val
245 250 255

Leu Leu Pro Val Ala Leu Glu Phe Gln Pro Gln Leu Val Leu Val Ala
260 265 270

Ala Gly Phe Asp Ala Leu Gln Gly Asp Pro Lys Gly Glu Met Ala Ala
275 280 285

Thr Pro Ala Gly Phe Ala Gln Leu Thr His Leu Leu Met Gly Leu Ala
290 295 300

Gly Gly Lys Leu Ile Leu Ser Leu Glu Gly Gly Tyr Asn Leu Arg Ala
305 310 315 320

Leu Ala Glu Gly Val Ser Ala Ser Leu His Thr Leu Leu Gly Asp Pro
325 330 335

Cys Pro Met Leu Glu Ser Pro Gly Ala Pro Cys Arg Ser Ala Gln Ala

340 345 350

Ser Val Ser Cys Ala Leu Glu Ala Leu Glu Pro Phe Trp Glu Val Leu
355 360 365

Val Arg Ser Thr Glu Thr Val Glu Arg Asp Asn Met Glu Glu Asp Asn
370 375 380

Val Glu Glu Ser Glu Glu Glu Gly Pro Trp Glu Pro Pro Val Leu Pro
385 390 395 400

Ile Leu Thr Trp Pro Val Leu Gln Ser Arg Thr Gly Leu Val Tyr Asp
405 410 415

Gln Asn Met Met Asn His Cys Asn Leu Trp Asp Ser His His Pro Glu
420 425 430

Val Pro Gln Arg Ile Leu Arg Ile Met Cys Arg Leu Glu Glu Leu Gly
435 440 445

Leu Ala Gly Arg Cys Leu Thr Leu Thr Pro Arg Pro Ala Thr Glu Ala
450 455 460

Glu Leu Leu Thr Cys His Ser Ala Glu Tyr Val Gly His Leu Arg Ala
465 470 475 480

Thr Glu Lys Met Lys Thr Arg Glu Leu His Arg Glu Ser Ser Asn Phe
485 490 495

Asp Ser Ile Tyr Ile Cys Pro Ser Thr Phe Ala Cys Ala Gln Leu Ala
500 505 510

Thr Gly Ala Ala Cys Arg Leu Val Glu Ala Val Leu Ser Gly Glu Val
515 520 525

Leu Asn Gly Ala Ala Val Val Arg Pro Pro Gly His His Ala Glu Gln
530 535 540

Asp Ala Ala Cys Gly Phe Cys Phe Phe Asn Ser Val Ala Val Ala Ala
545 550 555 560

Arg His Ala Gln Thr Ile Ser Gly His Ala Leu Arg Ile Leu Ile Val
565 570 575

Pro Val Gly Ile Gly Lys Cys Leu Lys Tyr Ile Leu Gln Trp Gln Leu
290 295 300

Ala Thr Leu Ile Leu Gly Gly Gly Gly Tyr Asn Leu Ala Asn Thr Ala
305 310 315 320

Arg Cys Trp Thr Tyr Leu Thr Gly Val Ile Leu Gly Lys Thr Leu Ser
325 330 335

Ser Glu Ile Pro Asp His Glu Phe Phe Thr Ala Tyr Gly Pro Asp Tyr
340 345 350

Val Leu Glu Ile Thr Pro Ser Cys Arg Pro Asp Arg Asn Glu Pro His
355 360 365

Arg Ile Gln Gln Ile Leu Asn Tyr Ile Lys Gly Asn Leu Lys His Val
370 375 380

Val
385

<210> 8
<211> 1181
<212> ADN
<213> Secuencia Artificial

<220>
<223> Secuencia de ADN usada para codificar los residuos 1-377 de HDAC8 y una marca de 6-histidina en el extremo N-terminal

<220>
<221> caract_misc
<222> (1164)..(1164)
<223> n is a, c, g, or t

<220>
<221> caract_misc

<222> (1171)..(1171)
<223> n es a, c, g, or t

<400> 8
atgcaccatc accatcacca tcccatggag gagccggagg aaccggcgga cagtgggcag 60

tcgctggtcc cggtttatat ctatagtccc gagtatgtca gtatgtgtga ctcccctggcc 120

aagatcccca aacgggccag tatggtgcat tctttgattg aagcatatgc actgcataag 180

cagatgagga tagttaagcc taaagtggcc tccatggagg agatggccgc cttccacact 240

gatgcttatc tgcagcatct ccagaaggtc agccaagagg gcgatgatga tcatccggac 300

tccatagaat atgggctagg ttatgactgc ccagccactg aagggatatt tgactatgca 360

gcagctatag gaggggctac gatcacagct gcccaatgcc tgattgacgg aatgtgcaaa 420

gtagcaatta actggtctgg agggtggcat catgcaaaga aagatgaagc atctggtttt 480

tgttatctca atgatgctgt cctgggaata ttacgattgc gacggaaatt tgagcgtatt 540

ctctacgtgg atttggatct gcaccatgga gatggtgtag aagacgcatt cagtttcacc 600

tccaaagtca tgaccgtgtc cctgcacaaa ttctccccag gatttttccc aggaacaggt 660

gacgtgtctg atgttggcct agggaaggga cggtactaca gtgtaaatgt gcccattcag 720

gatggcatac aagatgaaaa atattaccag atctgtgaaa gtgtactaaa ggaagtatac 780

caagccttta atcccaaagc agtggtctta cagctgggag ctgacacaat agctggggat 840

cccatgtgct cctttaacat gactccagtg ggaattggca agtgtcttaa gtacatcctt 900

caatggcagt tggcaacact cattttggga ggaggaggct ataaccttgc caacacggct 960

cgatgctgga catacttgac cggggtcatc ctagggaaaa cactatcctc tgagatccca 1020

gatcatgagt ttttcacagc atatggtcct gattatgtgc tggaaatcac gccaagctgc 1080

cggccagacc gcaatgagcc ccaccgaatc caacaaatcc tcaactacat caaagggaat 1140

ctgaagcatg tggtctagrs smanvsdckt nsyrhdacsh t 1181

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

WEITZ, David J.
TAKEDA SAN DIEGO, INC.
10410 Science Center Drive
San Diego, California 92121
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 27 September 2006 (27.09.2006)	
Applicant's or agent's file reference HDAC-5015-WO	**IMPORTANT NOTIFICATION**
International application No. PCT/US2006/027118	International filing date *(day/month/year)* 13 July 2006 (13.07.2006)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 14 July 2005 (14.07.2005)
Applicant TAKEDA SAN DIEGO, INC. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
14 July 2005 (14.07.2005)	60/699,139	US	28 August 2006 (28.08.2006)

The International Bureau of WIPO
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-002327- -00000-0000

Fecha: 2008-01-11 16:08:40 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 628

SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

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- 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 [ ]

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- 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 [ ]

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1084 632

TRADUCCIÓN OFICIAL No. 08/192 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Juan Pablo Piedrahita Aguilera, Traductor e Intérprete Oficial debidamente reconocido por el Ministerio del Interior y de Justicia, por resolución número 718 de 2003 y autorizado por el Ministerio de relaciones Exteriores de Colombia.

(Se traduce un certificado de existencia de la compañía TAKEDA SAN DIEGO INC., certificado notarial, legalización y Apostillas Nos. 0340442 y 511799, escritos en inglés, adjuntos a un poder otorgado por la compañía, firmado por David J. Weitz, con fecha 18 de marzo, 2008 escrito en inglés y español.)

(En español e inglés, poder otorgado por la compañía, firmado por David J. Weitz, con fecha 18 de marzo, 2008, una (1) hoja).

CALIFORNIA RECONOCIMIENTO PARA TODOS LOS FINES

ESTADO DE CALIFORNIA

CONDADO DE LOS ANGELES } D.J.

El día 18 de Marzo, 2008, ante mí, Megumi Novak, Notario Público (Nombre y Cargo del Funcionario (p.ej. "Jane Doe, Notario Público"), compareció personalmente David J. Weitz, (Nombre(s) de el (los) firmante(s)),

(en blanco)	a quien(es) conozco personalmente o
X	quien presentó pruebas basadas en evidencia suficiente quien es (son) la(s) persona(s) cuyo(s) nombre(s) está(n) suscrito(s) en el instrumento adjunto y reconoció (eron) ante mí que él(ellos) suscribió(eron) el mismo en su(s) calidad(es) de autorizado(s) y que por su(s) firma(s) sobre el instrumento la(s) persona(s) o la entidad a nombre de quien la(s) persona(s) actúa(n) suscribió(eron) el instrumento.

DA FE mi firma y sello oficial.

Firma: (Firmado) Megumi Novak

Firma del Notario Público,

18 ABR 2008
08 / 192
TRADUCCIÓN OFICIAL No.
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

2

(Sello a Tinta: Megumi Novak, Comisión # 1516793, Notario Público - California, Condado de los Angeles, mi comisión vence Octubre 9,2008).

Estampe el Sello Oficial Arriba

OPCIONAL

Aunque la información a continuación no se requiere por ley, puede ser valiosa para quienes se basen en el documento y podrían evitar que fraudulentamente se desprendan y se vuelvan a adjuntar otros documentos a este formulario.

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Facultad(es) Reivindicadas por el Firmante

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en blanco	FUNCIONARIO CORPORATIVO-CARGO(S):
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en blanco	APODERADO
en blanco	SÍNDICO
en blanco	CUSTODIO
en blanco	OTRO:

EL FIRMANTE REPRESENTA:

(en blanco)

(Sello Redondo en Relieve y Sello de Oblea Dorada)

HUELLA DACTILAR DEL PULGAR DERECHO DEL FIRMANTE

Parte Superior del Pulgar Aquí

TRADUCCION OFICIAL No: 08
JUAN PABLO PIEDRAHITA A.
TRADUCTOR E INTERPRETE OFICIAL
DEL MIN. INTERIOR Y DE JUSTICIA

634

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(Sellos Pre-impresos)

Gregory J. Smith

CONDADO DE SAN DIEGO

ASESOR / REGISTRADOR / ESCRIBANO DEL CONDADO

OFICINA DEL ASESOR	**www.sdarcc.com**	REGISTRADOR / OFICINA DEL ESCRIBANO DEL CONDADO
1600 PACIFIC HIGHWAY, ROOM 103		1600 PACIFIC HIGHWAY, ROOM 260
SAN DIEGO CA 92101-2480		P.O. BOX 121750
TEL. (619) 236-3771 FAX (619) 557-4056		SAN DIEGO CA 92112-1750
		TEL. (619) 237-0502 FAX (619) 557-4155

Yo, GREGORY J. SMITH Asesor/Registrador/Escribano del Condado del Condado de San Diego, Estado de California, teniendo por ley un sello, POR EL PRESENTE CERTIFICO que:

MEGUMI NOVAK, cuyo nombre está suscrito en el juramento, o Certificado de Prueba de Reconocimiento del instrumento adjunto y sobre él escrito, era, en el momento de tomar tal juramento, o Certificado de Prueba de Reconocimiento, un Notario Público, en y para dicho Condado, debidamente nombrado y juramentado y debidamente autorizado por las leyes del Estado para tomar los mismos y administrar juramentos y para tomar Reconocimiento de Pruebas de Escrituras y otros instrumentos por escrito a ser registrados en este Estado. Estoy

Ma. DEL PILAR M. DE ALVARADO
16 ABR 2008

TRADUCCION OFICIAL No.
JUAN PABLO
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

4

familiarizado con la caligrafía de dicho Notario Público y creo que la firma sobre dicho juramento o Certificado de Prueba de Reconocimiento es auténtica. Además certifico que bajo las leyes del Estado de California se requiere que dicho juramento o Certificado de Prueba de Reconocimiento esté bajo un sello, pero no se requiere que la impresión de dicho sello se encuentre archivada en mi oficina o en cualquier otra parte.

FECHA: Marzo 18,2008.

Da fe mi firma: (Firmado) GREGORY J. SMITH,

Asesor del Condado / Registrador/Escribano

Sello Pre-impreso

Oficinas Sucursales Disponibles para Servirle

CHULA VISTA	EL CAJÓN	KEARNY MESA	SAN MARCOS
590 Third Avenue Chula Vista CA 91910-5617 (619) 498-2200	200 S. Magnolia Avenue El Cajón CA 92020-4524 (619) 401-5700	9225 Clairemont Mesa Blvd. San Diego CA 92123-1211 (858) 505-6262	334 Via vera Cruz, Suite 150 San Marcos CA 92078-2638 (760) 940-6868

Estado de California

(Sello Pre-Impreso)

SECRETARIO DE ESTADO

APOSTILLA

(Convención de La Haya de Octubre 5 1961)

1. *País: Estados Unidos de América*
   Este documento público
2. *Ha sido firmado por Gregory J. Smith*

16 ABR 2008

TRADUCCION OFICIAL
JUAN PABLO PI
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2005
DEL MIN. INTERIOR Y DE JUSTICIA

3.	*Obrando en calidad de Asesor/Registrador/Escribano del Condado/, Condado de San Diego, Estado de California*
4.	*Lleva el sello/estampilla del Condado de San Diego, Estado de California*
	CERTIFICADA
5.	*En San Diego, California*
6.	*El 18 de Marzo, 2008*
7.	*Por el Sub-Secretario de Estado, Estado de California*
8.	*No.* ***511799***
9.	*Sello/Estampilla* *(Sello de Oblea Dorada del Estado de California)* *(Sello Redondo a Tinta del Secretario de Estado)*
10.	*Firma (Firmado) Debra Bowen* *Secretario de Estado* *Por (Firmado) Ilegible*
NP-24 A (Rev 1-07)	OSP 07 104059

Estado de Delaware

El Primer Estado

PAG 1

YO, HARRIET SMITH WINDSOR, SECRETARIO DE ESTADO DEL ESTADO DE DELAWARE, POR EL PRESENTE CERTIFICO QUE "TAKEDA SAN DIEGO, INC." SE ENCUENTRA DEBIDAMENTE CONSTITUIDA BAJO LAS LEYES DEL ESTADO DE DELAWARE, CUMPLE CON SU OBJETO SOCIAL Y LEGALMENTE TIENE EXISTENCIA SOCIAL, COMO LO INDICAN LOS REGISTROS DE ESTA OFICINA, HOY DÍAVEINTITRES DE ENERO 2008 A.D.

Y ADEMÁS CERTIFICO QUE LOS INFORMES ANUALES SE HAN PRESENTADO DEBIDAMENTE A LA FECHA.

TRADUCCION OFICIAL
JUAN PABLO RIEDSATTEL
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2005
DEL MIN. INTERIOR Y DE JUSTICIA

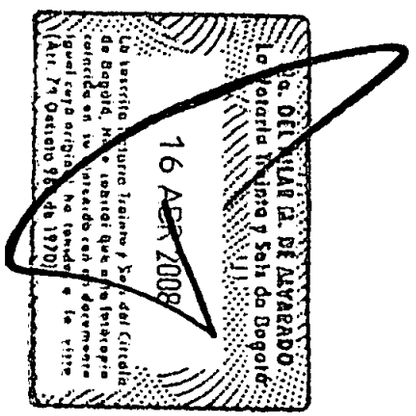
MINISTERIO DE
RELACIONES
EXTERIORES

013090
Juan Piedrahita
CUYA FIRMA APARECE EN EL
DOCUMENTO ADJUNTO
LAS FUNCIONES INDICADAS

NO ASUME
RESPONSABILIDAD
DEL TEXTO

2008 APR 15 P 11:41

JEFE DE LEGALIZACIONES
BOGOTA D.C.



Y ADEMÁS CERTIFICO QUE LOS IMPUESTOS DE FRANQUICIA SE HAN PAGADO DEBIDAMENTE A LA FECHA.

(Gran Sello preimpreso del Estado de Delaware)

(FIRMADO) *Harriet Smith Windsor*

Secretario de Estado

3445582 8300 AUTENTICACIÓN: 6331011

080074356 FECHA: 01-23-08

Apostilla

(Convención de la Haya de Octubre 5 de 1961)

1. *País: Estados Unidos de América*
   Este documento público
2. *Ha sido firmado por Harriet Smith Windsor*
3. *Obrando en calidad de Secretario de Estado del Estado de Delaware.*
4. *Lleva el sello/estampilla Oficial de la Secretaría de Estado.*

Certificada

5. *En Dover, Delaware*
6. *Hoy 23 de Enero, 2008 A.D.*
7. *Por El Secretario de Estado, Departamento de Estado de Delaware*
8. *Número* ***0340442***
9. *Sello (Sello Redondo de Oblea, de la a Secretaria de Estado, Estado de Delaware)*
10. *Firma (Firmado)*
    Harriet Smith Windsor
    Secretario de Estado

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Bogotá, Abril 15, 2008.

ABR 2008

TRADUCCION OFICIAL No. 08

JUAN PABLO [illegible] ALQUILES

TRADUCTOR E INTERPRETE OFICIAL

RES. 718 DE MAYO 2003

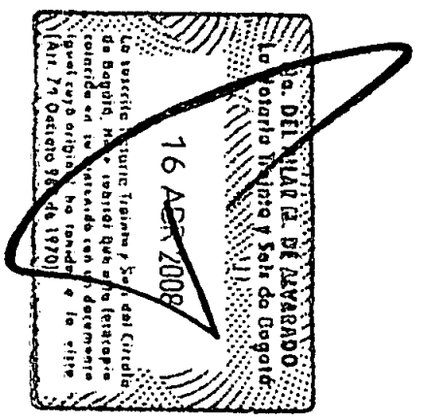
MINISTERIO DE
RELACIONES
EXTERIORES

013090
Juan Piedrahita
CUYA FIRMA APARECE EN EL
DOCUMENTO PRECEDENTE
LAS FORMALIDADES INSCRITAS

NO ASUME
RESPONSABILIDAD
DEL TEXTO

2008 APR 15 P 11:41

JEFE DE LEGALIZACIONES
BOGOTA D.C.



P. 1184

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by Gregory J. Smith*
3. *acting in the capacity of Assessor/Recorder/County Clerk, County of San Diego, State of California*
4. *bears the seal/stamp of the County of San Diego, State of California*

CERTIFIED

5. *At San Diego, California*
6. *the 18th day of March 2008*
7. *by Deputy Secretary of State, State of California*
8. *No. 511799*
9. *Seal/Stamp:*

10. *Signature*

TRADUCCION OFICIAL No. 08
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
DEL MINISTERIO DEL INTERIOR Y DE JUSTICIA
15 ABR 2008

Secretary of State

BY

NP-24 (REV. 1-07)

OSP 07 104059

Gregory J. Smith

COUNTY OF SAN DIEGO

ASSESSOR / RECORDER / COUNTY CLERK

ASSESSOR'S OFFICE
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 236-3771 • Fax (619) 557-4056

www.sdarcc.com

RECORDER / COUNTY CLERK'S OFFICE
1600 Pacific Highway, Room 260
P.O. Box 121750 • San Diego, CA 92112-1750
Tel. (619) 237-0502 • Fax (619) 557-4155

I, GREGORY J SMITH, Assessor/Recorder/County Clerk of the County of San Diego, State of California, having by law a Seal, DO HEREBY CERTIFY that:

MEGUMI NOVAK whose name is subscribed to the oath or Certificate of Proof or Acknowledgement of the annexed instrument and thereon written, was at the time of taking such oath, or Proof or Acknowledgement, a Notary Public, in and for said County, duly commissioned and sworn and duly authorized by the laws of said State to take the same and administer oaths and to take the Acknowledgements and Proofs of Deeds and other instruments in writing to be recorded in this State. I am acquainted with the handwriting of such Notary Public and believe that the signature to said oath or Certificate of Proof Acknowledgement is genuine. I further certify that under the laws of the State of California the said oath or Certificate of Proof or Acknowledgement is required to be under seal, but the impression of said seal is not required by the laws of the State of California to be filed in my office or in any other place.

DATED: March 18, 2008 **Witness by hand**

GREGORY J SMITH, County Assessor/Recorder/Clerk

...ION OFICIAL No. _____
...O PIEDRAHITA ...QUILLA
...TOR E INTERPRETE OFICIAL
...13 DE MAYO 2008
...NTERIOR Y DE JUSTICIA

16 ABR 2008

Branch Offices Available To Serve You

CHULA VISTA
590 Third Avenue
Chula Vista, CA 91910-5617
(619) 498-2200

EL CAJON
200 S. Magnolia Avenue
El Cajon, CA 92020-4524
(619) 401-5700

KEARNY MESA
9225 Clairemont Mesa Blvd
San Diego, CA 92123-1211
(858) 505-6262

SAN MARCOS
141 E. Carmel St.
San Marcos, CA 92078-4309
(760) 940-6868

Clarke, Modet & C°

COLOMBIA

Carrera 11 N° 86-53 Piso 6 Bogotá Colombia Tel: (57 1) 6181088 ·Fax: (57 1) 6350824·Email: info@clarkemodet.com.co

PODER

Yo (nosotros), abajo firmante(s)

David J. Weitz

en mi (nuestro) carácter de representante(s) legales de

TAKEDA SAN DIEGO, INC.

una sociedad organizada y existente de acuerdo con las leyes de

Delaware (US)

y en actual cumplimiento de su objeto social, con domicilio en

por el presente instrumento confiero (conferimos) poder especial a favor de DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía No. 41.654.882 de Bogotá, y tp. 20824 y CLAUDIA LUCIA CARO RAMIREZ, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp. 36448, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos:

1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como: patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres y enseñas comerciales y denominaciones de origen; así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how.
3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
4) Ejercer acciones de oposición, observación, reclamos, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; en acciones o juicios promovidos por el (la) mandante o en contra el (ella).
5) Registrar nombres de dominio ante la entidad competente.
6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso.
7) Ratificar o no la agencia oficiosa.
8) Así mismo faculto (facultamos) a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en

a los 18 días de Marzo de 2008

Firma / signatura

POWER OF ATTORNEY

I (we), the undersigned

David J. Weitz

legal representative(s) of

TAKEDA SAN DIEGO, INC.

an organization existing under the laws of

Delaware, (US)

and in present execution of its business activity, domiciled at

do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No. 40.017.374 of Tunja, residing in Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

1) To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models; Designs, plant varieties; Marks, Slogans, Trade Names and emblems and appellations of Origin; as well as their renewals, assignments, changes of name and/or domicile, agreements and licenses.
2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.
3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses; as well as their renewals or assignments, changes of name and/or domicile, agreements and licenses.
4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection to the consumer, granting of licenses, protection of trade secrets and other actions related with rights derived from the above- mentioned matters and against the unfair competition, actions resulting from the obtaining or exploitation of licenses, recovering damages actions. They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative Trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him.
5) To register domain names before the competent entity.
6) To the effect of this mandate the above-named proxy are empowered to: conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation related objet and waive or renounce the rights granted or in process of granting, admit the facts of the case.
7) To ratify or not the officious agency.
8) I (we) hereby appoint the afore mentioned attorneys with powers to receive notifications and to designate judicial and extrajudicial attorneys, substitute this Power of Attorney and to revoke such sustitutions.

Granted and signed at

on this 18th day of March of 2008

16 ABR 2008

Art. 71 Decreto 960 de 1970

10

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of San Diego } ss.

On March 18, 2008 (Date) before me, Megumi Novak, Notary Public (Name and Title of Officer (e.g., "Jane Doe, Notary Public"))

personally appeared David J. Weitz (Name(s) of Signer(s)),

☐ personally known to me
☒ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is/~~are~~ subscribed to the within instrument and acknowledged to me that he/~~she/they~~ executed the same in his/~~her/their~~ authorized capacity(~~ies~~), and that by his/~~her/their~~ signature(~~s~~) on the instrument the person(~~s~~), or the entity upon behalf of which the person(~~s~~) acted, executed the instrument.

WITNESS my hand and official seal.

Signature of Notary Public

MEGUMI NOVAK
Commission # 1516793
Notary Public - California
San Diego County
My Comm. Expires Oct 9, 2008

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

Description of Attached Document

Title or Type of Document: Power of Attorney

Document Date: _____ Number of Pages: 1

Signer(s) Other Than Named Above: _____

Capacity(ies) Claimed by Signer

Signer's Name: _____

☐ Individual
☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General
☐ Attorney-in-Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer Is Representing: _____

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

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TRADUCCION OFICIAL No. 08
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. *Country: United States of America*

This public document:

2. *has been signed by Harriet Smith Windsor*

3. *acting in the capacity of Secretary of State of Delaware*

4. *bears the seal/stamp of Office of Secretary of State*

Certified

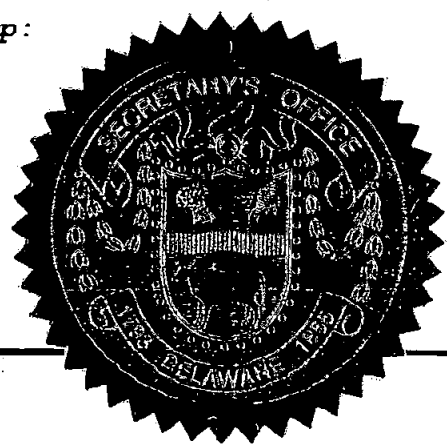
5. *at Dover, Delaware*

6. *the twenty-third day of January, A.D. 2008*

7. *by Secretary of State, Delaware Department of State*

8. *No. 0340442*

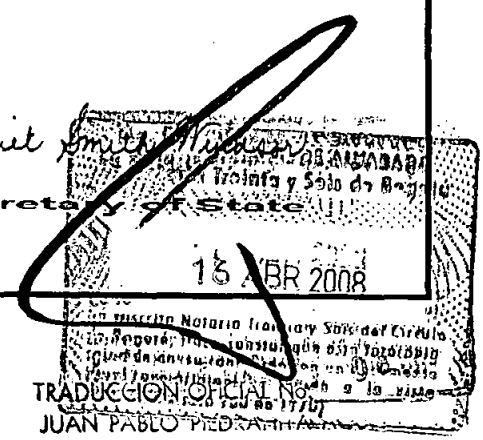
9. *Seal/Stamp:*



10. *Signature:*

Harriet Smith Windsor

Secretary of State



TRADUCCION OFICIAL No.
JUAN PABLO PIEDRAHITA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY "TAKEDA SAN DIEGO, INC." IS DULY INCORPORATED UNDER THE LAWS OF THE STATE OF DELAWARE AND IS IN GOOD STANDING AND HAS A LEGAL CORPORATE EXISTENCE SO FAR AS THE RECORDS OF THIS OFFICE SHOW, AS OF THE TWENTY-THIRD DAY OF JANUARY, A.D. 2008.

AND I DO HEREBY FURTHER CERTIFY THAT THE ANNUAL REPORTS HAVE BEEN FILED TO DATE.

AND I DO HEREBY FURTHER CERTIFY THAT THE FRANCHISE TAXES HAVE BEEN PAID TO DATE.

TRADUCCION OFICIAL No. _____
JUAN PABLO PEÑA ACUÑA
TRADUCTOR E INTERPRETE OFICIAL
13 MAR 2008

Harriet Smith Windsor, Secretary of State

3445582 8300

080074356

You may verify this certificate online at corp.delaware.gov/authver.shtml

AUTHENTICATION: 6331011

DATE: 01-23-08

P. 1084 644

TRADUCCIÓN OFICIAL No. 08/193 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Juan Pablo Piedrahita Aguilera, Traductor e Intérprete Oficial debidamente reconocido por el Ministerio del Interior y de Justicia, por resolución número 718 de 2003 y autorizado por el Ministerio de relaciones Exteriores de Colombia.

(Se traduce un documento de Cesión cesión favor de la compañía TAKEDA SAN DIEGO INC., certificados notariales, legalizaciones y Apostillas Nos. 514608 y 516231, escritos en inglés.)

CLARKE, MODET & Cº.

Colombia

CORREO-ELECTRÓNICO: clarkemodet@ clarkemodet.com.co

SANTAFÉ DE BOGOTÁ, AA. 92397, COLOMBIA

CESIÓN

Los suscritos, (en adelante los CEDENTES)

1. Jerome C. BTESSI
2. Anthony R. GANGLOFF
3. Lily KWOK

en calidad de inventores/diseñadores de "INHIBIDORES DE HISTONA DEACETILASA", con domicilio en

1. 3799 Ibis Street, San Diego, California 92103, Estados Unidos de América
2. 4969 Dick Street, San Diego, California 92115, Estados Unidos de América
3. 10937 Caminito Arcada, San Diego, California 92131, Estados Unidos de América

Por el presente declaran que ceden todos y cada uno de los derechos y privilegios que le correspondan o que le puedan corresponder sobre la siguiente invención, diseño industrial o modelo de utilidad a favor de

Takeda San Diego Inc.

con domicilio en 10410 Science Center Drive, San Diego, California 92121, Estados Unidos de América.

Ma. DEL [illegible] DE ALVARADO
La Notaria Treinta y Seis de Bogotá
TRADUCCION OFICIAL No.
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
16 ABR 2003
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA
La suscrita Notaria [illegible] que esta [illegible] contenido con un documento [illegible] original, [illegible] (Res. 74 Decreto 960 de 1970)

14

El Cedente y el Cesionario firman este documento como prueba de aceptación de la cesión.

Dada y firmada en San Diego, California a los 14 días del mes de Marzo, 2008.

1. (Firmado) Ilegible
   El Cedente
2. (Firmado) Ilegible
   El Cedente
3. (Firmado) Ilegible
   El Cedente

TAKEDA SAN DIEGO, INC.

Nombre: (Firmado) David J. Weitz

Cargo: Asesor Legal General y Vicepresidente de Propiedad Intelectual

(Este documento debe ser otorgado ante Notario Público y legalizado por el Cónsul Colombia o mediante Apostilla).

CALIFORNIA CERTIFICADO DE RECONOCIMIENTO PARA TODOS LOS FINES

ESTADO DE CALIFORNIA

CONDADO DE SAN DIEGO } D.J.

El día 14 de Marzo, 2008, (Fecha) ante mí, Paula Gabriola, Notario Público (Inserte aquí el Nombre y Cargo del Funcionario,), compareció personalmente Jerome C. Bressi, Lily Kwde, (Nombre del (los) Firmante(s)),

quienes presentaron pruebas basadas en evidencia suficiente quien es ~~(son)~~ la persona- cuyo- nombre- está- suscrito- en el instrumento adjunto y reconoció - ante mí que él~~(ellos)~~ suscribió~~(eron)~~ el mismo en su~~(s)~~ calidad~~(es)~~ de autorizado~~(s)~~ y que por su~~(s)~~ firma~~(s)~~ sobre el instrumento la~~(s)~~ persona~~(s)~~ o la entidad a nombre de

16 ABR 2008

La suscrita Notaria Treinta y Seis del Círculo de Bogotá, hace constar que esta fotocopia coincide en su contenido con la fotocopia igual cuyo original ha tenido a la vista (Art. 74 Decreto 960 de 1970)

TRADUCCION OFICIAL No. 08 / 193
JUAN PABLO PEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

646

quien la~~(s)~~ persona~~(s)~~ obra~~(n)~~ suscribió(eron) el instrumento.

Certifico, bajo LA PENA DE FALSEDAD, bajo las leyes del Estado de California, que el párrafo anterior es verdadero y correcto.

DA FE mi firma y sello oficial.

Firma: (Firmado) Paula Gabriola

(Firma del Notario Público)

Estampe el Sello Oficial Arriba

(Sello a tinta: PAULA GABRIOLA, Comisión # 1592496, Notario Público – California, Condado de San Diego, Comisión Vence Junio 28, 2009)

---------- ***OPCIONAL*** ----------

Aunque la información a continuación no se requiere por ley, puede ser valiosa para personas que se basan en el documento y podría evitar que fraudulentamente supriman o se adjunten otros documentos a este formulario.

D scripción del Documento Adjunto

Título o Tipo de Documento: Cesión para Colombia HDAC-5015-WO-CO

Fecha del Documento: Marzo 14, 2008 Número de Páginas 1

Firmante(s) diferente(s) al mencionado N/D

Facultad(es) Reivindicadas por el Firmante (Otorgante)

Nombre del Firmante (en blanco)

en blanco	INDIVIDUO
En blanco	FUNCIONARIO EMPRESARIAL-CARGO(S): (en blanco)
en blanco	SOCIO(s) ☐ Compañía Limitada ☐ Sociedad Anónima
en blanco	APODERADO / REPRESENTNTE LEGAL

Ma. DEL PILAR M. DE ALVARADO
La Notaría Treinta y Seis de Bogotá
14 ABR 2008
El suscrito Notario Treinta y Seis del Círculo de Bogotá, Hace constar que la presente copia es la contenida con un documento que el 14 de abril de 2008 ha tenido (Art. 74 Decreto 960 de 1970)

TRADUCCION OFICIAL No. 08 / 193
JUAN PABLO HEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

16

647

en blanco	FIDUCIARIO
en blanco	SÍNDICO o CUSTODIO
en blanco	OTRO: (en blanco)

EL FIRMANTE REPRESENTA a:

(en blanco).

HUELLA DACTILAR DEL PULGAR DERECHO DEL FIRMANTE
Parte Superior del Pulgar Aquí

(EN BLANCO)

Facultad(es) Reivindicadas por el Firmante (Otorgante)

Nombre del Firmante (en blanco)

en blanco	INDIVIDUO
en blanco	FUNCIONARIO EMPRESARIAL-CARGO(S): (en blanco)
en blanco	☐ CIO(s) Compañía Limita ☐ Sociedad Anónima
en blanco	APODERADO / REPRESENTNTE LEGAL
en blanco	FIDUCIARIO
en blanco	SÍNDICO O CUSTODIO
en blanco	OTRO: (en blanco)

EL FIRMANTE REPRESENTA a:

(en blanco).

HUELLA DACTILAR DEL PULGAR DERECHO DEL FIRMANTE
Parte Superior del Pulgar Aquí

(EN BLANCO)

Ma. DEL PILAR ... La Notaria Treinta y Seis de Bogotá

16 ABR 2008

La suscrita Notaria Treinta y Seis del Círculo de Bogotá, Hace constar que esta fotocopia coincide con la contenida con un documento igual al original, de ... (Art. 74 Decreto 960 de 1970)

TRADUCCION OFICIAL No. 08 / 193
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003

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17

Chatsworth, CA 91313-2402 Prod. No. 5907 v609 Pedido: Llamar a Línea Gratuita 1-800-876-6827

(Sellos Pre-impresos)

Gregory J. Smith

CONDADO DE SAN DIEGO

ASESOR / REGISTRADOR / ESCRIBANO DEL CONDADO

OFICINA DEL ASESOR
1600 PACIFIC HIGHWAY, ROOM 103
SAN DIEGO CA 92101-2480
TEL. (619) 236-3771 FAX (619) 557-4056

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REGISTRADOR / OFICINA DEL ESCRIBANO DEL CONDADO
1600 PACIFIC HIGHWAY, ROOM 260
P.O. BOX 121750
SAN DIEGO CA 92112-1750
TEL. (619) 237-0502 FAX (619) 557-4155

Yo, GREGORY J. SMITH Asesor/Registrador/Escribano del Condado del Condado de San Diego, Estado de California, teniendo por ley un sello, POR EL PRESENTE CERTIFICO que:

PAULA GABRIOLA, cuyo nombre está suscrito en el juramento, o Certificado de Prueba de Reconocimiento del instrumento adjunto y sobre él escrito, era, en el momento de tomar tal juramento, o Certificado de Prueba de Reconocimiento, un Notario Público, en y para dicho Condado, debidamente nombrado y juramentado y debidamente autorizado por las leyes del Estado para tomar los mismos y administrar juramentos y para tomar Reconocimiento de Pruebas de Escrituras y otros instrumentos por escrito a ser registrados en este Estado. Estoy familiarizado

16 ABR 2008

La suscrita Notaria Treinta y ... del Circulo de Bogotá, Hace constar que esta fotocopia ... Decreto 960 de 1970)

TRADUCCIÓN OFICIAL No. 08 / 1 9 3

JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

con la caligrafía de dicho Notario Público y creo que la firma sobre dicho juramento o Certificado de Prueba de Reconocimiento es auténtica. Además certifico que bajo las leyes del Estado de California se requiere que dicho juramento o Certificado de Prueba de Reconocimiento esté bajo un sello, pero no se requiere que la impresión de dicho sello se encuentre archivada en mi oficina o en cualquier otra parte.

FECHA: Marzo 26,2008.

Da fe mi firma: (Firmado) GREGORY J. SMITH,

Asesor del Condado / Registrador/Escribano

Sello Pre-impreso

Oficinas Sucursales Disponibles para Servirle

CHULA VISTA	EL CAJÓN	KEARNY MESA	SAN MARCOS
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Estado de California

(Sello Pre-Impreso)

SECRETARIO DE ESTADO

APOSTILLA

(Convención de La Haya de Octubre 5 1961)

1. *País: Estados Unidos de América*
   Este documento público
2. *Ha sido firmado por Gregory J. Smith*

MA. DEL PILAR M. DE ALVARADO
La Notaria Treinta y Seis de Bogotá
16 ABR 2008
La suscrita Notaria Treinta y Seis del Círculo de Bogotá, Hace constar que esta fotocopia coincide en su contenido con un documento igual cuyo original ha tenido a la vista (Art. 1 Decreto 960 de 1970)

TRADUCCION OFICIAL No. 08 / ...
JUAN PABLO PIEDRAHITA ...
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO ...
DEL MIN. INTERIOR Y DE JUSTICIA

650

3.	*Obrando en calidad de Asesor/Registrador/Escribano del Condado/, Condado de San Diego, Estado de California*
4.	*Lleva el sello/estampilla del Condado de San Diego, Estado de California*
	CERTIFICADA
5.	*En San Diego, California*
6.	*El 26 de Marzo, 2008*
7.	*Por el Sub-Secretario de Estado, Estado de California*
8.	*No.* ***514608***
9.	*Sello/Estampilla*
	(Sello de Oblea Dorada del Estado de California)
	(Sello Redondo a Tinta del Secretario de Estado)
10.	*Firma (Firmado) Debra Bowen*
	Secretario de Estado
	Por (Firmado) Ilegible
NP-24 A (Rev 1-07)	OSP 07 104059

CALIFORNIA CERTIFICADO DE RECONOCIMIENTO PARA TODOS LOS FINES

ESTADO DE CALIFORNIA

CONDADO DE SAN DIEGO } D.J.

El día 31 de Marzo, 2008, (Fecha) ante mí, Paula Gabriola, Notario Público (Inserte aquí el Nombre y Cargo del Funcionario,), compareció personalmente David J. Weitz, (Nombre del (los) Firmante(s)),

quienes presentaron pruebas basadas en evidencia suficiente quien es ~~(son)~~ la persona- cuyo- nombre- está- suscrito en el instrumento adjunto y reconoció - ante mí que él~~(ellos)~~ suscribió~~(eron)~~ el mismo en su~~(s)~~ calidad~~(es)~~ de autorizado~~(s)~~ y que por su~~(s)~~ firma~~(s)~~ sobre el instrumento la~~(s)~~ persona~~(s)~~ o la entidad a nombre de

La Notaría Treinta y Seis de Bogotá
16 ABR 2008
(Art. 74 Decreto 960 de 1970)

TRADUCCION OFICIAL No. 008 / 10 F\
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

20

MINISTERIO DE
RELACIONES
EXTERIORES

013095
Juan Piedrahita
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO ASUME
RESPONSABILIDAD
DEL TEXTO

2008 APR 15 P 11:45

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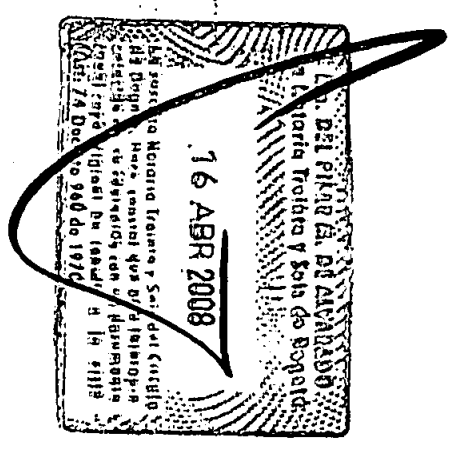
BOGOTA D.C.



651

quien la~~(s)~~ persona~~(s)~~ obra~~(n)~~ suscribió(eron) el instrumento.

Certifico, bajo LA PENA DE FALSEDAD, bajo las leyes del Estado de California, que el párrafo anterior es verdadero y correcto.

DA FE mi firma y sello oficial.

Firma: (Firmado) Paula Gabriola

(Firma del Notario Público)

Estampe el Sello Oficial Arriba

(Sello a tinta: PAULA GABRIOLA, Comisión # 1592496, Notario Público – California, Condado de San Diego, Comisión Vence Junio 28, 2009)

---------- ***OPCIONAL*** ----------

Aunque la información a continuación no se requiere por ley, puede ser valiosa para personas que se basan en el documento y podría evitar que fraudulentamente supriman o se adjunten otros documentos a este formulario.

Descripción del Documento Adjunto

Título o Tipo de Documento: Cesión para Colombia HDAC-5015-WO-CO

Fecha del Documento: Marzo 31, 2008 Número de Páginas 1

Firmante(s) diferente(s) al mencionado N/D

Facultad(es) Reivindicadas por el Firmante (Otorgante)

Nombre del Firmante David J. Weitz

en blanco	INDIVIDUO
en blanco	FUNCIONARIO EMPRESARIAL-CARGO(S): (en blanco)
en blanco	SOCIO(s) ☐ Compañía Limitada ☐ Sociedad Anónima
en blanco	APODERADO / REPRESENTNTE LEGAL

Ma. DEL PILAR M. DE ALVARADO
La Notaría Treinta y Seis de Bogotá
2008
La suscrita Notaria Treinta y Seis del Círculo de Bogotá, hace constar que la presente copia es tomada de su contenido como documento igual cuyo original ha tenido a la vista
(Art. 74 Decreto 960 de 1970)

TRADUCCION OFICIAL No. 09
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

21

652

en blanco	FIDUCIARIO
en blanco	SÍNDICO o CUSTODIO
en blanco	OTRO: (en blanco)

EL FIRMANTE REPRESENTA a:

(en blanco).

HUELLA DACTILAR DEL PULGAR DERECHO DEL FIRMANTE
Parte Superior del Pulgar Aquí
(EN BLANCO)

Facultad(es) Reivindicadas por el Firmante (Otorgante)

Nombre del Firmante (en blanco)

en blanco	INDIVIDUO
en blanco	FUNCIONARIO EMPRESARIAL-CARGO(S): (en blanco)
en blanco	☐ CIO(s) Compañía Limita ☐ Sociedad Anónima
en blanco	APODERADO / REPRESENTNTE LEGAL
en blanco	FIDUCIARIO
en blanco	SÍNDICO O CUSTODIO
en blanco	OTRO: (en blanco)

EL FIRMANTE REPRESENTA a:

(en blanco).

HUELLA DACTILAR DEL PULGAR DERECHO DEL FIRMANTE
Parte Superior del Pulgar Aquí
(EN BLANCO)

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Ma. DEL PILAR M. DE ALVARADO
La Notaria Treinta y Seis de Bogotá
16 ABR 2008
La suscrita Notaria Treinta y Seis del Círculo de Bogotá, hace constar que la presente fotocopia coincide con el documento que se le ha tenido a la vista
(Art. 74 Decreto 960 de 1970)

TRADUCCIÓN OFICIAL No. 08 1 5 3
JUAN PABLO PIEDRAHITA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO
DEL MIN. INTERIOR Y DE JUSTICIA

22

653

1-800-876-6827

(Sellos Pre-impresos)

Gregory J. Smith

CONDADO DE SAN DIEGO

ASESOR / REGISTRADOR / ESCRIBANO DEL CONDADO

OFICINA DEL ASESOR

1600 PACIFIC HIGHWAY, ROOM 103

SAN DIEGO CA 92101-2480

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P.O. BOX 121750

SAN DIEGO CA 92112-1750

TEL. (619) 237-0502 FAX (619) 557-4155

Yo, GREGORY J. SMITH Asesor/Registrador/Escribano del Condado del Condado de San Diego, Estado de California, teniendo por ley un sello, POR EL PRESENTE CERTIFICO que:

PAULA GABRIOLA, cuyo nombre está suscrito en el juramento, o Certificado de Prueba de Reconocimiento del instrumento adjunto y sobre él escrito, era, en el momento de tomar tal juramento, o Certificado de Prueba de Reconocimiento, un Notario Público, en y para dicho Condado, debidamente nombrado y juramentado y debidamente autorizado por las leyes del Estado para tomar los mismos y administrar juramentos y para tomar Reconocimiento de Pruebas de Escrituras y otros instrumentos por escrito a ser registrados en este Estado. Estoy familiarizado con la caligrafía de dicho Notario Público y creo que la firma sobre dicho juramento o

DELILAH E. DE ALVARADO
16 APR 2008
(Art. 79 Decreto 960 de 1970)

TRADUCCION OFICIAL No. _____
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

23

654

Certificado de Prueba de Reconocimiento es auténtica. Además certifico que bajo las leyes del Estado de California se requiere que dicho juramento o Certificado de Prueba de Reconocimiento esté bajo un sello, pero no se requiere que la impresión de dicho sello se encuentre archivada en mi oficina o en cualquier otra parte.

FECHA: Abril 1,2008.

Da fe mi firma: (Firmado) GREGORY J. SMITH,

Asesor del Condado / Registrador/Escribano

Sello Pre-impreso

Oficinas Sucursales Disponibles para Servirle

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Estado de California

(Sello Pre-Impreso)

SECRETARIO DE ESTADO

APOSTILLA

(Convención de La Haya de Octubre 5 1961)

1. *País: Estados Unidos de América*
   Este documento público
2. *Ha sido firmado por Gregory J. Smith*
3. *Obrando en calidad de Asesor/Registrador/Escribano del Condado/, Condado de San Diego, Estado de California*
4. *Lleva el sello/estampilla del Condado de San Diego, Estado de California*

MO. DEL PILAR M. DE ALVARADO
La Notaria Treinta y Seis de Bogotá
16 ABR 2008
(Art. 74 Decreto 960 de 1970)

TRADUCCION OFICIAL No. 38
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2003

24

CERTIFICADA

5. *En San Diego, California*

6. *El 1 de Abril, 2008*

7. *Por el Sub-Secretario de Estado, Estado de California*

8. *No.* ***516231***

9. *Sello/Estampilla*

(Sello de Oblea Dorada del Estado de California)

(Sello Redondo a Tinta del Secretario de Estado)

10. *Firma (Firmado) Debra Bowen*

Secretario de Estado

Por (Firmado) Ilegible

NP-24 A (Rev 1-07) OSP 07 104059

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Bogotá, Abril 15, 2008.

TRADUCCION OFICIAL No. 28
JUAN PABLO PIEDRAHITA AGUILAR
TRADUCTOR E INTERPRETE OFICIAL
RES. 718 DE MAYO 2008
DEL MIN. INTERIOR Y DE JUSTICIA

MA. DEL PILAR M. DE ALVARADO
La Notaria Treinta y Seis de Bogotá
16 ABR 2008
La suscrita Notaria Treinta y Seis del Circulo de Bogotá, hace constar que la presente fotocopia coincide en su contenido con el documento igual copia original ha tenido a la vista (Art. 79 Decreto 960 de 1970)

MINISTERIO DE
RELACIONES
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013092
Juan Piedrahita
CUYA FIRMA APARECE EN EL
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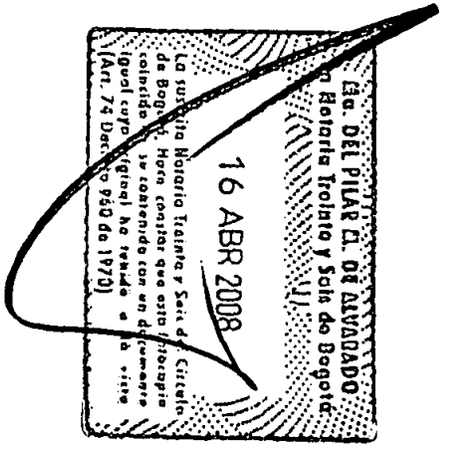

P. 1084

656

Clarke, Modet & C°

COLOMBIA

E-MAIL: info@clarkemodet.com.co
SANTAFÉ DE BOGOTA, A.A. 92397 COLOMBIA

CESION

El (la) abajo firmante (En adelante EL CEDENTE)

en su carácter de inventor /diseñador

con domicilio en:

por el presente documento declara que cede todos y cada uno de los derechos que le corresponden o puedan corresponderle sobre la siguiente invención ,-modelo de utilidad, diseño industrial

a:

con domicilio en

En prueba de la mutua aceptación de esta cesión ambas partes CEDENTE y CESIONARIO firman el presente documento.

Dado y firmado en
A los Días de De

_____
El Cedente /The Assignor

_____
El Cesionario/The Assignee

_____
El Cesionario/The Assignee

ASSIGNMENT

The undersigned (Hereinafter THE ASSIGNOR)

1. Jerome C. BRESSI
2. Anthony R. GANGLOFF
3. Lily KWOK

Inventor /designor of Histone Deacetylase Inhibitors

domiciled at

1. 3799 Ibis Street, San Diego, California 92103, U.S.A.
2. 4969 Dick Street, San Diego, California 92115, U.S.A.
3. 10937 Caminito Arcada, San Diego, California 92131, U.S.A.

do hereby declares that it assigns all and each of his rights and privileges on the following invention, industrial design, utility model

to Takeda San Diego, Inc.

with domicile in 10410 Science Center Drive, San Diego, California 92121, U.S.A.

As a proof of the mutual acceptance of this assignment, both parties ASSIGNOR and ASSIGNEE sign the present document.

Granted and signed at San Diego, California on this 14 day of March of 2008.

1. Jerome C. Bressi
El Cedente /The Assignor

2. Anthony R Gangloff
El Cedente /The Assignor

3. Lily Kwok
El Cedente /The Assignor

Ma. DEL PILAR M. DE ALVARADO
La Notaria Treinta y Seis de Bogotá
16 ABR 2008
La Notaria Treinta y Seis del Círculo de Bogotá, [illegible] Decreto 960 de 1970)

TAKEDA SAN DIEGO, INC.

Name: David J. Weitz
Title: General Counsel and VP of Intellectual Property

Este documento debe ser otorgado ante Notario público y legalizado por el Cónsul de Colombia) o por Apostilla

(This document must be signed before Notary Public and legalized before the colombian Consul) or by Apostille

26

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by Gregory J. Smith*
3. *acting in the capacity of Assessor/Recorder/County Clerk, County of San Diego, State of California*
4. *bears the seal/stamp of the County of San Diego, State of California*

CERTIFIED

5. *At San Diego, California*
6. *the 26th day of March 2008*
7. *by Deputy Secretary of State, State of California*
8. *No. 514608*
9. *Seal/Stamp:*

10. *Signature*

Secretary of State

BY

16 ABR 2008

NP-24 (REV. 1-07)

OSP 07 104059

658

Gregory J. Smith

COUNTY OF SAN DIEGO

ASSESSOR / RECORDER / COUNTY CLERK

ASSESSOR 'S OFFICE
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 236-3771 • Fax (619) 557-4056

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RECORDER / COUNTY CLERK 'S OFFICE
1600 Pacific Highway, Room 260
P.O. Box 121750 • San Diego, CA 92112-1750
Tel. (619) 237-0502 • Fax (619) 557-4155

I, GREGORY J SMITH, Assessor/Recorder/County Clerk of the County of San Diego, State of California, having by law a Seal, DO HEREBY CERTIFY that:

PAULA GABRIOLA whose name is subscribed to the oath or Certificate of Proof or Acknowledgement of the annexed instrument and thereon written, was at the time of taking such oath, or Proof or Acknowledgement, a Notary Public, in and for said County, duly commissioned and sworn and duly authorized by the laws of said State to take the same and administer oaths and to take the Acknowledgements and Proofs of Deeds and other instruments in writing to be recorded in this State. I am acquainted with the handwriting of such Notary Public and believe that the signature to said oath or Certificate of Proof Acknowledgement is genuine. I further certify that under the laws of the State of California the said oath or Certificate of Proof or Acknowledgement is required to be under seal, but the impression of said seal is not required by the laws of the State of California to be filed in my office or in any other place.

DATED: March 26, 2008 **Witness by hand**

G. J. Smith

GREGORY J SMITH, County Assessor/Recorder/Clerk

[illegible] M. DE ALVARADO
[illegible] y Seis de Bogotá
1[illegible] ABR 2008
La suscrita [illegible] y Seis del Círculo [illegible] Bogotá, Hace constar que esta fotocopia coincide en su contenido con un documento [illegible] cuyo original ha tenido a la vista (Art. 24 Decreto 960 de 1970)

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San Diego, CA 92123-1211
(858) 505-6262

SAN MARCOS
141 E. Carmel St.
San Marcos, CA 92078-4309
(760) 940-6868

28

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of San Diego }

On March 14, 2008 (Date) before me, Paula Gabriola, Notary Public (Here Insert Name and Title of the Officer),

personally appeared Jerome C. Bressi; Anthony R. Gangloff; Lily Kwok (Name(s) of Signer(s)),

who proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) ~~is~~/are subscribed to the within instrument and acknowledged to me that ~~he/she~~/they executed the same in ~~his/her~~/their authorized capacity(ies), and that by ~~his/her~~/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

PAULA GABRIOLA
Commission # 1592496
Notary Public - California
San Diego County
My Comm. Expires Jun 28, 2009

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature Paula Gabriola (Signature of Notary Public)

Place Notary Seal Above

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

Description of Attached Document

Title or Type of Document: Assignment for Columbia HOAC-5015-WO-CO

Document Date: March 14, 2008 Number of Pages: 1

Signer(s) Other Than Named Above: n/a

Capacity(ies) Claimed by Signer(s)

Signer's Name: _____
☐ Individual
☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____
Signer Is Representing: _____

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

Signer's Name: _____
☐ Individual
☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____
Signer Is Representing: _____

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

16 ABR 2008

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660

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by Gregory J. Smith*
3. *acting in the capacity of Assessor/Recorder/County Clerk, County of San Diego; State of California*
4. *bears the seal/stamp of the County of San Diego, State of California*

CERTIFIED

5. *At San Diego,California*
6. *the 1st day of April 2008*
7. *by Deputy Secretary of State, State of California*
8. *No. 516231*
9. *Seal/Stamp:*

10. *Signature*

Secretary of State

BY

NP-24 (REV. 1-07)

OSP 07 104059

30

661

Gregory J. Smith

COUNTY OF SAN DIEGO

ASSESSOR / RECORDER / COUNTY CLERK

ASSESSOR'S OFFICE
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 236-3771 • Fax (619) 557-4056

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RECORDER / COUNTY CLERK'S OFFICE
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P.O. Box 121750 • San Diego, CA 92112-1750
Tel. (619) 237-0502 • Fax (619) 557-4155

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DATED: April 1, 2008 **Witness by hand**

G. J. Smith

GREGORY J SMITH, County Assessor/Recorder/Clerk

16 ABR 2008

(Art. 74 Decreto 960 de 1970)

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CALIF RNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California

County of San Diego

On March 31, 2008 (Date) before me, Paula Gabriola, Notary Public (Here Insert Name and Title of the Officer),

personally appeared David J. Weitz (Name(s) of Signer(s))

_____,

PAULA GABRIOLA
Commission # 1592496
Notary Public - California
San Diego County
My Comm. Expires Jun 28, 2009

Place Notary Seal Above

who proved to me on the basis of satisfactory evidence to be the person(~~s~~) whose name(~~s~~) is/~~are~~ subscribed to the within instrument and acknowledged to me that he/~~she/the~~y executed the same in his/~~her/the~~ir authorized capacity(~~ies~~), and that by his/~~her/their~~ signature(~~s~~) on the instrument the person(~~s~~), or the entity upon behalf of which the person(~~s~~) acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature Paula Gabriola
Signature of Notary Public

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

Description of Attached Document

Title or Type of Document: Assignment HDAC-5015-WO-CO

Document Date: March 31, 2008 Number of Pages: 1

Signer(s) Other Than Named Above: ——

Capacity(~~ies~~) Claimed by Signer(~~s~~)

Signer's Name: David J. Weitz
- ☑ Individual
- ☐ Corporate Officer — Title(s): _____
- ☐ Partner — ☐ Limited ☐ General
- ☐ Attorney in Fact
- ☐ Trustee
- ☐ Guardian or Conservator
- ☐ Other: _____

Signer Is Representing: _____

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

Signer's Name: _____
- ☐ Individual
- ☐ Corporate Officer — Title(s): _____
- ☐ Partner — ☐ Limited ☐ General
- ☐ Attorney in Fact
- ☐ Trustee
- ☐ Guardian or Conservator
- ☐ Other: _____

Signer Is Representing: _____

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

Ma. DEL PILAR M. DE ALVARADO
La Notaria Treinta y Seis de Bogotá
16 ABR 2008
Suscrita Notaria Treinta y Seis del Círculo de Bogotá. Hace constar que esta fotocopia ... (Art. 74 Decreto 960 de 1970)

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 663

2020
Bogotá D.C.,

Doctor(a)
RODRIGUEZ DILIA MARIA
Apoderado(a) y/o Representante de
TAKEDA SAN DIEGO INC

REFERENCIA	Radicación No.	8 2327
	Solicitud internacional	PCT/US2006/027118
	Fecha inicio fase nacional	14/02/2008
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	7383
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 23 DIC. 2008

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

jfernand