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71. **SOLICITANTE** takeda Pharmaceutical Company limited

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22. **BOGOTÁ, D. C.,** Sept. 19, 2006.

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Industria y Comercio
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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
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ENTRADA EN FASE NACIONAL

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1) SOLICITUD DE:

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☐ Capitulo I ☒ Capitulo II.

2) SOLICITANTE (71)	**Nombre: TAKEDA PHARMACEUTICAL COMPANY LIMITED** **Dirección: 1-1, Doshomachi 4-chome Chuo-ku, Osaka-shi Osaka 541-0045 Japón** **Nacionalidad o domicilio: Osaka, Japón** **Lugar de constitución: Japón**	**IDENTIFICACIÓN** **C.C.** ☐ **NIT** ☐ **C.E** ☐ **OTRO** ☐ **Cual** _____ **NÚMERO** _____
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[redacted]	RENTISTICO		CONCEPTO		TOTAL CONCEPTO
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				TOTAL : $	463,000.00

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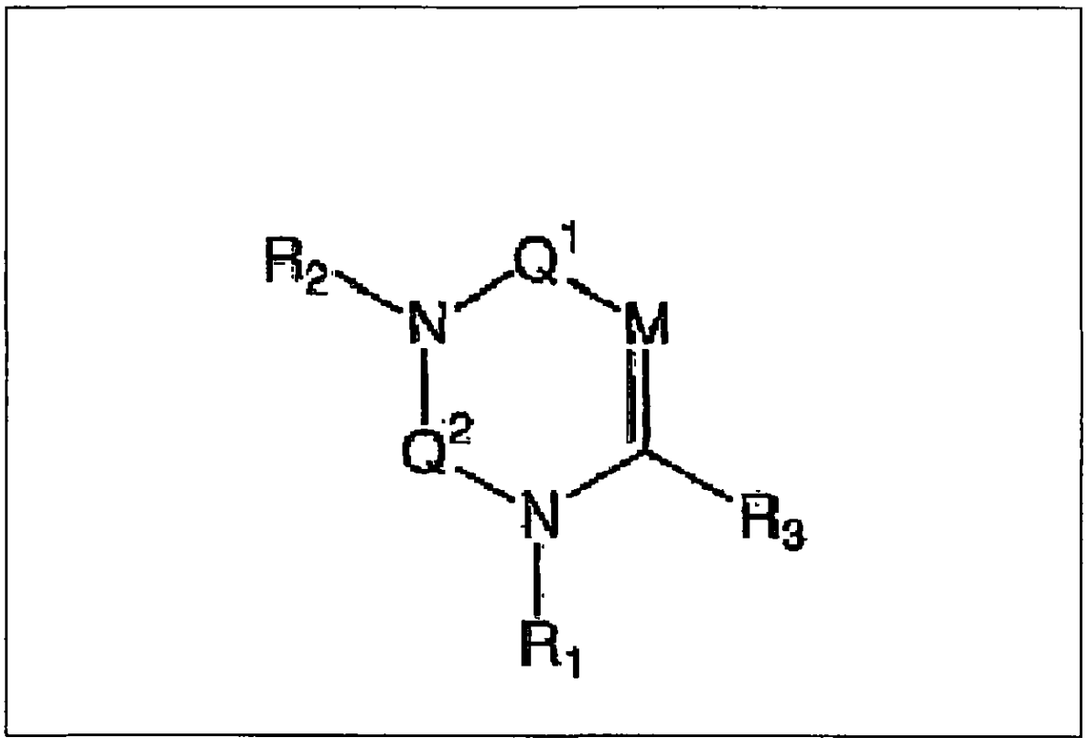
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10) ANEXOS

- [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 Opinión escrita
  3 Documentos de cambios internacionales

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

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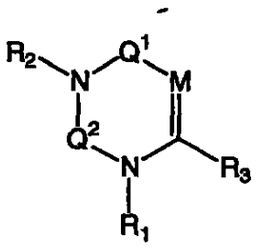
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WO 2005/095381 A1

(54) Title: DIPEPTIDYL PEPTIDASE INHIBITORS



(I)

(57) Abstract: Compounds, pharmaceuticals, kits and methods are provided for use with DPP-IV and other S9 proteases that comprise a compound comprising Formula (I) ##STR1## wherein M is N or CR4, Q1 and Q2 are each independently selected from the group consisting of CO, SO, SO2, and C=NR9, and each R1, R2, R3, R4 and R9 are as defined herein

DIPEPTIDYL PEPTIDASE INHIBITORS

Field of the Invention

[0001] The invention relates to compounds that may be used to inhibit dipeptidyl peptidases as well as compositions of matter and kits comprising these compounds The present invention also relates to methods for inhibiting dipeptidyl peptidases as well as treatment methods using compounds according to the present invention

Description of Related Art

[0002] Dipeptidyl Peptidase IV (IUBMB Enzyme Nomenclature EC 3.4 14 5) is a type II membrane protein that has been referred to in the literature by a wide a variety of names including DPP4, DP4, DAP-IV, FAPβ, adenosine deaminase complexing protein 2, adenosine deaminase binding protein (ADAbp), dipeptidyl aminopeptidase IV; Xaa-Pro-dipeptidyl-aminopeptidase, Gly-Pro naphthylamidase; postproline dipeptidyl aminopeptidase IV, lymphocyte antigen CD26, glycoprotein GP110, dipeptidyl peptidase IV; glycylproline aminopeptidase, glycylproline aminopeptidase; X-prolyl dipeptidyl aminopeptidase; pep X; leukocyte antigen CD26, glycylprolyl dipeptidylaminopeptidase; dipeptidyl-peptide hydrolase; glycylprolyl aminopeptidase; dipeptidyl-aminopeptidase IV; DPP IV/CD26; amino acyl-prolyl dipeptidyl aminopeptidase; T cell triggering molecule Tp103; X-PDAP Dipeptidyl Peptidase IV is referred to herein as "DPP-IV."

[0003] DPP-IV is a non-classical serine aminodipeptidase that removes Xaa-Pro dipeptides from the amino terminus (N-terminus) of polypeptides and proteins. DPP-IV dependent slow release of dipeptides of the type X-Gly or X-Ser has also been reported for some naturally occurring peptides.

[0004] DPP-IV is constitutively expressed on epithelial and endothelial cells of a variety of different tissues (intestine, liver, lung, kidney and placenta), and is also found in body fluids. DPP-IV is also expressed on circulating T-lymphocytes and has been shown to be synonymous with the cell-surface antigen, CD-26. DPP-IV has been implicated in a number of disease states, some of which are discussed below

[0005] DPP-IV is responsible for the metabolic cleavage of certain endogenous peptides (GLP-1 (7-36), glucagon) *in vivo* and has demonstrated proteolytic activity against a variety of other peptides (GHRH, NPY, GLP-2, VIP) *in vitro*.

[0006] GLP-1 (7-36) is a 29 amino-acid peptide derived by post-translational processing of proglucagon in the small intestine GLP-1 (7-36) has multiple actions *in vivo* including the stimulation of insulin secretion, inhibition of glucagon secretion, the promotion of satiety, and the slowing of gastric emptying Based on its physiological profile, the actions of GLP-1 (7-36) are believed to be beneficial in the prevention and treatment of type II diabetes and potentially obesity For example, exogenous administration of GLP-1 (7-36) (continuous infusion) in diabetic patients has been found to be efficacious in this patient population. Unfortunately, GLP-1 (7-36) is degraded rapidly *in vivo* and has been shown to have a short half-life *in vivo* ($t_{1/2}$=1 5 minutes)

[0007] Based on a study of genetically bred DPP-IV knock out mice and on *in vivo / in vitro* studies with selective DPP-IV inhibitors, DPP-IV has been shown to be the primary degrading enzyme of GLP-1 (7-36) *in vivo* GLP-1 (7-36) is degraded by DPP-IV efficiently to GLP-1 (9-36), which has been speculated to act as a physiological antagonist to GLP-1 (7-36). Inhibiting DPP-IV *in vivo* is therefore believed to be useful for potentiating endogenous levels of GLP-1 (7-36) and attenuating the formation of its antagonist GLP-1 (9-36). Thus, DPP-IV inhibitors are believed to be useful agents for the prevention, delay of progression, and/or treatment of conditions mediated by DPP-IV, in particular diabetes and more particularly, type 2 diabetes mellitus, diabetic dislipidemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose (IFG), metabolic acidosis, ketosis, appetite regulation and obesity.

[0008] DPP-IV expression is increased in T-cells upon mitogenic or antigenic stimulation (Mattem, T., et al., *Scand. J Immunol.*, 1991, 33, 737). It has been reported that inhibitors of DPP-IV and antibodies to DPP-IV suppress the proliferation of mitogen-stimulated and antigen-stimulated T-cells in a dose-dependant manner (Schon, E , et al., *Biol. Chem* , 1991, 372, 305). Various other functions of T-lymphocytes such as cytokine production, IL-2 mediated cell proliferation and B-cell helper activity have been shown to be dependent on DPP-IV activity (Schon, E., et al., *Scand. J Immunol* , 1989, 29, 127). DPP-IV inhibitors, based on boroProline, (Flentke, G R., et al , *Proc. Nat. Acad. Sci. USA*, 1991, 88, 1556) although unstable, were effective at inhibiting antigen-induced lymphocyte proliferation and IL-2 production in murine CD4+ T-helper cells. Such boronic acid inhibitors have been shown to have an effect *in vivo* in mice causing

suppression of antibody production induced by immune challenge (Kubota, T et al , *Clin Exp. Immun.*, 1992, 89, 192). The role of DPP-IV in regulating T lymphocyte activation may also be attributed, in part, to its cell-surface association with the transmembrane phosphatase, CD45 DPP-IV inhibitors or non-active site ligands may possibly disrupt the CD45-DPP-IV association CD45 is known to be an integral component of the T-cell signaling apparatus It has been reported that DPP-IV is essential for the penetration and infectivity of HIV-1 and HIV-2 viruses in CD4+ T-cells (Wakselman, M , Nguyen, C., Mazaleyrat, J -P , Callebaut, C., Krust, B , Hovanessian, A. G , Inhibition of HIV-1 infection of CD 26+ but not CD 26-cells by a potent cyclopeptidic inhibitor of the DPP-IV activity of CD 26. Abstract P 44 of the 24 sup.th European Peptide Symposium 1996) Additionally, DPP-IV has been shown to associate with the enzyme adenosine deaminase (ADA) on the surface of T-cells (Kameoka, J , et al., *Science,* 193, 26 466). ADA deficiency causes severe combined immunodeficiency disease (SCID) in humans. This ADA-CD26 interaction may provide clues to the pathophysiology of SCID It follows that inhibitors of DPP-IV may be useful immunosuppressants (or cytokine release suppressant drugs) for the treatment of among other things: organ transplant rejection; autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis; and the treatment of AIDS.

[0009] It has been shown that lung endothelial cell DPP-IV is an adhesion molecule for lung-metastatic rat breast and prostate carcinoma cells (Johnson, R. C , et al., *J Cell. Biol*, 1993, 121, 1423). DPP-IV is known to bind to fibronectin and some metastatic tumor cells are known to carry large amounts of fibronectin on their surface. Potent DPP-IV inhibitors may be useful as drugs to prevent metastases of, for example, breast and prostrate tumors to the lungs.

[0010] High levels of DPP-IV expression have also been found in human skin fibroblast cells from patients with psoriasis, rheumatoid arthritis (RA) and lichen planus (Raynaud, F., et al., *J. Cell. Physiol.*, 1992, 151, 378) Therefore, DPP-IV inhibitors may be useful as agents to treat dermatological diseases such as psoriasis and lichen planus.

[0011] High DPP-IV activity has been found in tissue homogenates from patients with benign prostate hypertrophy and in prostatosomes. These are prostate derived organelles important for the enhancement of sperm forward motility (Vanhoof, G., et al., *Eur J. Clin.*

Chem. Clin. Biochem., 1992, 30, 333) DPP-IV inhibitors may also act to suppress sperm motility and therefore act as a male contraceptive agent Conversely, DPP-IV inhibitors have been implicated as novel for treatment of infertility, and particularly human female infertility due to Polycystic ovary syndrome (PCOS, Stein-Leventhal syndrome) which is a condition characterized by thickening of the ovarian capsule and formation of multiple follicular cysts. It results in infertility and amenorrhea

[0012] DPP-IV is thought to play a role in the cleavage of various cytokines (stimulating hematopoietic cells), growth factors and neuropeptides.

[0013] Stimulated hematopoietic cells are useful for the treatment of disorders that are characterized by a reduced number of hematopoietic cells or their precursors *in vivo* Such conditions occur frequently in patients who are immunosuppressed, for example, as a consequence of chemotherapy and/or radiation therapy for cancer. It was discovered that inhibitors of dipeptidyl peptidase type IV are useful for stimulating the growth and differentiation of hematopoietic cells in the absence of exogenously added cytokines or other growth factors or stromal cells. This discovery contradicts the dogma in the field of hematopoietic cell stimulation, which provides that the addition of cytokines or cells that produce cytokines (stromal cells) is an essential element for maintaining and stimulating the growth and differentiation of hematopoietic cells in culture. (See, e g , PCT Intl. Application No PCT /US93/017173 published as WO 94/03055).

[0014] DPP-IV in human plasma has been shown to cleave N-terminal Tyr-Ala from growth hormone-releasing factor and cause inactivation of this hormone. Therefore, inhibitors of DPP-IV may be useful in the treatment of short stature due to growth hormone deficiency (Dwarfism) and for promoting GH-dependent tissue growth or re-growth.

[0015] DPP-IV can also cleave neuropeptides and has been shown to modulate the activity of neuroactive peptides substance P, neuropeptide Y and CLIP (Mentlein, R., Dahms, P., Grandt, D., Kruger, R , Proteolytic processing of neuropeptide Y and peptide YY by dipeptidyl peptidase IV, *Regul. Pept.*, 49, 133, 1993; Wetzel, W , Wagner, T , Vogel, D , Demuth, H.-U , Balschun, D., Effects of the CLIP fragment ACTH 20-24 on the duration of REM sleep episodes, *Neuropeptides*, 31, 41, 1997). Thus DPP-IV

inhibitors may also be useful agents for the regulation or normalization of neurological disorders.

[0016] Several compounds have been shown to inhibit DPP-IV Nonetheless, a need still exists for new DPP-IV inhibitors that have advantageous potency, stability, selectivity, toxicity and/or pharmacodynamics properties In this regard, a novel class of DPP-IV inhibitors are provided herein

SUMMARY OF THE INVENTION

[0017] The present invention relates to compounds that have activity for inhibiting DPP-IV It is noted that these compounds may also have activity for inhibiting other S9 proteases and thus may be used against these other S9 proteases as well as DPP-IV The present invention also provides compositions, articles of manufacture and kits comprising these compounds.

[0018] In one embodiment, a pharmaceutical composition is provided that comprises a DPP-IV 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 DPP-IV 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, intraocularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, or intrathecally. The compositions may also be administered or coadministered in slow release dosage forms.

[0019] The invention is also directed to kits and other articles of manufacture for treating disease states associated with DPP-IV.

[0020] In one embodiment, a kit is provided that comprises a composition comprising at least one DPP-IV 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

[0021] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one DPP-IV 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

[0022] 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.

[0023] Also provided are methods for using compounds, compositions, kits and articles of manufacture according to the present invention.

[0024] In one embodiment, the compounds, compositions, kits and articles of manufacture are used to inhibit DPP-IV.

[0025] In another embodiment, the compounds, compositions, kits and articles of manufacture are used to treat a disease state for which DPP-IV possesses activity that contributes to the pathology and/or symptomology of the disease state.

[0026] In another embodiment, a compound is administered to a subject wherein DPP-IV activity within the subject is altered, preferably reduced.

[0027] In another embodiment, a prodrug of a compound is administered to a subject that is converted to the compound *in vivo* where it inhibits DPP-IV.

[0028] In another embodiment, a method of inhibiting DPP-IV is provided that comprises contacting DPP-IV with a compound according to the present invention

[0029] In another embodiment, a method of inhibiting DPP-IV is provided that comprises causing a compound according to the present invention to be present in a subject in order to inhibit DPP-IV *in vivo*.

[0030] In another embodiment, a method of inhibiting DPP-IV 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 DPP-IV *in vivo*. It is noted that the compounds of the present invention may be the first or second compounds

[0031] In another embodiment, a therapeutic method is provided that comprises administering a compound according to the present invention

[0032] In another embodiment, a method of inhibiting cell proliferation is provided that comprises contacting a cell with an effective amount of a compound according to the present invention

[0033] In another embodiment, a method of inhibiting cell proliferation in a patient is provided that comprises administering to the patient a therapeutically effective amount of a compound according to the present invention

[0034] In another embodiment, a method of treating a condition in a patient which is known to be mediated by DPP-IV, or which is known to be treated by DPP-IV inhibitors, comprising administering to the patient a therapeutically effective amount of a compound according to the present invention

[0035] 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 disease state which is known to be mediated by DPP-IV, or which is known to be treated by DPP-IV inhibitors.

[0036] In another embodiment, a method is provided for treating a disease state for which DPP-IV 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.

[0037] In another embodiment, a method is provided for treating a disease state for which DPP-IV 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.

[0038] In another embodiment, a method is provided for treating a disease state for which DPP-IV 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.

[0039] In another 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

[0040] Examples of diseases that may be treated by administration of compounds and compositions according to the present invention include, but are not limited to conditions mediated by DPP-IV, in particular diabetes, more particular type 2 diabetes mellitus, diabetic dislipidemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose (IFG), metabolic acidosis, ketosis, appetite regulation, obesity, immunosuppressants or cytokine release regulation, autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis, AIDS, cancers (prevention of metastases, for example, breast and prostrate tumors to the lungs), dermatological diseases such as psoriasis and lichen planus, treatment of female infertility, osteoporosis, male contraception and neurological disorders

[0041] 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 known 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

[0042] 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 DPP-IV and thus may themselves be prodrugs for another compound. Such prodrugs of another compound may or may not themselves independently have DPP-IV inhibitory activity.

BRIEF DESCRIPTION OF THE FIGURE

[0043] Figure 1 illustrates a ribbon diagram overview of the structure of DPP-IV, highlighting the secondary structural elements of the protein.

DEFINITIONS

[0044] Unless otherwise stated, the following terms used in the specification and claims shall have the following meanings for the purposes of this Application.

[0045] "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 C3 - C8 rings such as cyclopropyl, cyclohexane, cyclopentane, cyclopentene, cyclopentadiene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, cycloheptene, cycloheptadiene, cyclooctane, cyclooctene, and cyclooctadiene.

[0046] "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.

[0047] "Alkenyl" represented by itself means a straight or branched, unsaturated, aliphatic radical having a chain of carbon atoms having at least one double bond between adjacent carbon atoms. C_X alkenyl and C_{X-Y} alkenyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{2-6} alkenyl includes alkenyls that have a chain of between 2 and 6 carbons

[0048] "Alkoxy" means an oxygen moiety having a further alkyl substituent The alkoxy groups of the present invention can be optionally substituted.

[0049] "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).

[0050] "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).

[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$_2$CH$_3$), allylidene (=CH-CH=CH$_2$), and the like).

[0052] "Alkynyl" represented by itself means a straight or branched, unsaturated, aliphatic radical having a chain of carbon atoms having at least one triple bond between adjacent carbon atoms. C_X alkynyl and C_{X-Y} alkynyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{2-6} alkynyl includes alkynyls that have a chain of between 2 and 6 carbons

[0053] "Amino" means a nitrogen moiety having two further substituents where 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_{1-3}-alkyl, -$N(C_{1-3}$-alkyl$)_2$ and the like. 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] "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

[0066] "Cyano" means the radical -CN

[0067] "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.

[0068] "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.

[0069] "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

[0070] "Fused ring" as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure where 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.

[0071] "Halo" means fluoro, chloro, bromo or iodo

[0072] "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).

[0073] "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.

[0074] "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.

[0075] "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

[0076] "Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms is replaced by a heteroatom.

[0077] "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.

[0078] "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_{4-10})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.

[0079] "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.

[0080] "Hydroxy" means the radical -OH

[0081] "Iminoketone derivative" means a derivative comprising the moiety -C(NR)-, wherein R comprises a hydrogen or carbon atom attached to the nitrogen

[0082] "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)

[0083] "Nitro" means the radical -NO_2

[0084] "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

[0085] "Oxoalkyl" means an alkyl, further substituted with a carbonyl group. The carbonyl group may be an aldehyde, ketone, ester, amide, acid or acid chloride

[0086] "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

[0087] "Pharmaceutically acceptable salts" means salts of inhibitors 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, tartatic 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.

[0088] 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

[0089] "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

DPP-IV 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.

[0090] "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.

[0091] "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, 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.

[0092] "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.

[0093] "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.

[0094] "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.

[0095] "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

[0096] "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 disease (i.e., reversing the pathology and/or symptomatology).

[0097] 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 -$R_aR_bR_c$ 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

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DETAILED DESCRIPTION OF THE INVENTION

[0098] The present invention relates to compounds, compositions, kits and articles of manufacture that may be used to inhibit dipeptidyl peptidases IV (referred to herein as DPP-IV)

[0099] DPP-IV (EC 3 4.14 5 also known as DPP4, DP4, DAP-IV, adenosine deaminase complexing protein 2, adenosine deaminase binding protein (ADAbp) or CD26) is a 766 residue, 240kDa protein that is a highly specific membrane bound non-classical serine aminodipeptidase DPP-IV has a serine type mechanism of protease activity, cleaving off dipeptides from the amino-terminus of peptides with proline or alanine at the penultimate position. In addition the slow release of dipeptides of the type X-Gly or X-Ser is reported for some naturally occurring peptides DPP-IV is constitutively expressed on epithelial and endothelial cells of a variety of different tissues (intestine, liver, lung, kidney and placenta), and is also found in body fluids DPP-IV is also expressed on circulating T-lymphocytes and has been shown to be synonymous with the cell-surface antigen, CD-26. The wild-type form of full length DPP-IV is described in GenBank Accession Number NM_001935 ("Dipeptidyl peptidase IV (CD 26) gene expression in enterocyte-like colon cancer cell lines HT-29 and Caco-2 Cloning of the complete human coding sequence and changes of dipeptidyl peptidase IV mRNA levels during cell differentiation", Darmoul, D., Lacasa, M., Baricault, L., Marguet, D., Sapin, C , Trotot, P , Barbat, A. and Trugnan, G., J Biol Chem., 267 (7), 4824-4833, 1992).

[0100] DPP-IV is a member of the S9 family of serine proteases, more particularly the S9B family. Other members of the S9 family include, but are not limited to

Subfamily S9A: Dipeptidyl-peptidase; Oligopeptidase B (EC 3 4.21.83); Oligopeptidase B; Prolyl oligopeptidase (EC 3.4 21.26);

Subfamily S9B: Dipeptidyl aminopeptidase A, Dipeptidyl aminopeptidase B Dipeptidyl-peptidase IV (EC 3.4.14 5); Dipeptidyl-peptidase V Fibroblast activation protein alpha subunit; Seprase

Subfamily S9C: Acylaminoacyl-peptidase (EC 3.4.19.1)

[0101] It is noted that the compounds of the present invention may also possess inhibitory activity for other S9 family members and thus may be used to address disease states associated with these other family members.

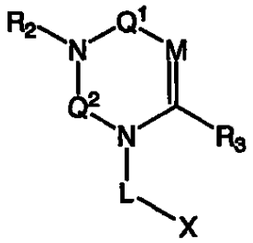
1. CRYSTAL STRUCTURE OF DPP-IV

[0102] Syrrx, Inc (San Diego, California) recently solved the crystal structure of DPP-IV. Knowledge of the crystal structure was used to guide the design of the DPP-IV inhibitors provided herein.

[0103] Figure 1 illustrates a ribbon diagram overview of the structure of DPP-IV, highlighting secondary structural elements of the protein. DPP-IV is a cylindrical shaped molecule with an approximate height of 70 Å and a diameter of 60 Å The catalytic triad of DPP-IV (Ser642, Asp720 and His752) is illustrated in the center of the figure by a "ball and stick" representation. This triad of amino acids is located in the peptidase domain or catalytic domain of DPP-IV. The catalytic domain is covalently linked to the β-propeller domain. The catalytic domain of DPP-IV includes residues 1-67 and 511-778. The catalytic domain of DPP-IV adopts a characteristic α/β hydrolase fold The core of this domain contains an 8-stranded β-sheet with all strands being parallel except one. The α-sheet is significantly twisted and is flanked by three α-helices on one side and five α-helices on the other The topology of the β-strands is 1, 2, -1x, 2x and (1x) (J. S. Richardson· The anatomy and taxonomy of protein structure, (1981) *Adv. Protein Chem.* 269, 15076-15084.) A number of residues were identified that contribute to the shape and charge characteristics of the active site. Knowledge of these residues has been an important contribution to the design of DPP-IV inhibitors of the present invention.

2. DPP-IV INHIBITORS

[0104] In one embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



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wherein

M is N or CR_4,

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and $C=NR_9$,

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring,

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

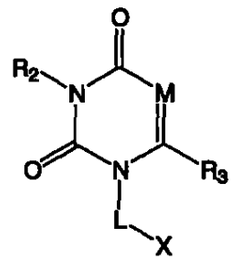
R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted,

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl,

sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0105] In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising.



wherein

M is N or CR_4;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted

Substituent L:

[0106] In one variation of the above embodiments, DPP-IV inhibitors of the present invention comprise compounds wherein the 1, 2 or 3 atoms of L providing the separation consist of carbon atoms In another variation, the 1, 2 or 3 atoms of L providing the separation are selected from the group of linkers consisting of at least one oxygen or at least one nitrogen atom In yet another variation, L separates X from the ring atom by one atom.

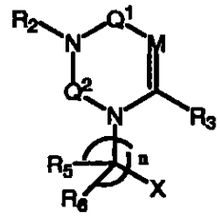
[0107] In one particular variation of the above embodiments, L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -C(O)-, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, -O-, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, $-NH-C(O)-$, $-NCH_3-C(O)-$, $-C(O)NH-$, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, -S-, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, $-C(O)S-$, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, and $-CH_2SC(O)-$, each substituted or unsubstituted.

[0108] In another particular variation of the above embodiments, L is selected from the group consisting of $-CH_2-$, -C(O)-, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, and $-CH_2CH_2C(O)-$, each substituted or unsubstituted

[0109] In one particular variation of the above embodiments, -L-X taken together is selected from the group consisting of $-(CH_2)$-(2-cyano)phenyl; $-(CH_2)$-(3-cyano)phenyl; $-(CH_2)$-(2-hydroxy)phenyl; $-(CH_2)$-(3-hydroxy)phenyl; $-(CH_2)$-(2-alkenyl)phenyl, $-(CH_2)$-(3-alkenyl)phenyl; $-(CH_2)$-(2-alkynyl)phenyl; $-(CH_2)$-(3-alkynyl)phenyl; $-(CH_2)$-(2-

methoxy)phenyl; -(CH_2)-(3-methoxy)phenyl; -(CH_2)-(2-nitro)phenyl; -(CH_2)-(3-nitro)phenyl; -(CH_2)-(2-carboxy)phenyl, -(CH_2)-(3-carboxy)phenyl; -(CH_2)-(2-carboxamido)phenyl; -(CH_2)-(3-carboxamido)phenyl; -(CH_2)-(2-sulfonamido)phenyl, -(CH_2)-(3-sulfonamido)phenyl, -(CH_2)-(2-tetrazolyl)phenyl; -(CH_2)-(3-tetrazolyl)phenyl, -(CH_2)-(2-aminomethyl)phenyl; -(CH_2)-(3-aminomethyl)phenyl; -(CH_2)-(2-hydroxymethyl)phenyl; -(CH_2)-(3-hydroxymethyl)phenyl; -(CH_2)-(2-phenyl)phenyl; -(CH_2)-(3-phenyl)phenyl; -(CH_2)-(2-halo)phenyl, -(CH_2)-(3-halo)phenyl; -(CH_2)-(2-$CONH_2$)phenyl, -(CH_2)-(3-$CONH_2$)phenyl; -(CH_2)-(2-$CONH(C_{1-7})$alkyl)phenyl; -(CH_2)-(3-$CONH(C_{1-7})$alkyl)phenyl, -(CH_2)-(2-$CO_2(C_{1-7})$alkyl)phenyl; -(CH_2)-(3-$CO_2(C_{1-7})$alkyl)phenyl; -(CH_2)-(2-NH_2)phenyl, -(CH_2)-(3-NH_2)phenyl; -(CH_2)-(2-(C_{3-7})alkyl)phenyl; -(CH_2)-(3-(C_{3-7})alkyl)phenyl, -(CH_2)-(2-(C_{3-7})cycloalkyl)phenyl; -(CH_2)-(3-(C_{3-7})cycloalkyl)phenyl, -(CH_2)-(2-aryl)phenyl; -(CH_2)-(3-aryl)phenyl, -(CH_2)-(2-heteroaryl)phenyl; -(CH_2)-(3-heteroaryl)phenyl; -(CH_2)-2-bromo-5-fluoro phenyl; -(CH_2)-2-chloro-5-fluoro phenyl; -(CH_2)-2-cyano-5-fluoro phenyl; -(CH_2)-2,5-dichloro phenyl; -(CH_2)-2,5-difluoro phenyl; -(CH_2)-2,5-dibromo phenyl; -(CH_2)-2-bromo-3,5-difluoro phenyl; -(CH_2)-2-chloro-3,5-difluoro phenyl, -(CH_2)-2,3,5-trifluoro phenyl; -(CH_2)-2,3,5,6-tetrafluorophenyl, -(CH_2)-2-bromo-3,5,6-trifluoro phenyl, -(CH_2)-2-chloro-3,5,6-trifluoro phenyl; -(CH_2)-2-cyano-3,5-difluoro phenyl, -(CH_2)-2-cyano-3,5,6-trifluoro phenyl; -(CH_2)-(2-heterocycloalkyl)phenyl; and -(CH_2)-(3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

[0110] In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

n is 1, 2, or 3;

M is N or CR_4;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and $C=NR_9$;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent X:

[0111] In regard to particular variations of the present invention, there is provided compounds wherein X is a substituted or unsubstituted (C_{3-7})cycloalkyl According to each of the above variations, the invention provides compounds wherein X is a substituted or unsubstituted (C_{3-7})heterocycloalkyl, or wherein X is a substituted or unsubstituted aryl.

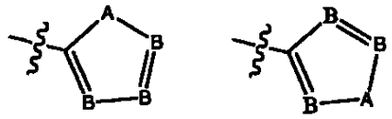
[0112] Further, according to each of the above variations, the invention provides compounds wherein X is a substituted or unsubstituted phenyl, or wherein X is a substituted or unsubstituted heteroaryl In another variation according to the above variation, X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring

[0113] According to the above variations, there is provided compounds wherein X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, cyano, nitro, halo, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted. In another variation of the above, X is a substituted or unsubstituted halophenyl or dihalophenyl. In yet another variation, X is a substituted or unsubstituted haloaryl, haloheteroaryl, dihaloaryl or dihaloheteroaryl

[0114] According to the above variations, X is selected from the group consisting of (2-cyano)phenyl, (3-cyano)phenyl, (2-hydroxy)phenyl; (3-hydroxy)phenyl; (2-alkenyl)phenyl; (3-alkenyl)phenyl; (2-alkynyl)phenyl; (3-alkynyl)phenyl; (2-methoxy)phenyl; (3-methoxy)phenyl; (2-nitro)phenyl; (3-nitro)phenyl, (2-carboxy)phenyl; (3-carboxy)phenyl; -(CH_2)-(2-carboxamido)phenyl; (3-carboxamido)phenyl, (2-sulfonamido)phenyl; (3-sulfonamido)phenyl; (2-tetrazolyl)phenyl; (3-tetrazolyl)phenyl; (2-aminomethyl)phenyl; (3-aminomethyl)phenyl; (2-hydroxymethyl)phenyl; (3-hydroxymethyl)phenyl; (2-phenyl)phenyl, (3-phenyl)phenyl; (2-halo)phenyl; (3-halo)phenyl; (2-$CONH_2$)phenyl, (3-$CONH_2$)phenyl; (2-CONH(C_{1-7})alkyl)phenyl; (3-CONH(C_{1-7})alkyl)phenyl; (2-CO_2(C_{1-7})alkyl)phenyl; (3-CO_2(C_{1-7})alkyl)phenyl, (2-NH_2)phenyl, (3-NH_2)phenyl, (2-(C_{3-7})alkyl)phenyl, (3-(C_{3-7})alkyl)phenyl, (2-(C_{3-7})cycloalkyl)phenyl; (3-(C_{3-7})cycloalkyl)phenyl; (2-aryl)phenyl; (3-aryl)phenyl; (2-heteroaryl)phenyl;

(3-heteroaryl)phenyl, 2-bromo-5-fluoro phenyl, 2-chloro-5-fluoro phenyl; 2-cyano-5-fluoro phenyl, 2,5-dichloro phenyl; 2,5-difluoro phenyl; 2,5-dibromo phenyl; 2-bromo-3,5-difluoro phenyl; 2-chloro-3,5-difluoro phenyl, 2,3,5-trifluoro phenyl, 2,3,5,6-tetrafluorophenyl, 2-bromo-3,5,6-trifluoro phenyl, 2-chloro-3,5,6-trifluoro phenyl, 2-cyano-3,5-difluoro phenyl, 2-cyano-3,5,6-trifluoro phenyl, (2-heterocycloalkyl)phenyl; and (3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

[0115] In regard to the above particular variations, the invention also include compounds wherein X is selected from the group consisting of



wherein

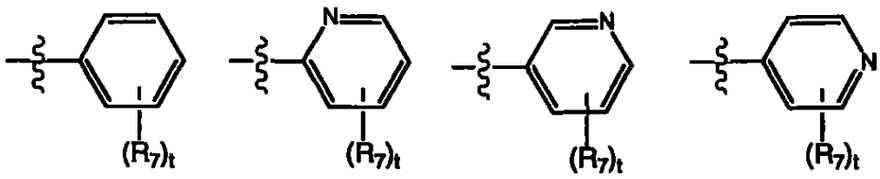
A is S, O or NR_{24},

B is CR_{23} or N;

R_{23} is independently selected from the group consisting of hydrogen, halo, perhalo(C_{1-10})alkyl, amino, thio, cyano, CF_3, nitro, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and

R_{24} is independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted

[0116] In one variation of the above embodiments and variations, X is selected from the group consisting of

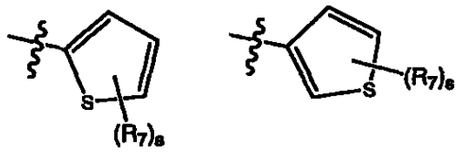


wherein

t is 0, 1, 2, 3, 4 or 5, and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0117] In another variation of the above compounds, X is selected from the group consisting of



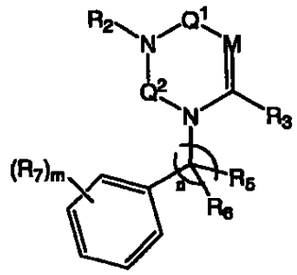
wherein

s is 0, 1, 2, or 3, and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0118] In one particular variation of the above compounds, R_7 is independently selected from the group consisting of -cyano, -methoxy, -nitro, -carboxy, -sulfonamido, -tetrazolyl, -aminomethyl, -hydroxymethyl, -phenyl, -halo, $-CONH_2$, $-CONH(C_{1-7})$alkyl, $-CO_2(C_{1-7})$alkyl, $-NH_2$, -OH, $-(C_{1-5})$alkyl, -alkenyl, -alkynyl, (C_{1-5})cycloalkyl, aryl, heteroaryl, and heterocycloalkyl, each substituted or unsubstituted

[0119] In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

m is 0, 1, 2, 3, 4, or 5,

n is 1, 2, or 3;

M is N or CR_4;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring,

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl

(C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

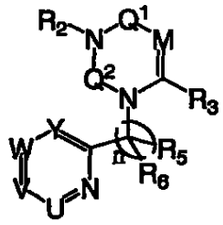
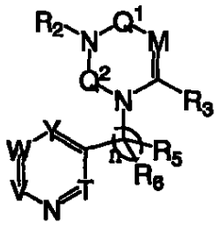
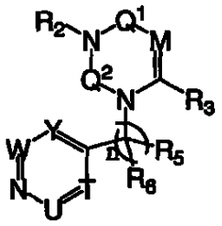
each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring,

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; and

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted.

[0120] In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising.

a member selected from the group consisting of

wherein

n is 1, 2, or 3;

M is N or CR_4;

each of T, U, V, W and Y is independently nitrogen or CR_{16}, provided that no more than two of T, U, V, W and Y are nitrogen;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and $C{=}NR_9$;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl,

aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring,

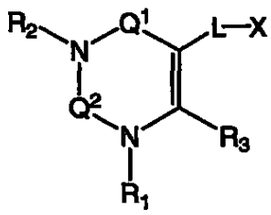
R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

each R_{16} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0121] In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and $C=NR_9$,

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

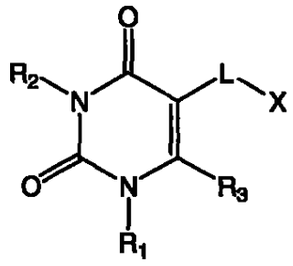
R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring,

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0122] In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising



wherein

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl

group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted

Substituent L:

[0123] In one variation of the present invention, there is provided compounds wherein the 1, 2 or 3 atoms of L providing the separation consist of carbon atoms In another variation, the 1, 2 or 3 atoms of L providing the separation are selected from the group of linkers consisting of at least one oxygen or at least one nitrogen atom. In one particular variation, L separates X from the ring atom by one atom.

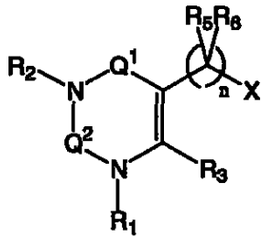
[0124] In regard to particular variation of the present invention, L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, $-NH-C(O)-$, $-NCH_3-C(O)-$, $-C(O)NH-$, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, $-S-$, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, $-C(O)S-$, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, and $-CH_2SC(O)-$, each substituted or unsubstituted.

[0125] In regard to another variation of the above compounds, L is selected from the group consisting of $-CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, and $-CH_2CH_2C(O)-$, each substituted or unsubstituted

[0126] In another variation of the above compounds, -L-X taken together is selected from the group consisting of -(CH_2)-(2-cyano)phenyl, -(CH_2)-(3-cyano)phenyl; -(CH_2)-(2-hydroxy)phenyl; -(CH_2)-(3-hydroxy)phenyl; -(CH_2)-(2-alkenyl)phenyl; -(CH_2)-(3-

alkenyl)phenyl; -(CH_2)-(2-alkynyl)phenyl; -(CH_2)-(3-alkynyl)phenyl; -(CH_2)-(2-methoxy)phenyl; -(CH_2)-(3-methoxy)phenyl, -(CH_2)-(2-nitro)phenyl; -(CH_2)-(3-nitro)phenyl; -(CH_2)-(2-carboxy)phenyl; -(CH_2)-(3-carboxy)phenyl, -(CH_2)-(2-carboxamido)phenyl; -(CH_2)-(3-carboxamido)phenyl, -(CH_2)-(2-sulfonamido)phenyl; -(CH_2)-(3-sulfonamido)phenyl, -(CH_2)-(2-tetrazolyl)phenyl; -(CH_2)-(3-tetrazolyl)phenyl; -(CH_2)-(2-aminomethyl)phenyl; -(CH_2)-(3-aminomethyl)phenyl, -(CH_2)-(2-hydroxymethyl)phenyl, -(CH_2)-(3-hydroxymethyl)phenyl, -(CH_2)-(2-phenyl)phenyl; -(CH_2)-(3-phenyl)phenyl; -(CH_2)-(2-halo)phenyl, -(CH_2)-(3-halo)phenyl; -(CH_2)-(2-$CONH_2$)phenyl, -(CH_2)-(3-$CONH_2$)phenyl, -(CH_2)-(2-$CONH(C_{1-7})$alkyl)phenyl; -(CH_2)-(3-$CONH(C_{1-7})$alkyl)phenyl; -(CH_2)-(2-$CO_2(C_{1-7})$alkyl)phenyl, -(CH_2)-(3-$CO_2(C_{1-7})$alkyl)phenyl, -(CH_2)-(2-NH_2)phenyl; -(CH_2)-(3-NH_2)phenyl; -(CH_2)-(2-(C_{3-7})alkyl)phenyl; -(CH_2)-(3-(C_{3-7})alkyl)phenyl, -(CH_2)-(2-(C_{3-7})cycloalkyl)phenyl, -(CH_2)-(3-(C_{3-7})cycloalkyl)phenyl; -(CH_2)-(2-aryl)phenyl; -(CH_2)-(3-aryl)phenyl; -(CH_2)-(2-heteroaryl)phenyl, -(CH_2)-(3-heteroaryl)phenyl, -(CH_2)-2-bromo-5-fluoro phenyl; -(CH_2)-2-chloro-5-fluoro phenyl; -(CH_2)-2-cyano-5-fluoro phenyl; -(CH_2)-2,5-dichloro phenyl, -(CH_2)-2,5-difluoro phenyl; -(CH_2)-2,5-dibromo phenyl, -(CH_2)-2-bromo-3,5-difluoro phenyl; -(CH_2)-2-chloro-3,5-difluoro phenyl; -(CH_2)-2,3,5-trifluoro phenyl; -(CH_2)-2,3,5,6-tetrafluorophenyl, -(CH_2)-2-bromo-3,5,6-trifluoro phenyl; -(CH_2)-2-chloro-3,5,6-trifluoro phenyl, -(CH_2)-2-cyano-3,5-difluoro phenyl; -(CH_2)-2-cyano-3,5,6-trifluoro phenyl; -(CH_2)-(2-heterocycloalkyl)phenyl; and -(CH_2)-(3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

[0127] In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising.



wherein

n is 1, 2, or 3,

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring,

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy,

heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted

Substituent X:

[0128] According to the above variations, the invention provides compounds wherein X is a substituted or unsubstituted (C_{3-7})cycloalkyl. In another particular variation of the above compounds, wherein X is a substituted or unsubstituted (C_{3-7})heterocycloalkyl, wherein X is a substituted or unsubstituted aryl, or wherein X is a substituted or unsubstituted phenyl In another particular variation, X is a substituted or unsubstituted heteroaryl

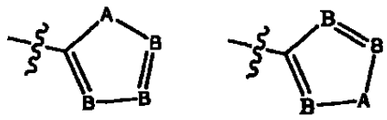
[0129] In one particular variation of the above compounds, X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring In one variation of the above compounds, X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, cyano, nitro, halo, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0130] In another particular variation, X is a substituted or unsubstituted halophenyl or dihalophenyl. In yet another particular variation, there is provided compounds wherein X is a substituted or unsubstituted haloaryl, haloheteroaryl, dihaloaryl or dihaloheteroaryl.

[0131] In regard to particular variations, the present invention provides compounds wherein X is selected from the group consisting of (2-cyano)phenyl; (3-cyano)phenyl; (2-hydroxy)phenyl; (3-hydroxy)phenyl, (2-alkenyl)phenyl; (3-alkenyl)phenyl, (2-alkynyl)phenyl, (3-alkynyl)phenyl; (2-methoxy)phenyl; (3-methoxy)phenyl; (2-nitro)phenyl; (3-nitro)phenyl; (2-carboxy)phenyl; (3-carboxy)phenyl, -(CH_2)-(2-carboxamido)phenyl; (3-carboxamido)phenyl; (2-sulfonamido)phenyl; (3-sulfonamido)phenyl; (2-tetrazolyl)phenyl; (3-tetrazolyl)phenyl, (2-aminomethyl)phenyl; (3-aminomethyl)phenyl; (2-hydroxymethyl)phenyl, (3-hydroxymethyl)phenyl; (2-phenyl)phenyl; (3-phenyl)phenyl; (2-halo)phenyl, (3-halo)phenyl; (2-$CONH_2$)phenyl; (3-$CONH_2$)phenyl, (2-CONH(C_{1-7})alkyl)phenyl, (3-CONH(C_{1-7})alkyl)phenyl; (2-CO_2(C_1-

$_7$)alkyl)phenyl; (3-CO_2(C_1–$_7$)alkyl)phenyl; (2-NH_2)phenyl; (3-NH_2)phenyl; (2-(C_3–$_7$)alkyl)phenyl; (3-(C_3–$_7$)alkyl)phenyl, (2-(C_3–$_7$)cycloalkyl)phenyl, (3-(C_3–$_7$)cycloalkyl)phenyl, (2-aryl)phenyl; (3-aryl)phenyl, (2-heteroaryl)phenyl; (3-heteroaryl)phenyl; 2-bromo-5-fluoro phenyl; 2-chloro-5-fluoro phenyl; 2-cyano-5-fluoro phenyl; 2,5-dichloro phenyl, 2,5-difluoro phenyl; 2,5-dibromo phenyl; 2-bromo-3,5-difluoro phenyl; 2-chloro-3,5-difluoro phenyl; 2,3,5-trifluoro phenyl; 2,3,5,6-tetrafluorophenyl, 2-bromo-3,5,6-trifluoro phenyl; 2-chloro-3,5,6-trifluoro phenyl, 2-cyano-3,5-difluoro phenyl; 2-cyano-3,5,6-trifluoro phenyl; (2-heterocycloalkyl)phenyl, and (3-heterocycloalkyl)phenyl, each substituted or unsubstituted

[0132] In one variation of the above compounds, X is selected from the group consisting of



wherein

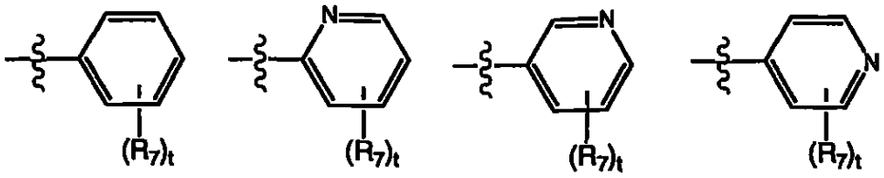
A is S, O or NR_{24},

B is CR_{23} or N;

R_{23} is independently selected from the group consisting of hydrogen, halo, perhalo(C_1-$_{10}$)alkyl, amino, thio, cyano, CF_3, nitro, (C_1-$_{10}$)alkyl, ($C_{3\text{-}12}$)cycloalkyl, hetero(C_3-$_{12}$)cycloalkyl, aryl(C_1-$_{10}$)alkyl, heteroaryl (C_1-$_5$)alkyl, ($C_{9\text{-}12}$)bicycloaryl, hetero($C_{8\text{-}12}$)bicycloaryl, carbonyl ($C_{1\text{-}3}$)alkyl, thiocarbonyl ($C_{1\text{-}3}$)alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and

R_{24} is independently selected from the group consisting of hydrogen, perhalo(C_1-$_{10}$)alkyl, amino, (C_1-$_{10}$)alkyl, ($C_{3\text{-}12}$)cycloalkyl, hetero(C_3-$_{12}$)cycloalkyl, aryl(C_1-$_{10}$)alkyl, heteroaryl (C_1-$_5$)alkyl, ($C_{9\text{-}12}$)bicycloaryl, hetero($C_{8\text{-}12}$)bicycloaryl, carbonyl ($C_{1\text{-}3}$)alkyl, thiocarbonyl ($C_{1\text{-}3}$)alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

[0133] In another particular variation of the above compounds, X is selected from the group consisting of

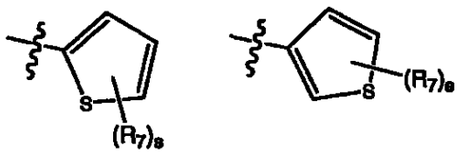


wherein

t is 0, 1, 2, 3, 4, or 5, and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0134] In yet another variation, X is selected from the group consisting of



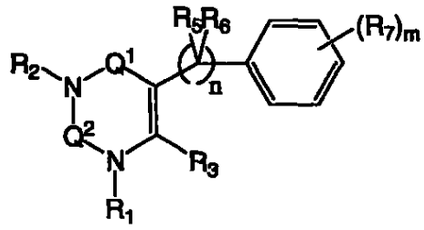
wherein

s is 0, 1, 2, or 3; and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0135] In one particular variation of the above compounds, R_7 is independently selected from the group consisting of -cyano, -methoxy, -nitro, -carboxy, -sulfonamido, -tetrazolyl, -aminomethyl, -hydroxymethyl, -phenyl, -halo, -$CONH_2$, -$CONH(C_{1-7})$alkyl, -$CO_2(C_{1-7})$alkyl, -NH_2, -OH, -(C_{1-5})alkyl, -alkenyl, -alkynyl, (C_{1-5})cycloalkyl, aryl, heteroaryl, and heterocycloalkyl, each substituted or unsubstituted.

[0136] In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising



wherein

m is 0, 1, 2, 3, 4 or 5,

n is 1, 2, or 3;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9,

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

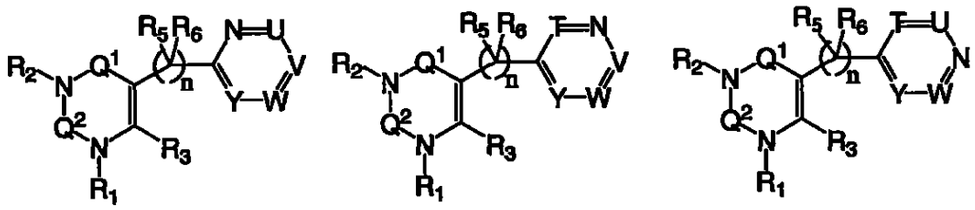
each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring,

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; and

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted.

[0137] In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:

a member selected from the group consisting of



wherein

n is 1, 2, or 3;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

each of T, U, V, W and Y is independently nitrogen or CR_{16}, provided that no more than two of T, U, V, W and Y are nitrogen;

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

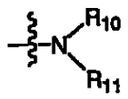
R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted, and

each R_{16} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent R_3:

[0138] In regard to each of the above embodiments and variations, the present invention provides compounds wherein R_3 is selected from the group consisting of amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring.

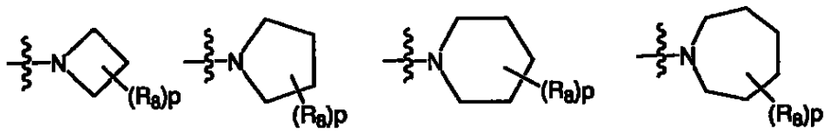
[0139] Further, according to each of the above embodiments and variations, the present invention also provides compounds wherein R_3 comprises the formula



wherein R_{10} and R_{11} are each independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, and sulfinyl group, each substituted or unsubstituted, or R_{10} and R_{11} are taken together to form a 4, 5, 6, or 7 membered ring, each substituted or unsubstituted.

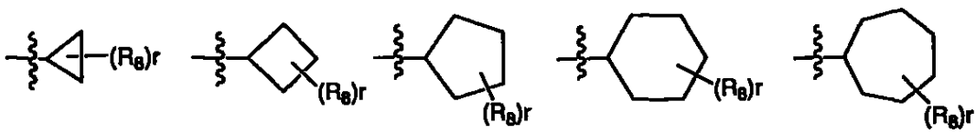
[0140] According to another variation of each of the above embodiments and variations, R_3 is a substituted or unsubstituted 3, 4, 5, 6, or 7 membered ring, wherein R_3 is a substituted or unsubstituted 3, 4, 5, 6, or 7 membered cycloalkyl, or wherein R_3 is a substituted or unsubstituted 4, 5, 6, or 7 membered heterocycloalkyl. In another variation of the above, R_3 is a substituted or unsubstituted aryl, or wherein R_3 is a substituted or unsubstituted heteroaryl.

[0141] In one particular variation of the above embodiments and variations, R_3 is selected from the group consisting of



wherein p is 0-12 and each R_8 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0142] In another particular variation of the above embodiments and variations, R_3 is selected from the group consisting of



wherein r is 0-13 and each R_8 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted

[0143] According to each of the above embodiments and variations, DPP-IV inhibitors of the present invention may comprise compounds wherein R_3 is a substituted or unsubstituted heteroaryl selected from the group consisting of furan, thiophene, pyrrole, pyrazole, triazole, isoxazole, oxazole, thiazole, isothiazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, imidazole, benzimidazole, indole, isoindole, quinoline, isoquinoline, cinnoline, quinazoline, naphthyridine, pyridopyridine, quinoxaline, phthalazine, and benzothiazole, each substituted or unsubstituted

[0144] Further, according to the above embodiments and variations, R_3 may be selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted. In another variation, R_3 is a substituted or unsubstituted (C_{3-7})cycloalkyl ring, optionally comprising O, N(O), N, S, SO, SO_2 or a carbonyl group in the ring.

[0145] According to each of the above embodiments and variations, R_3 may also be substituted such that R_3 comprises a substituent selected from the group consisting of a primary, secondary or tertiary amine, a heterocycloalkyl comprising a nitrogen ring atom, and a heteroaryl comprising a nitrogen ring atom.

[0146] In particular variations of the present invention, R_3 comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein. In one variation, the basic nitrogen of R_3 is separated from the ring atom to which R_3 is attached by between 1-5 atoms. In another variation, the basic nitrogen atom forms part of a primary, secondary or tertiary amine. In yet another

variation, the basic nitrogen atom is a nitrogen ring atom of a heterocycloalkyl or a heteroaryl

[0147] In one variation of each of the embodiments of the present invention, R_3 includes a basic nitrogen that is capable of interacting with a carboxylic acid side chain of a residue in the DP-4 active site and thus contributes to the binding affinity of the compound to DP-4 Based on co-crystal structures obtained by Applicants, the observed interaction between the basic nitrogen substituent and the carboxylic acid appears to be via hydrogen bonding or by the formation of a salt bridge

[0148] The basic nitrogen of R_3 in this variation that provides the desired carboxylic acid side chain interaction is not typically directly attached to the ring atom to which R_3 is attached In this regard, the basic nitrogen may be viewed as a substituent of the overall R_3 moiety. For example, in the case where R_3 is 3-amino-piperidinyl-1-yl, the basic nitrogen is the 3-amino group and not the nitrogen of the piperidine ring Thus, R_3 may be viewed as a substituted piperidine ring further comprising an amine as a basic nitrogen substituent. In a particular variation, the basic nitrogen of R_3 is optionally separated from the ring atom to which R_3 is attached by between 1-5 atoms.

[0149] The basic nitrogen atom moiety of R_3 may optionally be selected from the group consisting of a primary, secondary or tertiary amine, a heterocycloalkyl comprising a nitrogen ring atom, a heteroaryl comprising a nitrogen ring atom, as well as other nitrogen containing moieties where the nitrogen can act as a Lewis base. In addition to basic nitrogen containing moieties, it is envisioned that other Lewis bases, such as oxygen with basic lone pairs, may be capable of interacting with a carboxylic acid side chain of a residue in the DP-4 active site.

[0150] In certain embodiments, R_3 is said to be further substituted with one or more R_8 substituents. It is noted that at least one of the R_8 substituents may comprise the basic nitrogen atom capable of providing the interaction with the carboxylic acid side chain. In this regard, R_8 may optionally comprise a moiety selected from the group consisting of a primary, secondary or tertiary amine, a heterocycloalkyl comprising a nitrogen ring atom, a heteroaryl comprising a nitrogen ring atom, as well as other nitrogen containing moieties where the nitrogen can act as a Lewis base

[0151] Particular examples of moieties with basic nitrogens according to this variation include, but are not limited to $-NH_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl)$_2$, piperazine, imidazole, and pyridine. Additional particular R_3 groups that comprise a basic nitrogen include, but are not limited to 3-amino-piperidinyl-1-yl, 3-aminomethyl-pyrrolidin-1-yl, 3-aminoazetidin-1-yl, 3-amino-3-methylpiperidin-1-yl, 3-aminocyclopent-1-yl, 3-aminomethylcyclopent-1-yl, 3-aminomethylcyclohex-1-yl, 3-aminohexahydroazepin-1-yl, 3-amino-cyclohex-1-yl, piperazin-1-yl, homopiperazin-1-yl, 3-amino-pyrrolidin-1-yl, R-3-aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, 3-amino-cyclohex-1-yl, 3-amino-cyclopent-1-yl, and 3-amino-pyrrolidin-1-yl, each optionally further substituted.

[0152] In regard to a particular variation, at least one R_8 comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein. In another particular variation, the basic nitrogen atom forms part of a primary, secondary or tertiary amine. In another variation of the above compounds, the basic nitrogen atom is a nitrogen ring atom of a heterocycloalkyl comprising a nitrogen ring atom or a heteroaryl comprising a nitrogen ring atom.

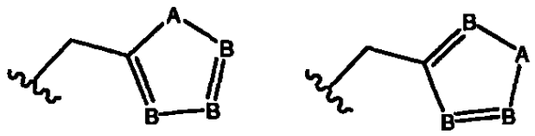
[0153] In one variation of each of the embodiments of the present invention, at least one R_8 is a primary, secondary or tertiary amine. In another variation, at least one R_8 is a substituted or unsubstituted heterocycloalkyl comprising a nitrogen ring atom or a substituted or unsubstituted heteroaryl comprising a nitrogen ring atom. In yet another particular variation, at least one R_8 is selected from the group consisting of $-NH_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl)$_2$, piperazine, imidazole, and pyridine.

[0154] According to each of the above embodiments and variations, R_3 is selected from the group consisting of 3-amino-piperidinyl-1-yl, 3-aminomethyl-pyrrolidin-1-yl, 3-aminoazetidin-1-yl, 3-amino-3-methylpiperidin-1-yl, 3-aminocyclopent-1-yl, 3-aminomethylcyclopent-1-yl, 3-aminomethylcyclohex-1-yl, 3-aminohexahydroazepin-1-yl, 3-amino-cyclohex-1-yl, piperazin-1-yl, homopiperazin-1-yl, 3-amino-pyrrolidin-1-yl, R-3-aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, 3-amino-cyclohex-1-yl, 3-amino-cyclopent-1-yl, and 3-amino-pyrrolidin-1-yl, each substituted or unsubstituted.

[0155] In one particular variation, at least one of Q^1 and Q^2 is CO. In another variation of the above compounds, Q^1 and Q^2 are CO.

Substituent M:

[0156] In another particular variation, the present invention provides compounds wherein M is nitrogen. In yet another particular variation, M is CR_4 and where R_4 is selected from the group consisting of



wherein

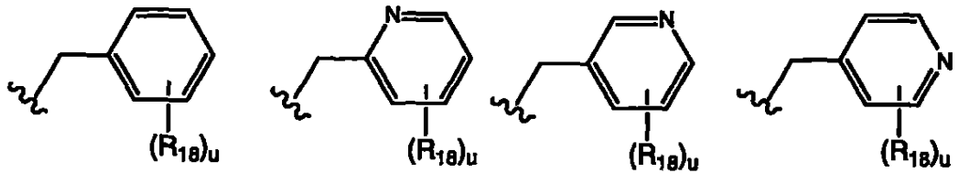
A is S, O or NR_{24},

B is CR_{23} or N,

R_{23} is independently selected from the group consisting of hydrogen, halo, perhalo(C_{1-10})alkyl, amino, thio, cyano, CF_3, nitro, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted, and

R_{24} is independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

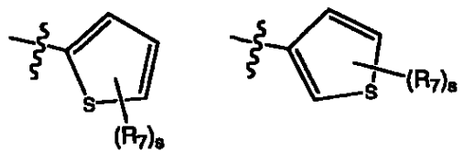
[0157] In another particular variation, the present invention provides compounds wherein M is CR_4 and where R_4 is selected from the group consisting of



wherein u is 0, 1, 2, 3, 4, or 5; and each R_{18} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl,

aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imine group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0158] In yet another variation, there is provided compounds wherein M is CR_4 and where R_4 is selected from the group consisting of



wherein s is 0, 1, 2, or 3, and each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted

Substituent R_5 and R_6:

[0159] In particular variations of the present invention, there is provided compounds wherein R_5 and R_6 are hydrogen. In yet another variation, R_5 and R_6 are taken together to form a ring In yet another variation, at least one of R_5 and R_6 is a halide, such as fluorine

[0160] In another variation of the invention, there is provided compounds wherein at least one of R_5 and R_6 is a substituted or unsubstituted -(C_{1-8})alkyleneR_{13}, wherein R_{13} is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{4-12})cycloalkyl, (C_{6-12})aryl, hetero(C_{5-12})aryl, (C_{9-12})bicycloalkyl, hetero(C_{9-12})bicycloalkyl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted

[0161] In another particular variation of the above compounds, R_5 and R_6 are hydrogen, m is 1 or 2, and each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, cyano, nitro, hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0162] In regard to particular variations of the invention, there is provided compounds wherein two R_7 are taken together to form a substituted or unsubstituted fused or bridged ring.

[0163] In yet another particular variation, there is provided compounds wherein n is 1, 2 or 3; and R_5 and R_6 are hydrogen. In another variation, n is 1 or 2; R_3 is selected from the group consisting of amino, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, and a substituted or unsubstituted 4, 5, 6 or 7 membered ring; and R_5 and R_6 are hydrogen.

[0164] In one particular variation of the above compounds, R_5 and R_6 are hydrogen and R_7 is 2-cyano. In another variation of the above compound, n is 1. In yet another particular variation of the above compounds, n is 1, 2 or 3; R_5 and R_6 are hydrogen; and R_3 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0165] According to particular variation of the above compounds, n is 1, 2 or 3; R_5 and R_6 are hydrogen; and each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, alkenyl, alkynyl, CF_3, cyano, nitro, hydroxy, heteroaryl, aryloxy, heteroaryloxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent R_7:

[0166] In particular variations of the above, there is provided compounds wherein two R_7 are taken together to form a substituted or unsubstituted fused ring. In another particular variation, two R_7 are taken together to form a substituted or unsubstituted bridged ring.

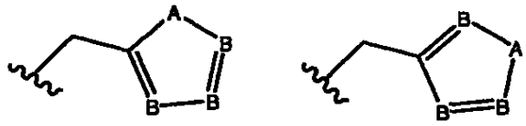
[0167] According to particular variations of the above compounds, two of T, U, V, W and Y are taken together and substituted through available valencies to form a substituted or unsubstituted ring fused or bridged to the ring formed by T U, V, W and Y.

Substituent R_2:

[0168] According to each of the above embodiments and variations, the present invention provides compounds wherein R_2 is a substituted or unsubstituted (C_{1-10})alkyl. In another variation, R_2 is a substituted or unsubstituted (C_{1-4})alkyl. In yet another variation,

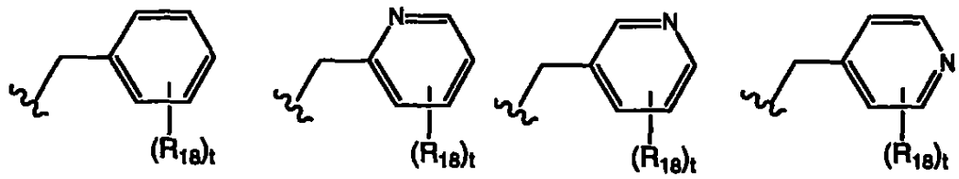
R_2 is -Y-Z wherein Y a linker providing 1, 2 or 3 atom separation between Z and the ring to which Y is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and Z is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0169] In yet another variation, R_2 is selected from the group consisting of



wherein A is S, O or NR_{24}; B is CR_{23} or N; R_{23} is independently selected from the group consisting of hydrogen, halo, perhalo(C_{1-10})alkyl, amino, thio, cyano, CF_3, nitro, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and R_{24} is independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

[0170] In yet another variation, R_2 is selected from the group consisting of



wherein t is 0, 1, 2, 3, 4, or 5; and each R_{18} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl,

aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imine group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

[0171] Particular examples of DPP-IV inhibitors according to the present invention include, but are not limited to:

2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

2-{6-[Azepan-3(±)-ylamino]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (14);

2-{6-[3(±)-Amino-azepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;

3-{4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester;

3-{4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid;

6-[3-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione;

2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-*di*-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-*di*-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

(R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile; and

2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile.

[0172] Particular examples of DPP-IV inhibitors according to the present invention further include:

2-{6-[3(R)-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;

3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester;

3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid;

6-[3(R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione; and

2-[6-(3(R)-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile.

[0173] In another embodiment, the present invention provides the compounds in the form of a pharmaceutically acceptable salt.

[0174] In yet another embodiment, the present invention provides the compounds present in a mixture of stereoisomers. In yet another embodiment, the present invention provides the compounds as a single stereoisomer.

[0175] In yet another embodiment, the present invention provides pharmaceutical compositions comprising the compound as an active ingredient. In yet another variation, the present invention provides pharmaceutical compositions wherein the composition is a solid formulation adapted for oral administration. In yet another particular variation, the present invention provides pharmaceutical composition wherein the composition is a tablet. In another particular variation, the present invention provides the pharmaceutical composition wherein the composition is a liquid formulation adapted for oral administration. In yet another particular variation, the present invention provides pharmaceutical composition wherein the composition is a liquid formulation adapted for parenteral administration.

[0176] In yet another particular variation, the present invention provides the pharmaceutical composition comprising the compound of the invention 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, intraocculariy, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, and intrathecally.

[0177] In another embodiment, the present invention provides a kit comprising a compound of the present invention 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. In another embodiment, the present invention provides the kit that comprises the compound in a multiple dose form.

[0178] In another embodiment, the present invention provides an article of manufacture comprising a compound of the present invention, and packaging materials. In another variation, the packaging material comprises a container for housing the compound. In yet another variation, the invention provides the article of manufacture 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 composition.

[0179] In another variation, the present invention provides the article of manufacture wherein the article of manufacture comprises the compound in a multiple dose form.

[0180] In another embodiment, the present invention provides a method of inhibiting DPP-IV comprising contacting DPP-IV with a compound according to the present invention.

[0181] In another embodiment, the present invention provides a method of inhibiting DPP-IV comprising causing a compound according to the present invention to be present in a subject in order to inhibit DPP-IV *in vivo*.

[0182] In another embodiment, the present invention provides a method of inhibiting DPP-IV comprising: administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits DPP-IV *in vivo*, the second compound being a compound of the present invention.

[0183] In another embodiment, the present invention provides therapeutic method comprising: administering a compound according to the present invention to a subject.

[0184] In another embodiment, the present invention provides a method of treating a disease state for which DPP-IV possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising causing a compound of the present invention to be present in a subject in a therapeutically effective amount for the disease state.

[0185] In another embodiment, the present invention provides a method of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

[0186] In another embodiment, the present invention provides a method of treating a disease where the disease is type I or type II diabetes.

[0187] In another embodiment, the present invention provides a method of treating autoimmune disorders such as, but not limited to, rheumatoid arthritis, psoriasis, and multiple sclerosis in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

[0188] In yet another embodiment, the present invention provides a method of treating cancer where the cancer treated is colorectal, prostate, breast, thyroid, skin, lung, or head and neck.

[0189] In another embodiment, the present invention provides a method of treating a condition characterized by inadequate lymphocyte or hemapoietic cell activation or concentration in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

[0190] In another embodiment, the present invention provides a method of treating HIV infection in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

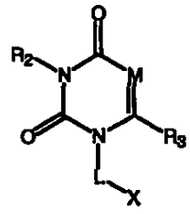
[0191] In yet another embodiment, the present invention provides a method of treating a condition characterized by inadequate lymphocyte or hemapoietic cell activation or concentration in a patient in need thereof, wherein the condition is a side effect of chemotherapy or radiation therapy.

[0192] In yet another embodiment, the present invention provides a method of treating a condition characterized by inadequate lymphocyte or hemapoietic cell activation or concentration in a patient in need thereof, wherein the condition is a result of kidney failure.

[0193] In yet another embodiment, the present invention provides a method of treating a condition characterized by inadequate lymphocyte or hemapoietic cell activation or concentration in a patient in need thereof, wherein the condition is a result of a bone marrow disorder.

[0194] In another embodiment, the present invention provides a method of treating a condition characterized by immunodeficiency symptoms in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

[0195] In yet another embodiment, the present invention provides a process for producing a pyrimidin-dione of the formula:



wherein

M is N or CR_4;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino $(C_{1-}$

$_3$)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

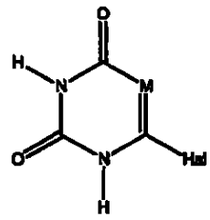
R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

the process comprising the steps of:

(i) contacting a compound of the formula **A**



A

wherein Hal is halogen;

with a compound of the formula **B**



B

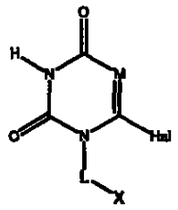
wherein LG is a leaving group;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the

separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each *substituted* or *unsubstituted*;

under conditions sufficient to produce a compound of the formula C



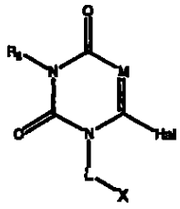
C

(ii) contacting the compound of formula C with a compound of formula D

$$R_2—LG' \qquad D$$

wherein LG' is a leaving group;

under conditions sufficient to produce a compound of the formula E;



E

wherein R_2 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; and

(iii) contacting the compound of formula E with a compound of formula R_3-H under conditions sufficient to produce the pyrimidin-dione.

[0196] In one variation the pyrimidin-dione product is further converted to an acid addition salt. In particular variations, the acid addition salt is selected from the group consisting of acetate, citrate, hydrochloride, L-lactate, succinate, sulfate, p-toluenesulfonate, benzenesulfonate, benzoate, methanesulfonate, naphthylene-2-sulfonate, propionate, p-toluenesulfonate, hydrobromate, hydroiodate, R-mandelate, and L-tartrate.

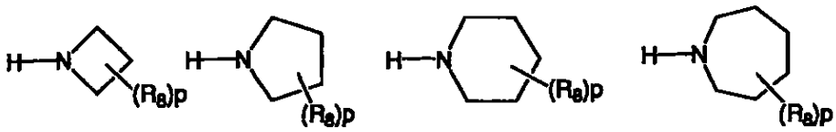
[0197] In another variation of each of the above embodiments and variations, Hal is selected from the group consisting of Br, Cl and F in the compound of formula A.

[0198] In yet another variation of each of the above embodiments and variations, the leaving group LG is selected from the group consisting of Br, Cl and I.

[0199] In a further variation of each of the above embodiments and variations, step (ii) further comprises the addition of a base. In particular variations, the base is potassium carbonate.

[0200] In still another variation of each of the above embodiments and variations, product E is further purified before subjecting it to step (iii). In a particular variation, the purification of product E is performed by solvent washes and/or by chromatography.

[0201] In another variation of each of the above embodiments and variations, R_3-H is a secondary amine or an amine hydrochloride. In a particular variation, R_3-H is selected from the group consisting of



wherein p is 0-12 and each R_8 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, or the mono- or di-hydrochloride salt.

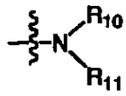
[0202] In yet another variation of each of the above embodiments and variations, step iii) further comprises purifying the product by washing the product with one or more organic solvents or mixtures of solvents and/or by column chromatography.

[0203] In a further variation of each of the above embodiments and variations, L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -C(O)-, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, -O-, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, -NH-C(O)-, $-NCH_3-C(O)-$, -C(O)NH-, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, -S-, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, -C(O)S-, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, and $-CH_2SC(O)-$, each substituted or unsubstituted. In a particular variation, L is selected from the group consisting of $-CH_2-$, -C(O)-, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, and $-CH_2CH_2C(O)-$, each substituted or unsubstituted.

[0204] In still another variation of each of the above embodiments and variations, -L-X taken together is selected from the group consisting of $-(CH_2)$-(2-cyano)phenyl; $-(CH_2)$-(3-cyano)phenyl; $-(CH_2)$-(2-hydroxy)phenyl; $-(CH_2)$-(3-hydroxy)phenyl; $-(CH_2)$-(2-alkenyl)phenyl; $-(CH_2)$-(3-alkenyl)phenyl; $-(CH_2)$-(2-alkynyl)phenyl; $-(CH_2)$-(3-alkynyl)phenyl; $-(CH_2)$-(2-methoxy)phenyl; $-(CH_2)$-(3-methoxy)phenyl; $-(CH_2)$-(2-nitro)phenyl; $-(CH_2)$-(3-nitro)phenyl; $-(CH_2)$-(2-carboxy)phenyl; $-(CH_2)$-(3-carboxy)phenyl; $-(CH_2)$-(2-carboxamido)phenyl; $-(CH_2)$-(3-carboxamido)phenyl; $-(CH_2)$-(2-sulfonamido)phenyl; $-(CH_2)$-(3-sulfonamido)phenyl; $-(CH_2)$-(2-tetrazolyl)phenyl; $-(CH_2)$-(3-tetrazolyl)phenyl; $-(CH_2)$-(2-aminomethyl)phenyl; $-(CH_2)$-(3-aminomethyl)phenyl; $-(CH_2)$-(2-hydroxymethyl)phenyl; $-(CH_2)$-(3-hydroxymethyl)phenyl; $-(CH_2)$-(2-phenyl)phenyl; $-(CH_2)$-(3-phenyl)phenyl; $-(CH_2)$-(2-halo)phenyl; $-(CH_2)$-(3-halo)phenyl; $-(CH_2)$-(2-$CONH_2$)phenyl; $-(CH_2)$-(3-$CONH_2$)phenyl; $-(CH_2)$-(2-$CONH(C_{1-7})$alkyl)phenyl; $-(CH_2)$-(3-$CONH(C_{1-7})$alkyl)phenyl; $-(CH_2)$-(2-$CO_2(C_{1-7})$alkyl)phenyl; $-(CH_2)$-(3-$CO_2(C_{1-7})$alkyl)phenyl; $-(CH_2)$-(2-NH_2)phenyl; $-(CH_2)$-(3-NH_2)phenyl; $-(CH_2)$-(2-(C_{3-7})alkyl)phenyl; $-(CH_2)$-(3-(C_{3-7})alkyl)phenyl; $-(CH_2)$-(2-(C_{3-7})cycloalkyl)phenyl; $-(CH_2)$-(3-(C_{3-7})cycloalkyl)phenyl; $-(CH_2)$-(2-aryl)phenyl; $-(CH_2)$-(3-aryl)phenyl; $-(CH_2)$-(2-heteroaryl)phenyl; $-(CH_2)$-(3-heteroaryl)phenyl; $-(CH_2)$-2-bromo-5-fluoro phenyl; -

(CH_2)-2-chloro-5-fluoro phenyl; -(CH_2)-2-cyano-5-fluoro phenyl; -(CH_2)-2,5-dichloro phenyl; -(CH_2)-2,5-difluoro phenyl; -(CH_2)-2,5-dibromo phenyl; -(CH_2)-2-bromo-3,5-difluoro phenyl; -(CH_2)-2-chloro-3,5-difluoro phenyl; -(CH_2)-2,3,5-trifluoro phenyl; -(CH_2)-2,3,5,6-tetrafluorophenyl; -(CH_2)-2-bromo-3,5,6-trifluoro phenyl; -(CH_2)-2-chloro-3,5,6-trifluoro phenyl; -(CH_2)-2-cyano-3,5-difluoro phenyl; -(CH_2)-2-cyano-3,5,6-trifluoro phenyl; -(CH_2)-(2-heterocycloalkyl)phenyl; and -(CH_2)-(3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

[0205] In a further variation of each of the above embodiments and variations, M is CH, and R_3 comprises the formula

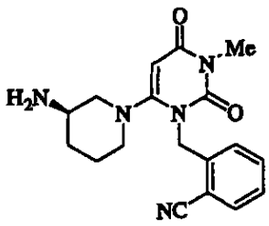


wherein R_{10} and R_{11} are each independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, and sulfinyl group, each substituted or unsubstituted, or R_{10} and R_{11} are taken together to form a 4, 5, 6, or 7 membered ring, each substituted or unsubstituted.

[0206] In yet a further variation, M is CH and R_3 is selected from the group consisting of 3-amino-piperidinyl-1-yl, 3-aminomethyl-pyrrolidin-1-yl, 2-aminoazetidin-1-yl, 3-amino-3-methylpiperidin-1-yl, 3-aminocyclopent-1-yl, 3-aminomethylcyclopent-1-yl, 3-aminomethylcyclohex-1-yl, 3-aminohexahydroazepin-1-yl, 3-amino-cyclohex-1-yl, piperazin-1-yl, homopiperazin-1-yl, 3-amino-pyrrolidin-1-yl, R-3-aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, 3-amino-cyclohex-1-yl, 3-amino-cyclopent-1-yl, and 3-amino-pyrrolidin-1-yl, each substituted or unsubstituted.

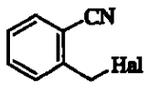
[0207] In still a further variation, M is CH and R_2 is a substituted or unsubstituted (C_{1-10})alkyl.

[0208] In another of its embodiments, the present invention provides a process for producing a pyrimidin-dione of the formula

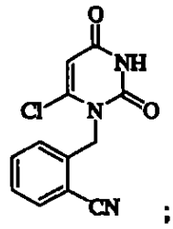


comprising:

(i) admixing 6-chloro-1H-pyrimidine-2,4-dione with an aryl halide of the formula

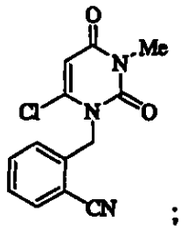


where Hal is Br, Cl, or I, under conditions sufficient to produce a compound of the formula



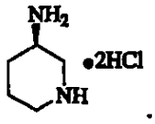
;

(ii) alkylating the above product with a methyl halide under conditions sufficient to form a compound of the formula



; and

(iii) condensing the above product with a compound of the formula



.

[0209] In one variation of the above embodiment, the process for producing a pyrimidin-dione further comprises the formation of an acid addition salt. In one particular variation, the acid addition salt is a benzoate salt.

[0210] In another variation of each of the above embodiments and variations, the pyrimidin-dione is selected from the group consisting of:

2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

2-{6-[Azepan-3(±)-ylamino]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (14);

2-{6-[3(±)-Amino-azepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;

3-{4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester;

3-{4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid;

2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-*di*-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-*di*-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

(R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile; and

6-[3-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione.

[0211] The process of Claim 133, wherein the pyrimidin-dione is selected from the group consisting of:

2-{6-[3(R)-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;

3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester;

3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid; and

6-[3(R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione.

[0212] In still another variation of each of the above embodiments and variations, the pyrimidin-dione is present as a mixture of stereoisomers. In yet another variation, the pyrimidin-dione comprises a single stereoisomer.

[0213] It is noted in regard to all of the embodiments, and any further embodiments, variations, or individual compounds described or claimed herein that all such embodiments, variations, and/or individual compounds are intended to encompass all pharmaceutical acceptable salt forms whether in the form of a single stereoisomer or mixture of stereoisomers unless it is specifically specified otherwise. Similarly, when one or more potentially chiral centers are present in any of the embodiments, variations, and/or individual compounds specified or claimed herein, both possible chiral centers are intended to be encompassed unless it is specifically specified otherwise.

A. Salts, Hydrates, and Prodrugs of DPP-IV Inhibitors

[0214] 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.

[0215] 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.

[0216] 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, diethylamine, 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.

[0217] 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.

[0218] *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.

[0219] 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.

[0220] 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.

[0221] 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.

[0222] 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 adsorption of the compound.

3. INDICATIONS FOR USE OF DPP-IV INHIBITORS

[0223] DPP-IV is believed to contribute to the pathology and/or symptomology of several different diseases such that reduction of the activity of DPP-IV in a subject through inhibition may be used to therapeutically address these disease states. Examples of various

diseases that may be treated using the DPP-IV inhibitors of the present invention are described herein. It is noted that additional diseases beyond those disclosed herein may be later identified as the biological roles that DPP-IV plays in various pathways becomes more fully understood.

[0224] One set of indications that DPP-IV inhibitors of the present invention may be used to treat are those involving the prevention and treatment of diabetes and obesity, in particular type 2 diabetes mellitus, diabetic dislipidemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose (IFG), metabolic acidosis, ketosis, appetite regulation and obesity.

[0225] DPP-IV inhibitors of the present invention may also be used as immunosuppressants (or cytokine release suppressant drugs) for the treatment of among other things: organ transplant rejection; autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis; and the treatment of AIDS.

[0226] DPP-IV inhibitors of the present invention may also be used for treating various cancers including breast cancer, lung cancer and prostate cancer.

[0227] DPP-IV inhibitors of the present invention may also be used to treat dermatological diseases such as psoriasis, rheumatoid arthritis (RA) and lichen planus.

[0228] DPP-IV inhibitors of the present invention may also be used to treat infertility and amenorrhea.

[0229] DPP-IV inhibitors of the present invention may also be used to modulate cleavage of various cytokines (stimulating hematopoietic cells), growth factors and neuropeptides. For example, such conditions occur frequently in patients who are immunosuppressed, for example, as a consequence of chemotherapy and/or radiation therapy for cancer.

[0230] DPP-IV inhibitors of the present invention may also be used prevent or reduce cleavage of N-terminal Tyr-Ala from growth hormone-releasing factor. Accordingly, these inhibitors may be used in the treatment of short stature due to growth hormone deficiency (Dwarfism) and for promoting GH-dependent tissue growth or re-growth.

[0231] DPP-IV inhibitors of the present invention may also be used to address disease states associated with cleavage of neuropeptides and thus may be useful for the regulation or normalization of neurological disorders.

[0232] For oncology indications, DPP-IV inhibitors of the present invention may be used in conjunction with other agents to inhibit undesirable and uncontrolled cell proliferation. Examples of other anti-cell proliferation agents that may be used in conjunction with the DPP-IV inhibitors of the present invention include, but are not limited to, retinoid acid and derivatives thereof, 2-methoxyestradiol, ANGIOSTATIN™ protein, ENDOSTATIN™ protein, suramin, squalamine, tissue inhibitor of metalloproteinase-I, tissue inhibitor of metalloproteinase-2, plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, cartilage-derived inhibitor, paclitaxel, platelet factor 4, protamine sulfate (clupeine), sulfated chitin derivatives (prepared from queen crab shells), sulfated polysaccharide peptidoglycan complex (sp-pg), staurosporine, modulators of matrix metabolism, including for example, proline analogs ((l-azetidine-2-carboxylic acid (LACA)), cishydroxyproline, d,l-3,4-dehydroproline, thiaproline, beta.-aminopropionitrile fumarate, 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone, methotrexate, mitoxantrone, heparin, interferons, 2 macroglobulin-serum, chimp-3, chymostatin, beta.-cyclodextrin tetradecasulfate, eponemycin; fumagillin, gold sodium thiomalate, d-penicillamine (CDPT), beta.-1-anticollagenase-serum, alpha.2-antiplasmin, bisantrene, lobenzarit disodium, n-2-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA", thalidomide; angostatic steroid, carboxyaminoimidazole; metalloproteinase inhibitors such as BB94. Other anti-angiogenesis agents that may be used include antibodies, preferably monoclonal antibodies against these angiogenic growth factors: bFGF, aFGF, FGF-5, VEGF isoforms, VEGF-C, HGF/SF and Ang-1/Ang-2. Ferrara N. and Alitalo, K. "Clinical application of angiogenic growth factors and their inhibitors" (1999) Nature Medicine 5:1359-1364.

4. COMPOSITIONS COMPRISING DPP-IV INHIBITORS

[0233] A wide variety of compositions and administration methods may be used in conjunction with the DPP-IV inhibitors of the present invention. Such compositions may include, in addition to the DPP-IV inhibitors of the present invention, conventional pharmaceutical excipients, and other conventional, pharmaceutically inactive agents. Additionally, the compositions may include active agents in addition to the DPP-IV inhibitors 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.

[0234] 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.

[0235] Compositions comprising DPP-IV inhibitors 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.

[0236] The DPP-IV 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 DPP-IV 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.

[0237] 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.

[0238] When DPP-IV inhibitors 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.

[0239] Upon mixing or adding DPP-IV inhibitors 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.

[0240] 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.

[0241] In addition to one or more DPP-IV inhibitors 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 DPP-IV inhibitor of the present invention to reduce DPP-IV activity *in vivo*, thereby treating the disease state of the subject.

[0242] Dosage forms or compositions may optionally comprise one or more DPP-IV inhibitors 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 DPP-IV inhibitors, optionally 0.1-95%, and optionally 1-95%.

[0243] Salts, preferably sodium salts, of the DPP-IV 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.

A. Formulations for oral administration

[0244] 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.

[0245] In certain embodiments, DPP-IV inhibitors 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.

[0246] 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.

[0247] Examples of lubricants that may be used include, but are not limited to, talc, starch, magnesium or calcium stearate, lycopodium and stearic acid.

[0248] Examples of diluents that may be used include, but are not limited to, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate.

[0249] Examples of glidants that may be used include, but are not limited to, colloidal silicon dioxide.

[0250] 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.

[0251] 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.

[0252] 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.

[0253] 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.

[0254] 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.

[0255] 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.

[0256] Examples of film coatings that may be used include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0257] 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.

[0258] 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.

[0259] 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.

[0260] The DPP-IV inhibitors 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.

[0261] Examples of pharmaceutically acceptable carriers that may be included in tablets comprising DPP-IV inhibitors 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.

[0262] 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.

[0263] 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

concentrated aqueous solutions of a sugar, for example, sucrose. Syrups may optionally further comprise a preservative.

[0264] Emulsions refer to two-phase systems in which one liquid is dispersed in the form of small globules throughout another liquid. Emulsions may optionally be oil-in-water or water-in-oil emulsions. Examples of pharmaceutically acceptable carriers that may be used in emulsions include, but are not limited to non-aqueous liquids, emulsifying agents and preservatives.

[0265] Examples of pharmaceutically acceptable substances that may be used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents.

[0266] Examples of pharmaceutically acceptable substances that may be used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic adds and a source of carbon dioxide.

[0267] Coloring and flavoring agents may optionally be used in all of the above dosage forms.

[0268] Particular examples of preservatives that may be used include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol.

[0269] Particular examples of non-aqueous liquids that may be used in emulsions include mineral oil and cottonseed oil.

[0270] Particular examples of emulsifying agents that may be used include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate.

[0271] Particular examples of suspending agents that may be used include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as sodium cyclamate and saccharin.

[0272] Particular examples of wetting agents that may be used include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether.

[0273] Particular examples of organic acids that may be used include citric and tartaric acid.

[0274] 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.

[0275] 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.

[0276] 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.

[0277] 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.

B. Injectables, solutions and emulsions

[0278] The present invention is also directed to compositions designed to administer the DPP-IV inhibitors of the present invention by parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously. 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.

[0279] 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.

[0280] 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.

[0281] 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.

[0282] 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.

[0283] 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.

[0284] 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.

[0285] 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 used include phenols or cresols,

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

[0286] 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.

[0287] 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.

[0288] The concentration of a DPP-IV 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 a DPP-IV 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.

[0289] 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 know and practiced in the art.

[0290] 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 DPP-IV inhibitor to the treated tissue(s). The DPP-IV 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.

[0291] The DPP-IV 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.

C. Lyophilized powders

[0292] The DPP-IV inhibitors 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.

[0293] 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 DPP-IV inhibitor is added to the resulting mixture, preferably above room temperature, more preferably at about 30-35 °C, 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 DPP-IV inhibitor.

D. Topical administration

[0294] The DPP-IV inhibitors 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.

[0295] The DPP-IV 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 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.

[0296] The DPP-IV 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 DPP-IV inhibitor alone or in combination with other pharmaceutically acceptable excipients can also be administered.

E. Formulations for other routes of administration

[0297] 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.

F. Examples of Formulations

[0298] 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%.

5. KITS COMPRISING DPP-IV INHIBITORS

[0299] The invention is also directed to kits and other articles of manufacture for treating diseases associated with DPP-IV. It is noted that diseases are intended to cover all conditions for which the DPP-IV possesses activity that contributes to the pathology and/or symptomology of the condition.

[0300] In one embodiment, a kit is provided that comprises a composition comprising at least one DPP-IV 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.

[0301] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one DPP-IV 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.

[0302] 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.

[0303] 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.

[0304] 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.

EXAMPLES

1. Preparation Of DPP-IV Inhibitors

[0305] 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.

[0306] 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 (enantiomers, diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

[0307] 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).

[0308] 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.

[0309] 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).

[0310] 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.

[0311] 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 °C.

[0312] 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).

[0313] 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.

[0314] 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.

[0315] 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 diasteromeric 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).

[0316] 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:

g (grams); mg (milligrams);
L (liters); mL (milliliters);
μL (microliters); psi (pounds per square inch);
M (molar); mM (millimolar);
i.v. (intravenous); Hz (Hertz);
MHz (megahertz); mol (moles);
mmol (millimoles); RT (ambient temperature);
min (minutes);h (hours);
mp (melting point); TLC (thin layer chromatography);
Tr (retention time); RP (reverse phase);
MeOH (methanol); i-PrOH (isopropanol);
TEA (triethylamine); TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride); THF (tetrahydrofuran);
DMSO (dimethylsulfoxide); EtOAc (ethyl acetate);
DME (1,2-dimethoxyethane); DCM (dichloromethane);
DCE (dichloroethane); DMF (N,N-dimethylformamide);
DMPU (N,N'-dimethylpropyleneurea); CDI (1,1-carbonyldiimidazole);
IBCF (isobutyl chloroformate); HOAc (acetic acid);
HOSu (N-hydroxysuccinimino); HOBT (1-hydroxybenzotriazole);
Et_2O (diethyl ether); EDCI (ethylcarbodiimino hydrochloride);
BOC (tert-butyloxycarbonyl); FMOC (9-fluorenylmethoxycarbonyl);
DCC (dicyclohexylcarbodiimino); CBZ (benzyloxycarbonyl);
Ac (acetyl); atm (atmosphere);
TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl);
TIPS (triisopropylsilyl); TBS (t-butyldimethylsilyl);
DMAP (4-dimethylaminopyridine); Me (methyl);
OMe (methoxy); Et (ethyl);
Et (ethyl); tBu (tert-butyl);
HPLC (high pressure liquid chomatography);
BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);

TBAF (tetra-n-butylammonium fluoride);

mCPBA (meta-chloroperbenzoic acid.

[0317] All references to ether or Et_2O are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted under an inert atmosphere at RT unless otherwise noted.

[0318] ^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).

[0319] 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).

2. Synthetic Schemes For DPP-IV Inhibitors Of The Present Invention

[0320] DPP-IV inhibitors according to the present invention may be synthesized according to a variety of reaction schemes. Some illustrative schemes are provided herein in the examples. Other reaction schemes could be readily devised by those skilled in the art.

[0321] 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.

[0322] By varying the Q^1 and Q^2, R_1, R_2, and R_3 groups, a wide variety of different DPP-IV inhibitors according to the present invention may be synthesized.

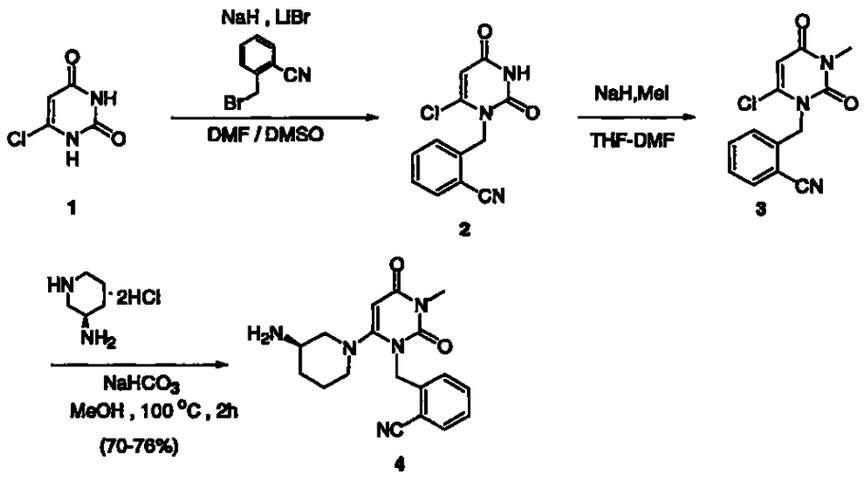
[0323] In each of the above reaction schemes, the various substituents may be selected from among the various substituents otherwise taught herein.

[0324] Descriptions of the syntheses of particular compounds according to the present invention based on the above reaction schemes are set forth herein.

3. Examples Of DPP-IV Inhibitors

[0325] The present invention is further exemplified, but not limited by, the following examples that describe the synthesis of particular compounds according to the invention.

Experimental Methods



[0326] **2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (2).** To a solution of 6-chlorouracil (20 g, 122 mmol) in a mixture of DMF-DMSO (6:1, 600 mL) under nitrogen at 0 °C, was added sodium hydride (60%, 5.5 g, 137 mmol) in portions. After 0.5h, lithium bromide (8 g, 96 mmol) was added into the mixture and stirred for 15 min at 0 °C. A solution of *α*-Bromo-*o*-tolunitrile (25.1 g, 128 mmol) in DMF (30 mL) was added dropwise, and stirred at this temperature for 1 h, and then RT overnight. It will be understood that alkylation of the amine may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH or the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may be used, including LiBr, LiI, NaI and the like. The mixture was evaporated and co-evaporated with water *in vacuo*

to remove most of the DMF, and then poured into ice water (1L). The precipitate was collected by filtration. The crude product was suspended in hot AcOEt-$CHCl_3$ and sonicated for 5 min, allowed to stand at 0 °C for 1h, and then filtered to give a white solid of the title compound (19 g) in 54% yield. It will also be understood by those skilled in the art that purification may be accomplished using various methods known in the art, including washing with an aqueous/organic solvent or mixture of solvents, recrystallization and/or column chromatography. Non-limiting examples of organic solvents and solvent mixtures may include ethyl acetate, isopropyl acetate, acetone, THF and the like. ^{1}H-NMR (400 MHz, DMSO): δ 11.82 (s, 1H), 7.87 (d, 1H, J = 7.6 Hz), 7.71 (t, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.37 (d, 1H, J = 8 Hz), 6.06 (s, 1H), 5.31 (s, 2H). MS (ES) [m+H] calc'd for $C_{12}H_9ClN_3O_2$, 262.0; found 262.0.

[0327] 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (3). To a cold (0 °C) solution of benzylated 6-chlorouracil 2 (10 g, 38 mmol) in DMF-THF (1:1, 300 mL) under nitrogen, was added NaH (60%, 1.6 g, 39.9 mmol) in portions, followed by adding LiBr (2g). The mixture was stirred at r.t for 20 min. After adding iodomethane (5.4 mL, 76 mmol), the flask was sealed and stirred at this temperature for 10 min, rt for 2h, and 35 °C overnight, and then concentrated *in vacuo*. It will be understood that alkylation of the amine may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH or the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may be used, including LiBr, LiI, NaI and the like. For example, the alkylation can be performed using methyliodide and K_2CO_3 in acetone. The reaction may be performed at about 15-45 °C, preferably at about 20-43 °C, and more preferably at about 35-41 °C until the reaction is complete. The residue was dissolved in $CHCl_3$ and washed with water and brine, dried (Na_2SO_4), and filtered then concentrated *in vacuo*. The crude product was crystallized from THF-Hexanes to give 7.6 g (72%) of the title compound 3. It will also be understood by those skilled in the art that the benzonitrile may be purified in a variety of organic solvents or solvent mixtures. For example, the benzonitrile can be purified by adding a mixture of dichloromethane and heptane. Optionally, the benzonitrile may be further purified in an organic solvent or mixture of solvents such as dichloromethane, chloroform, acetonitrile, THF, ethyl acetate,

isopropyl acetate and the like. Preferably, the product is purified and washed with ethyl acetate. ^{1}H NMR (400 MHz, DMSO): δ 7.87 (d, 1H, *J* = 7.6 Hz), 7.70 (t, 1H, *J* = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.40 (d, 1H, J = 8 Hz), 6.21 (s, 1H), 5.38 (s, 2H), 3.28 (s, 3H). MS (ES) [m+H] calc'd for $C_{13}H_{11}ClN_3O_2$, 276.1; found 276.1.

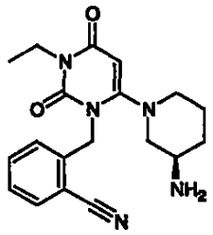
[0328] **2-{6-[3(R)-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (4).** 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2-H-pyrimidin-1-ylmethyl)-benzonitrile (330 mg, 1.08 mmol), (*R*)-3-amino-piperidine dihydrochloride (246 mg, 1.4 mmol) and sodium bicarbonate (500mg, 5.4 mmol) were stirred with 200 mg activated molecular sieves (4A) in dry MeOH (5 mL) at 100 °C for 2 h. The reaction was filtered through Celite, concentrated *in vacuo*, and then diluted with $CHCl_3$, and washed with water. The water phase was extracted with $CHCl_3$ and the combined organic phases were washed with water, dried (Na_2SO_4), and filtered. TFA (1mL) was added into the solution which was then concentrated *in vacuo*. The residue was dissolved in a small amount of MeOH, and Et_2O was added to force precipitation. The mixture was allowed to stand at RT overnight. It will be understood by those skilled in the art that condensation with the amine or amine hydrochloride may be performed in a solvent or mixture of solvents with a base, such as potassium carbonate, sodium bicarbonate and the like, or mixtures thereof. The solvent may comprise both protic and aprotic solvents, or mixtures thereof. For example, the solvent may comprise a mixture of isopropyl alcohol and water. Further, the reaction may be heated to about 30-100 °C, preferably about 35-55 °C, and more preferably about 45-50 °C until the reaction is complete. Solvents were decanted, and the solid was washed with Et_2O two times to give 270 mg product as off-white powder. It will also be understood that the product may be further purified by washing with an organic solvent or mixture of solvents. Non-limiting examples of solvent or solvent mixtures include isopropyl acetate, ethyl acetate, dichloromethane, heptane, and the like. Further, the product may optionally be purified by column chromatography.

[0329] The benzonitrile product may be isolated as the free base if desired, but preferably, the product may be further converted to the corresponding acid addition salt, such as the benzoic acid salt. Preferably, the benzonitrile product is treated with benzoic acid to form 2-[6-(3-amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-

1-ylmethyl]-benzonitrile benzoate (4). Preparation and isolation of the benzoate salt may be performed by conventional methods for the formation of acid addition salts. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.82 (d, 1H, J = 7.6 Hz), 7.65 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 8.0 Hz), 5.42 (s, 1H), 5.50-5.00 (ABq, 2H, J = 41.6, 15.2 Hz), 3.30 (m, 2H), 3.16 (s, 3H), 2.91 (m, 1H), 2.76 (m, 2H), 1.93 (m, 1H), 1.79 (m, 1H), 1.51 (m, 2H). MS (ES) [m+H] calc'd for $C_{18}H_{22}N_5O_2$, 340.2; found, 340.2.

[0330] In each of the above steps, the isolation and/or purification steps of the intermediate compounds may be avoided if the intermediates from the reaction mixture are obtained as relatively pure compounds and the by-products or impurities of the reaction mixture do not interfere with the subsequent reaction steps. Where feasible, one or more isolation steps may be eliminated to provide shorter processing times, and the elimination of further processing may also afford higher overall reaction yields.

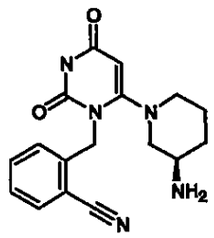
Compound 5



[0331] **2-{6-[3(R)-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile TFA salt (5).** The title compound, 5, was prepared from sample 2 using the procedures described in the preparation of samples 3 and 4, except that ethyl bromide was used in place of iodomethane. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.66 (d, *J*=7.8 Hz, 1 H), 7.59 (td, *J*=7.8, 1.4 Hz, 1 H), 7.40 (t, *J*=7.6 Hz, 1 H), 7.26 (d, *J*=7.6 Hz, 1 H), 5.41 (s, 1 H), 5.13 - 5.23 (ABq, 2H, J = 41.6, 15.2 Hz), 3.91 (q, *J*=7.1 Hz, 2 H), 3.37 (m, 2 H), 2.87 - 2.98 (m, 2 H), 2.70 (m, 1 H), 2.12 (m, 1 H), 1.88 (m, 1 H), 1.67 (m, 2 H), 1.15 (t, *J*=6.9 Hz, 3 H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

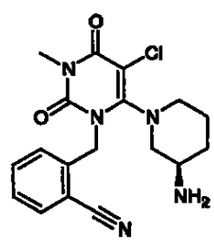
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Compound 6



[0332] 2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (6). The title compound 6 was prepared from compound 2 by the procedure used in preparation of compound 4. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.65 (d, *J*=7.5 Hz, 1 H), 7.58 (t, *J*=7.8 Hz, 1 H), 7.39 (t, *J*=7.5 Hz, 1 H), 7.27 (d, *J*=7.8 Hz, 1 H), 5.32 (s, 1 H), 5.13 - 5.13 (ABq, 2H, J = 30.0, 15.0 Hz), 3.39 (m, 2 H), 2.95 (m, 2 H), 2.69 (m, 1 H), 2.12 (m, 1 H), 1.85 (m, 1 H), 1.64 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{20}N_5O_2$, 326.2; found, 326.2.

Compound 7



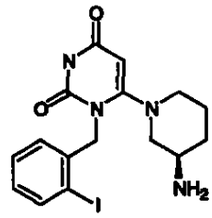
[0333] 2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (7). Compound 4 (40 mg, 0.1 mmol) in $CHCl_3$ (2 mL) was treated with $SOCl_2$ (200μL) at 100 °C for 30 min, concentrated, and then purified by LC-MS to give the title compound 7. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.73 (d, *J*=7.6 Hz, 1 H), 7.64 (t, *J*=7.6 Hz, 1 H), 7.45 (t, *J*=7.6 Hz, 1 H), 7.14 (d, *J*=8.1 Hz, 1 H), 5.32 - 5.42 (m, 2 H), 3.43 (s, 3 H), 3.33 - 3.40 (m, 2 H), 3.17 (m, 2 H), 2.87 (s, 1 H), 2.08 (m, 1 H), 1.70 (m, 1 H), 1.32 - 1.43 (m, 2 H). MS (ES) [m+H] calc'd for $C_{18}H_{21}ClN_5O_2$, 374.1; found, 374.1.

Compound 8



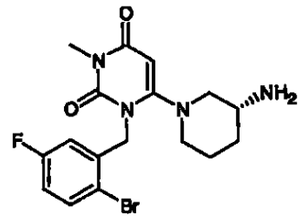
[0334] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione (8). The title compound was prepared in two steps. The first step was accomplished using the procedure for the preparation of compound 2, except that 2-bromobenzylbromide was used in the place of α-Bromo-*o*-tolunitrile. The crude product was then converted to the title compound by the method used in the preparation of compound 4. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.52 (d, *J*=8.1Hz, 1 H), 7.24 (t, *J*=7.8 Hz, 1 H), 7.10 (t, *J*=7.8 Hz, 1 H), 6.89 (d, *J*=7.579 Hz, 1 H), 5.27 (s, 1 H), 4.92 - 5.04 (ABq, *J* = 34.1, 15.0 Hz, 2H), 3.27 (bd, *J*=10.4Hz, 1 H), 3.09 - 3.18 (m, 1 H), 2.89 (m, 1 H), 2.70 (t, *J*=10.9Hz, 1 H), 2.48 (t, *J*=12.0 Hz, 1 H), 2.03 (m, 1 H), 1.60 - 1.71 (m, 1 H), 1.42 - 1.53 (m, 2 H). MS (ES) [m+H] calc'd for $C_{16}H_{20}BrN_4O_2$, 379.1; found, 379.1.

Compound 9



[0335] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione (9). The title compound was prepared by the procedure described in the preparation of compound 8, except that 2-iodobenzyl chloride was used as the benzylating reagent. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.76 (d, *J*=7.6Hz, 1 H), 7.21 (t, *J*=7.3 Hz, 1 H), 6.89 (t, *J*=7.2 Hz, 1 H), 6.79 (d, *J*=7.3 Hz, 1 H), 5.26 (s, 1H), 4.79 – 4.92 (ABq, *J* = 34.1, 6.7.0 Hz, 2H), 3.27 (m, 1 H), 3.13 (s, 1 H), 2.85 (d, *J*=11.6 Hz, 1 H), 2.70 (m, 1 H), 2.41 (m, 1 H), 2.02 (m, 1 H), 1.60 (m, 1 H), 1.45 (m, 2 H). MS (ES) [m+H] calc'd for $C_{16}H_{20}IN_4O_2$, 427.1; found, 427.1.

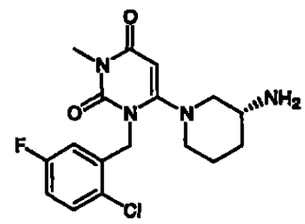
Compound 10



[0336] **6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (10).** To a solution of 6-chlorouracil (220 mg, 1.5 mmol) in a mixture of dry DMF-DMSO (6:1, 5 mL) under nitrogen at 0 °C, was added sodium hydride (60%, 61 mg, 1.8 mmol) in portions. After 0.5h, lithium bromide (83 mg, 1 mmol) was added and the mixture was stirred for 15 min at 0 °C. A solution of 2-bromo-5-fluoro-benzyl bromide (497 mg, 1.8 mmol) in DMF (30 mL) was added dropwise, and stirred at this temperature for 1 h, and then RT overnight. The mixture was evaporated and co-evaporated with water *in vacuo* to remove most of the DMF, and then poured into ice-water. The precipitate was collected by filtration, and then suspended in cold MeOH and filtered. The solution was concentrated to give the crude monobenzylated product.

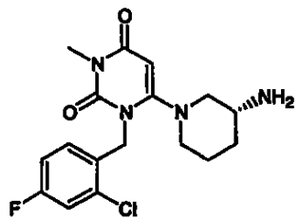
[0337] The crude product was treated with NaH and MeI using the procedure described in the preparation of compound 3, followed by the procedure used in the preparation of compound 4 to give the title compound. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.46 (dd, *J*=8.7, 5.2 Hz, 1 H), 6.82 (td, *J*=8.3, 2.9Hz, 1 H), 6.59 (dd, *J*=9.1, 3.0 Hz, 1 H), 5.28 (s, 1H), 4.99 - 5.06 (ABq, *J* = 41.7, 16.7 Hz, 2H), 3.28 (m, 1H), 3.23 (s, 3 H), 3.13 - 3.21 (m, 1 H), 2.86 (bd, *J*=12.6 Hz, 1 H), 2.71 (t, *J*=10.5 Hz, 1 H), 2.47 (t, *J*=11.0 Hz, 1 H), 2.00 - 2.08 (m, 1 H), 1.65 - 1.74 (m, 1 H), 1.42 - 1.53 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}BrFN_4O_2$, 411.1; found, 411.1.

Compound 11



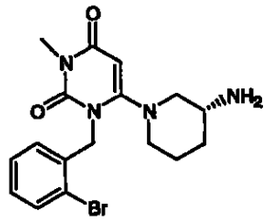
[0338] **6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (11).** The title compound was prepared from compound 1 using the same procedures as the preparation of compound 10, except that 2-chloro-5-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.34 - 7.40 (dd, *J*=8.5, 5.1 Hz, 1 H), 6.97 (td, *J*=8.3, 2.9 Hz, 1 H), 6.72 (dd, *J*=9.0, 2.9 Hz, 1 H), 5.41 (s, 1 H), 5.11 - 5.19 (ABq, *J* = 41.7, 16.7 Hz, 2H), 3.37 (s, 1 H), 3.32 (s, 3H), 3.23 - 3.30 (m, 1 H), 2.96 (d, *J*=12.1 Hz, 1 H), 2.81 (t, *J*=10.2 Hz, 1 H), 2.59 (t, *J*=11.1 Hz, 1 H), 2.13 (d, *J*=10.4 Hz, 1 H), 1.76 - 1.86 (m, 1 H), 1.52 - 1.63 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}ClFN_4O_2$, 367.1; found 367.1.

Compound 12



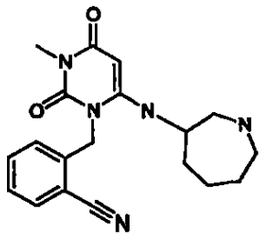
[0339] **6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (12).** The title compound was prepared from compound 1 using the same procedures as described the preparation of compound 10, except that 2-chloro-4-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.15 (dd, *J*=8.211, 2.400 Hz, 1 H), 6.95 - 7.06 (m, 2 H), 5.40 (s, 1 H), 5.09 - 5.18 (ABq, *J* = 37.7, 15.9 Hz, 2H), 3.33 - 3.39 (m, 1 H), 3.30 (s, 3 H), 3.23 - 3.29 (m, 1 H), 2.98 (bd, *J*=12.9 Hz, 1 H), 2.79 (t, *J*=10.4 Hz, 1 H), 2.55 - 2.66 (t, *J*=11.2 Hz, 1 H), 2.13 (m, 1 H), 1.78 - 1.88 (m, 1 H), 1.55 - 1.65 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}ClFN_4O_2$, 367.1; found 367.1.

Compound 13

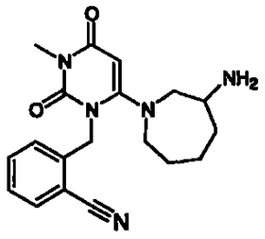


[0340] **6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (13).** The title compound was prepared from compound **1** used the procedures described in the synthesis of compound **10**, except that 2-bromo benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.45 (d, *J*=7.8 Hz, 1 H), 7.16 (t, *J*=7.5 Hz, 1 H), 7.03 (t, *J*=7.2 Hz, 1 H), 6.80 (d, *J*=7.3 Hz, 1 H), 5.28 (s, 1 H), 4.93 - 5.05 (ABq, 2H, J = 36.4, 16.4 Hz), 3.22 (m, 1H), 3.19 (m, 3 H), 3.09 (m, 1 H), 2.84 (d, *J*=12.6 Hz, 1 H), 2.63 (t, *J*=10.5 Hz, 1 H), 2.42 (t, *J*=10.9 Hz, 1 H), 1.97 (d, *J*=11.1 Hz, 1 H), 1.58 - 1.69 (m, 1 H), 1.38 - 1.48 (m, 2 H). *MS (ES) [m+H] calc'd for* $C_{17}H_{22}BrN_4O_2$, 393.1; *found*, 393.1.

Compound 14



Compound 15



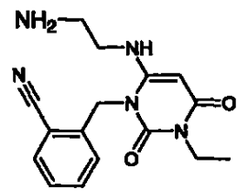
[0341] **2-{6-[Azepan-3(±)-ylamino]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (14) and 2-{6-[3(±)-Amino-azepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (15).** Title compounds 14 and 15 were prepared from compound 3 (70 mg, 0.27 mmol) and azepan-3-ylamine (70 mg, 0.61 mg) using the procedure for the preparation of compound 4. Both compounds were purified by LC-MS.

[0342] **14:** ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.77 (d, *J*=7.8 Hz, 1 H), 7.66 (t, *J*=7.6 Hz, 1 H), 7.47 (t, *J*=8.0 Hz, 1 H), 7.36 (d, *J*=8.1 Hz, 1 H), 5.54 (s, 1 H), 5.49 (s, 1 H), 5.27 - 5.36 (ABq, *J* = 26.0, 16.4 Hz, 2H), 3.50 (m, 2 H), 3.37 (s, 2 H), 3.26 (s, 3 H), 3.12 (m, 1H), 3.04 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.60 - 1.71 (m, 3H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

[0343] **15:** ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.77 (d, *J*=8.1 Hz, 1 H), 7.63 (t, *J*=7.6 Hz, 1 H), 7.46 (t, *J*=8.0 Hz, 1 H), 7.19 (d, *J*=7.6 Hz, 1 H), 5.48 (s, 1H), 5.44 - 5.52 (ABq, *J* = 61.9, 18.4 Hz, 2H), 3.80 (s, 1 H), 3.58-3.50 (m, 1 H), 3.39-3.39 (m, 1 H), 3.26 (s, 3 H), 3.13 (m, 1 H), 2.89 (t, *J* =12.4 Hz, 1 H), 2.04 (m, 1 H), 1.93 (m, 1 H), 1.86

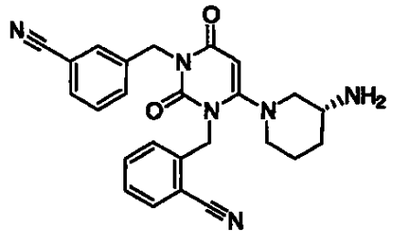
(m, 2 H), 1.59 - 1.70 (m, 2 H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

Compound 16



[0344] 2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (16). Compound 2 (150 mg, 0.57 mmol) in THF–DMSO (6:1, 4mL) was treated with 60% NaH (26 mg, 0.65 mmol), followed by adding ethyl bromide (300uL). In a sealed tube, ~20% crude product in dry MeOH (3 mL) was treated $NaHCO_3$ and ethane-1,2-diamine (200μL) at 120 °C for 2h, and purified by LC-MS to give the title compound 16. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.70 (d, *J*=7.8 Hz, 1 H), 7.58 (t, *J*=7.7 Hz, 1 H), 7.40 (t, *J*=7.4 Hz, 1 H), 7.12 (d, *J*=8.1 Hz, 1 H), 5.37 (s, 2 H), 3.95 (q, *J*=6.8 Hz, 2 H), 3.45 (t, *J*=5.9 Hz, 2 H), 3.11 (t, *J*=6.1 Hz, 2 H), 1.19 (t, *J*=6.8 Hz, 3 H). MS (ES) [m+H] calc'd for $C_{16}H_{20}N_5O_2$, 314.2; found 314.2.

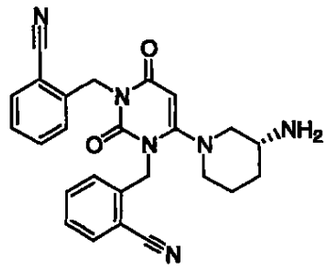
Compound 17



[0345] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (17). Compound 2 (65 mg, 0.25 mmol) in DMB-DMF (2:1, 2.5 mL) was treated with 60% NaH (15 mg, 0.38 mmol) at 0 °C for 20 min, and then LiBr (25 mg) was added. 10 min later, *m*-cyano-benzyl bromide (55mg, 0.28 mg) was added, and the mixture was stirred at RT for 5h, and concentrated. The crude residue was dissolved in MeOH (3 mL). (*R*)-3-Amino-piperidine dihydrochloride (52 mg, 0.3 mmol) and sodium bicarbonate (100 mg) were added. The mixture was heated in a sealed tube at 120 °C for 2h, and then filtered and concentrated. LC-MS purification

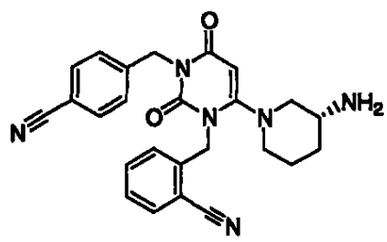
gave the title compound 17 in 84% yield. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.67 (d, *J*=7.8 Hz, 1 H), 7.52 - 7.62 (m, 4 H), 7.35 - 7.46 (m, 2 H), 7.27 (d, *J*=7.8 Hz, 1 H), 5.43 (s, 1 H), 5.15 - 5.31 (ABq, *J*=40.9, 13.7 Hz, 2 H), 5.04 (s, 2 H), 3.40 (s, 1 H), 3.40 (m 1 H), 3.03 (m,1 H), 2.91 (m, 1 H), 2.76 (s, 1 H), 2.13 (s, 1 H), 1.92 (m, 1 H), 1.63 - 1.74 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

Compound 18



[0346] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (18). Title compound 18 was prepared by the methods used in the preparation of compound 17, except that *α*-bromo-*o*-tolunitrile was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.64 (d, *J*=6.8Hz, 1H), 7.60 (d, *J*=7.8Hz, 1H), 7.55 (t, *J*=7.8Hz, 2 H), 7.44 (t, *J*=7.6Hz, 1 H), 7.38 (t, *J*=7.5 Hz, 1 H), 7.31 (t, *J*=7.6Hz, 1H), 7.27 (d, *J*=7.8 Hz, 1H), 7.12 (d, *J*=7.8 Hz, 1 H), 5.45 (s, 1 H), 5.15 - 5.32 (m, 4 H), 3.36 - 3.47 (m, 2 H), 2.98 (m, 2 H), 2.10 (m, 1 H), 1.91 (m, 1 H), 1.68 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

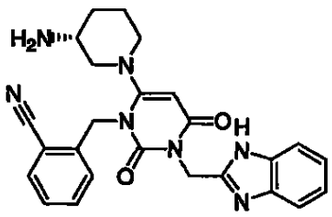
Compound 19



[0347] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (19). Title compound 19 was prepared by the methods used in the preparation of compound 17, except that *p*-cyano-benzyl bromide was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1)

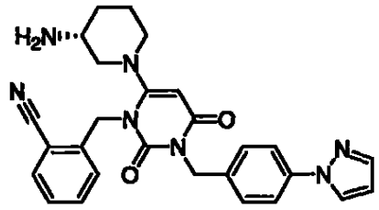
δ 7.70 (d, *J*=7.8 Hz, 1 H), 7.56 - 7.63 (m, 3 H), 7.46 (m, 3 H), 7.29 (d, *J*=7.8 Hz, 1 H), 5.47 (s, 1 H), 5.16 - 5.36 (ABq, *J*= 51.1, 14.7 Hz, 2 H), 5.11 (s, 2 H), 3.36 - 3.47 (m, 2 H), 2.90-3.07 (m, 2 H), 2.79 (s, 1 H), 2.15 (s, 1 H), 1.95 (s, 1 H), 1.73 (s, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

Compound 20



[0348] 2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (20). Title compound 20 was prepared by the methods used in the preparation of compound 17, except that 2-chloromethyl benzimidazole was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.67(d, *J*=3.0Hz, 1H), 7.65-7.56(m, 2 H), 7.47 (d, *J*=3.3 Hz, 2 H), 7.46 (d, *J*=3.3 Hz, 1 H), 7.37-7.40 (m, 2 H), 5.52 (s, 3 H), 5.23 (s, 2 H), 3.51 (d, *J*=9.6 Hz, 1 H), 3.36 (m, 1 H), 2.87 - 2.92 (m, 2 H), 2.64 - 2.72 (m, 1 H), 2.09 (m, 1 H), 1.76 (m, 1 H), 1.52-1.64 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{26}N_7O_2$, 456.2; found 456.2.

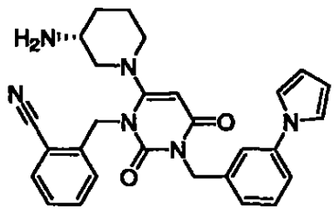
Compound 21



[0349] 2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (21). Title compound 21 was prepared by the methods used in the preparation of compound 17, except that 1-(4-bromomethyl-phenyl)-1H-pyrazole was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.90 (d, *J*=2.5 Hz, 1 H), 7.71 (d, *J*=1.8 Hz, 1 H), 7.65 (d, *J*=7.6 Hz, 1 H), 7.51 - 7.58 (m, 3 H), 7.43-7.37(m, 3 H), 7.22 (d, *J*=7.8 Hz, 1 H), 6.47 (t, *J*=2.1 Hz, 1 H), 5.43 (s, 1H), 5.14 - 5.30 (ABq, *J*=41.2, 16.4 Hz, 2 H), 5.05 (s, 2 H), 3.32-

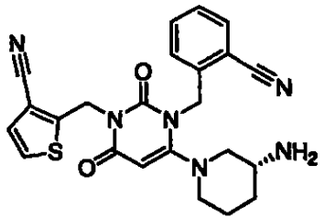
3.40 (m, 2H), 2.96 (m,1 H), 2.89 (m, 1 H), 2.70 (m, 1 H), 2.10 (m, 1 H), 1.88 (m, 1 H), 1.66 (s, 2 H). MS (ES) [m+H] calc'd for $C_{27}H_{28}N_7O_2$, 482.2; found 482.2.

Compound 22



[0350] 2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (22). Title compound 22 was prepared by the methods used in the preparation of compound 17, except that 1-(3-bromomethyl-phenyl)-1H-pyrrole was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.59 (d, *J*=7.3 Hz, 1 H), 7.48 (t, *J*=7.7 Hz, 1 H), 7.24 - 7.36 (m, 4 H), 7.21 (t, *J*=7.6 Hz, 2 H), 7.02 (t, *J* = 2.1 Hz, 2 H), 6.32 (t, *J* = 2.0 Hz, 2 H), 5.42 (s, 1H), 5.11 - 5.20 (ABq, *J*= 44.7, 15.9 Hz, 2 H), 5.06 (s, 2 H), 3.36 (m, 2 H), 2.98 (m, 1 H), 2.89 (m, 1 H), 2.70 (m, 1 H), 2.10 (m, 1 H), 1.88 (m, 1 H), 1.73-1.58 (m, 2 H). MS (ES) [m+H] calc'd for $C_{28}H_{29}N_6O_2$, 481.2; found 481.2.

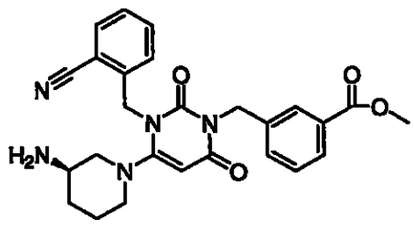
Compound 23



[0351] 6-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile (23). Title compound 23 was prepared by the methods used in the preparation of compound 17, except that 2-bromomethyl-thiophene-3-carbonitrile was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.65 (d, *J*=7.6 Hz, 1 H), 7.57 (t, *J*=7.8 Hz, 1 H), 7.40 (t, *J*=7.7 Hz, 1 H), 7.29 (d, *J*=7.8 Hz, 1 H), 7.25 (dd, *J*=5.3, 1.3 Hz, 1 H), 7.11 (dd, *J*=5.3, 1.0 Hz, 1 H), 5.45 (s, 1 H), 5.35 (s, 2 H), 5.15 - 5.33 (ABq, *J*=45.0, 15.5 Hz, 2 H), 3.38 (bd, *J*=10.1 Hz, 2 H), 2.98 (m, 2 H), 2.72 (s, 1 H), 2.12 (d, *J*=7.3 Hz, 1 H), 1.83 -

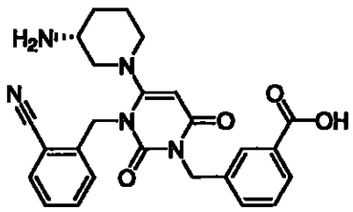
1.93 (m, 1 H), 1.61 - 1.72 (m, 2 H). MS (ES) [m+H] calc'd for $C_{23}H_{23}N_6O_4$, 447.1; found 447.1.

Compound 24



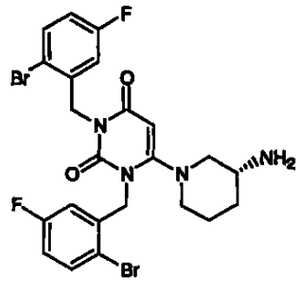
[0352] 3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester (24). Title compound 24 was prepared by the methods used in the preparation of compound 17, except that 3-bromomethyl-benzoic acid methyl ester was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.99 (s, 1 H), 7.91 (d, *J*=7.8 Hz, 1 H), 7.65 (d, *J*=7.6 Hz, 1 H), 7.56 (d, *J*=7.9 Hz, 1 H), 7.52 (d, *J*=7.6 Hz, 1 H), 7.39 (t, *J*=7.6 Hz, 1 H), 7.34 (t, *J*=7.6 Hz, 1 H), 7.23 (d, *J*=8.1 Hz, 1 H), 5.44 (s, 1 H), 5.12 - 5.31 (ABq, *J*=43.7, 15.9 Hz, 2 H), 5.08 (s, 2 H), 3.90 (s, 3 H), 3.31 - 3.39 (m, 2 H), 2.98 (d, *J*=11.9 Hz, 1 H), 2.87 (m, 1 H), 2.71 (m, 1 H), 2.11 (m, 1 H), 1.89 (m, 1 H), 1.73-1.59 (m, 2 H). MS (ES) [m+H] calc'd for $C_{26}H_{28}N_5O_4$, 474.2; found 474.2.

Compound 25



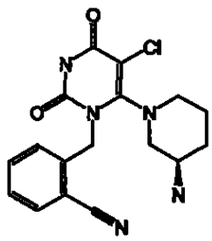
[0353] 3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid (25). A crude mixture of compound 24 (~50 mg) was treated with LiOH in THF-water (10:1) to give the title compound 25. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.90 (s, 1 H), 7.86 (d, *J*=7.6 Hz, 1 H), 7.60 (d, *J*=7.6 Hz, 1 H), 7.50 (t, *J*=8.2 Hz, 1 H), 7.45 (d, *J*=7.3 Hz, 1 H), 7.26 - 7.36 (m, 2H), 7.17 (d, *J*=8.1Hz, 1 H), 5.39 (s, 1 H), 5.10- 5.25 (ABq, *J*=36.9, 15.5 Hz, 2 H), 5.03 (s, 2 H), 3.31 (m,2H), 2.95 (m, 1 H), 2.81 (m, 1 H), 2.64 (m, 1 H), 2.07 (m, 1 H), 1.82 (m, 1 H), 1.51-1.68 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{26}N_5O_4$, 460.2; found 460.2.

Compound 26



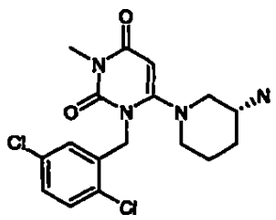
[0354] 6-[3 (R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione (26). The title compound was prepared from 1 by di-benzylation, using the procedure for the preparation of 2, except that 2-bromo-5-fluoro-benzyl bromide was used in the place of *α*-bromo-*o*-tolunitrile, followed by treatment with 3-(R)-amino-piperidine under the conditions described in the preparation of compound 4. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.42 (dd, *J*=8.6, 5.3 Hz, 2 H), 7.11 - 7.08 (dd, *J*=9.1, 2.2 Hz, 1 H), 7.06 (dd, *J*=9.3, 2.8 Hz, 1 H), 6.78 - 6.84 (m, 2 H), 5.71 (s, 1H), 5.29 (s, 4 H), 4.22 (d, *J*=11.1 Hz, 1 H), 3.82 (d, *J*=13.4 Hz, 1 H), 3.07 - 3.24 (m, 3 H), 2.06 (m, 1 H), 1.75 - 1.83 (m, 1 H), 1.63 - 1.72 (m, 1 H), 1.50 - 1.59 (m, 1 H). MS (ES) [m+H] calc'd for $C_{23}H_{23}Br_2F_2N_3O_2$, 583.01; found 583.01.

Compound 27



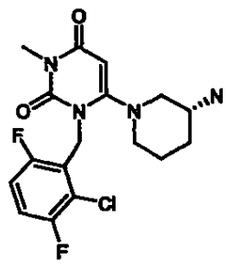
[0355] 2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (27). Compound 4 (100 mg) in THF (2 mL) was treated with 4M HCl in dioxane (1mL) at rt for 1 h, concentrated, and then purified by LC-MS to give the title compound. ^{1}H-NMR (400 MHz, DMSO-D6): δ ppm 12.0 (s, 1 H), 7.88 (d, *J*=7.6 Hz, 1 H), 7.68 (t, *J*=7.7 Hz, 1 H), 7.49 (t, *J*=7.7 Hz, 1 H), 7.36 (d, *J*=7.8 Hz, 1 H), 5.09 - 5.21 (m, 2 H), 3.17 (m, 2 H), 2.96 (t, *J*=11.1 Hz, 1 H), 2.86 (d, *J*=10.6 Hz, 1 H), 2.65 (m, 1 H), 1.90 (d, *J*=11.6 Hz, 1 H), 1.57 (d, *J*=13.1 Hz, 1 H), 1.19 - 1.31 (m, 1 H), 1.03 - 1.15 (m, 1 H). MS (ES) [m+H] calc'd for $C_{17}H_{19}ClN_5O_2$, 360.1; found, 360.1.

Compound 28



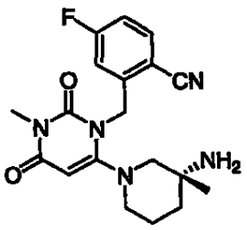
[0356] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-*di*-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (28). The title compound was prepared from compound 1 using the same procedures as in the preparation of compound 10, except that 2,5-di-chloro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ ppm 7.50 (d, *J*=8.6 Hz, 1 H), 7.39 (dd, *J*=8.3, 2.526 Hz, 1 H), 7.22 (d, *J*=2.5 Hz, 1 H), 5.41 (s, 1 H), 5.01 – 4.93 (ABq, *J* = 41.9, 16.2 Hz, 2H), 3.25 (m, 2 H), 3.10 (s, 3H), 2.85 (m, 1 H), 2.76 (m, 1 H), 2.67 (m, 1 H), 1.91 (m, 1 H), 1.75 (m, 1 H), 1.45 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}Cl_2N_4O_2$, 383.1; found 383.1.

Compound 29



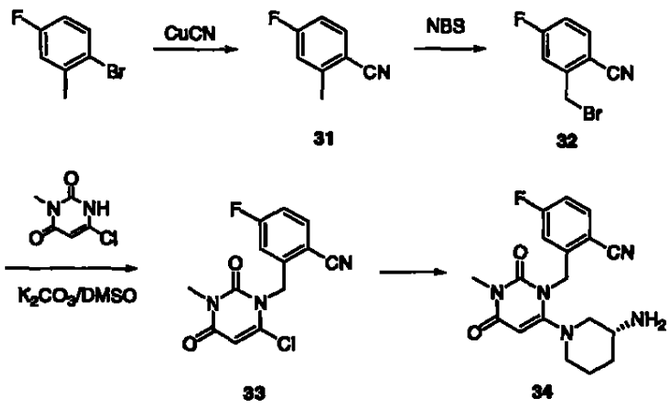
[0357] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-*di*-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (29). The title compound was prepared from compound 1 using the same procedures as in the preparation of compound 10, except that 2-chloro-3,6-*di*-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. 1H NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ ppm 6.98 - 7.06 (m, 2 H), 6.90 (m, 2 H), 5.31 (s, 1 H), 5.01 – 5.20 (ABq, *J* = 24.2, 14.4 Hz, 2H), 3.28 - 3.37 (m, 2 H) 3.13 (s,3H), 3.01 - 2.94 (m, 1 H), 2.6-2.9 (m, 2 H), 2.10 (m, 1 H), 1.92 (m, 2 H), 1.73 (s, 1 H), 1.6-1.75 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{20}ClF_2N_4O_2$, 385.1; found 385.1.

Compound 30



[0358] **(R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile (30).** 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (300 mg, 1.0 mmol), (R)-3-amino-3-methyl-piperidine dihydrochloride (266 mg, 1.4 mmol) and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100 °C for 2 hrs. The final compound was obtained as TFA salt after HPLC purification. 1H-NMR (400 MHz, CD3OD): δ. 7.78-7.83 (m, 1H), 7.14-7.26 (m, 2H), 5.47 (s, 1H), 5.12-5.36 (ABq, 2H, J = 105.2, 15.6 Hz), 3.21 (s, 1H), 2.72-3.15 (m, 4H), 1.75-1.95 (m, 4H), 1.39 (s, 3H). MS (ES) [m+H] calc'd for C19H22FN5O2, 372.41; found, 372.41.

Compound 34



[0359] **4-Fluoro-2-methylbenzonitrile (31).** A mixture of 2-bromo-5fluorotoluene (3.5 g, 18.5 mmol) and CuCN (2 g, 22 mmol) in DMF (100 mL) was refluxed for 24 hours. The reaction was diluted with water and extracted with hexane. The organics were dried over $MgSO_4$ and the solvent removed to give product **31** (yield 60%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, J=5.6, 8.8 Hz, 1H), 6.93-7.06 (m, 2H), 2.55 (s, 3H).

[0360] **2-Bromomethyl-4-fluorobenzonitrile (32).** A mixture of 4-fluoro-2-methylbenzonitrile (2 g, 14.8 mmol), NBS (2.64 g, 15 mmol) and AIBN (100 mg) in CCl_4 was refluxed under nitrogen for 2 hours. The reaction was cooled to room temperature. The solid was removed by filtration. The organic solution was concentrated to give crude product as an oil, which was used in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, J= 5.2, 8.4 Hz, 1H), 7.28 (dd, J= 2.4, 8.8 Hz, 1H), 7.12 (m, 1H), 4.6 (s, 2H).

[0361] **2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (33).** A mixture of crude 3-methyl-6-chlorouracil (0.6 g, 3.8 mmol), 2-bromomethyl-4-fluorobenzonitrile (0.86 g, 4 mmol) and K_2CO_3 (0.5 g, 4 mmol) in DMSO (10 mL) was stirred at 60 °C for 2 hours. The reaction was diluted with water and extracted with EtOAc. The organics were dried over $MgSO_4$ and the solvent removed. The residue was purified by column chromatography. 0.66 g of the product was obtained (yield: 60%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, J=7.2, 8.4Hz, 1H), 7.26 (d, J-4.0Hz, 1H), 7.11-7.17 (m, 1H), 6.94 (dd, J=2.0, 9.0 Hz, 1H), 6.034 (s, 2H), 3.39 (s, 3H). MS (ES) [m+H] calc'd for $C_{13}H_9ClFN_3O_2$, 293.68; found 293.68.

[0362] **2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile (34).** 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (300 mg, 1.0 mmol), (*R*)-3-amino-piperidine dihydrochloride (266 mg, 1.5 mmol) and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100 °C for 2 hrs. The final compound was obtained as TFA salt after HPLC purification. ^{1}H-NMR (400 MHz, CD_3OD): δ. 7.77-7.84 (m, 1H), 7.16-7.27 (m, 2H), 5.46 (s, 1H), 5.17-5.34 (ABq, 2H, J = 35.2, 15.6 Hz), 3.33-3.47 (m, 2H), 3.22 (s, 3H), 2.98-3.08 (m, 1H), 2.67-2.92 (m, 2H), 2.07-2.17 (m, 1H), 1.82-1.92 (m, 1H), 1.51-1.79 (m, 2H). MS (ES) [m+H] calc'd for $C_{18}H_{20}FN_5O_2$, 357.38; found, 357.38.

4. Examples Of *In vitro* Assays

[0363] The protease inhibitory activities of DPP-IV inhibitors can be readily determined by methods known to those of ordinary skill in the art since suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are

known. Examples of assays that may be used for measuring protease inhibitory activity and selectivity are set forth below.

DPP-IV Assay

[0364] Solutions of test compounds in varying concentrations (≤10mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 20mM Tris, pH 7.4; 20mM KCl; and 0.1mg/mL BSA. Human DPP-IV (0.1 nM final concentration) was added to the dilutions and pre-incubated for 10 minutes at ambient temperature before the reaction was initiated with A-P-7-amido-4-trifluoromethylcoumarin (AP-AFC; 10 μM final concentration). The total volume of the reaction mixture was 10-100 μL depending on assay formats used (384 or 96 well plates). The reaction was followed kinetically (excitation λ=400 nm; emission λ=505 nm) for 5-10 minutes or an end-point was measured after 10 minutes. Inhibition constants (IC_{50}) were calculated from the enzyme progress curves using standard mathematical models.

FAPα Assay

[0365] Solutions of test compounds in varying concentrations (≤10mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 20mM Tris, pH 7.4; 20mM KCl; and 0.1mg/mL BSA. Human FAPα (2 nM final concentration) was added to the dilutions and pre-incubated for 10 minutes at ambient temperature before the reaction was initiated with A-P-7-amido-4-trifluoromethylcoumarin (AP-AFC; 40 μM final concentration). The total volume of the reaction mixture was 10-100μL depending on assay formats used (384 or 96 well plates). The reaction was followed kinetically (excitation λ=400 nm; emission λ=505 nm) for 5-10 minutes or an end-point was measured after 10 minutes. Inhibition constants (IC_{50}) were calculated from the enzyme progress curves using standard mathematical models.

PREP Assay

[0366] Solutions of test compounds in varying concentrations (≤10mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 20mM Sodium Phosphate, pH 7.4; 0.5mM EDTA; 0.5mM DTT; and 0.1mg/mL BSA. PREP (EC3.4.21.26 from Flavobacterium meningosepticum; 0.2 nM

final concentration) was added to the dilutions. The PREP and compound were pre-incubated for 10 minutes at ambient temperature before the reaction was initiated with Z-G-P-AMC (10 μM final concentration). The total volume of the reaction mixture was 10-100 μL depending on assay formats used (384 or 96 well plates). The reaction was followed kinetically (excitation λ=375 nm; emission λ=460 nm) for 10 minutes or an end-point was measured after 10 minutes. Inhibition constants (IC_{50}) were calculated from the enzyme progress curves using standard mathematical models.

Tryptase Assay

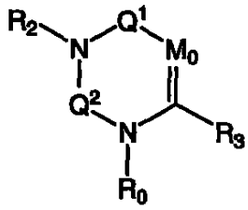
[0367] Solutions of test compounds in varying concentrations (≤10mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 100mM Hepes, pH 7.4; 0.01% Brij35; and 10% glycerol. Tryptase (rhLung beta; 0.1 nM final concentration) was added to the dilutions and pre-incubated with compound for 10 minutes at ambient temperature. The enzymatic reaction was initiated with 25 μM Z-lys-SBzl and 400μM DTNB. The total volume of the reaction mixture was 100μL in Costar A/2 96 well plates. The reaction was followed colorimetrically (λ=405 nm) for 10 minutes. Inhibition constants (IC_{50}) were calculated from the enzyme progress curves using standard mathematical models.

[0368] Compounds of the invention were tested according to the above-described assays for protease inhibition and observed to exhibit selective DPP-IV inhibitory activity. For example, compounds of the invention were found to inhibit DPP-IV activity at concentrations that are at least 50 fold less than those concentrations required to produce an equiactive inhibition of protease activity for FAPα. The apparent inhibition constants (K_i) for compounds of the invention, against DPP-IV, were in the range from about 10^{-9}M to about 10^{-5}M.

[0369] It will be apparent to those skilled in the art that various modifications and variations can be made to 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

M_0 is –C–LX, N or CR_4;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

R_0 is R_1 or –LX, with the proviso that only one of R_0 and M_0 is -LX;

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl

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group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

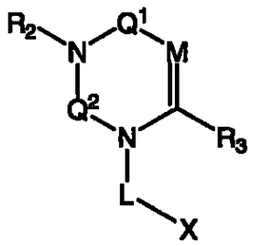
R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

2. A compound according to claim 1 comprising:



wherein

M is N or CR_4;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and $C{=}NR_9$;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

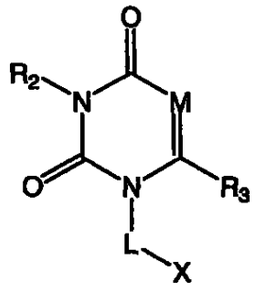
R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

3. A compound according to claim 2 comprising:



wherein

M is N or CR_4;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

4. The compound according to any one of claims 1-3, wherein the 1, 2 or 3 atoms of L providing the separation consist of carbon atoms.

5. The compound according to any one of claims 1-3, wherein the 1, 2 or 3 atoms of L providing the separation are selected from the group of linkers consisting of at least one oxygen or at least one nitrogen atom.

6. The compound according to any one of claims 1-3, wherein L separates X from the ring atom by one atom.

7. The compound according to any one of claims 1-3, wherein L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, $-NH-C(O)-$, $-NCH_3-C(O)-$, $-C(O)NH-$, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, $-S-$, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, $-C(O)S-$, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, and $-CH_2SC(O)-$, each substituted or unsubstituted.

8. The compound according to any one of claims 1-3, wherein L is selected from the group consisting of $-CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, and $-CH_2CH_2C(O)-$, each substituted or unsubstituted.

[0241] In addition to one or more DPP-IV inhibitors 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 DPP-IV inhibitor of the present invention to reduce DPP-IV activity *in vivo*, thereby treating the disease state of the subject.

[0242] Dosage forms or compositions may optionally comprise one or more DPP-IV inhibitors 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 DPP-IV inhibitors, optionally 0.1-95%, and optionally 1-95%.

[0243] Salts, preferably sodium salts, of the DPP-IV 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.

A. Formulations for oral administration

[0244] 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.

[0245] In certain embodiments, DPP-IV inhibitors 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.

[0246] 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.

[0247] Examples of lubricants that may be used include, but are not limited to, talc, starch, magnesium or calcium stearate, lycopodium and stearic acid.

[0248] Examples of diluents that may be used include, but are not limited to, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate.

[0249] Examples of glidants that may be used include, but are not limited to, colloidal silicon dioxide.

[0250] 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.

[0251] 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.

[0252] 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.

[0253] 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.

[0254] 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.

[0255] 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.

[0256] Examples of film coatings that may be used include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0257] 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.

[0258] 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.

[0259] 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.

[0260] The DPP-IV inhibitors 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.

[0261] Examples of pharmaceutically acceptable carriers that may be included in tablets comprising DPP-IV inhibitors 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.

[0262] 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.

[0263] 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

concentrated aqueous solutions of a sugar, for example, sucrose. Syrups may optionally further comprise a preservative.

[0264] Emulsions refer to two-phase systems in which one liquid is dispersed in the form of small globules throughout another liquid. Emulsions may optionally be oil-in-water or water-in-oil emulsions. Examples of pharmaceutically acceptable carriers that may be used in emulsions include, but are not limited to non-aqueous liquids, emulsifying agents and preservatives.

[0265] Examples of pharmaceutically acceptable substances that may be used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents.

[0266] Examples of pharmaceutically acceptable substances that may be used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic adds and a source of carbon dioxide.

[0267] Coloring and flavoring agents may optionally be used in all of the above dosage forms.

[0268] Particular examples of preservatives that may be used include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol.

[0269] Particular examples of non-aqueous liquids that may be used in emulsions include mineral oil and cottonseed oil.

[0270] Particular examples of emulsifying agents that may be used include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate.

[0271] Particular examples of suspending agents that may be used include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as sodium cyclamate and saccharin.

[0272] Particular examples of wetting agents that may be used include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether.

[0273] Particular examples of organic acids that may be used include citric and tartaric acid.

[0274] 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.

[0275] 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.

[0276] 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.

[0277] 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.

B. Injectables, solutions and emulsions

[0278] The present invention is also directed to compositions designed to administer the DPP-IV inhibitors of the present invention by parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously. 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.

[0279] 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.

[0280] 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.

[0281] 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.

[0282] 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.

[0283] 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.

[0284] 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.

[0285] 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 used include phenols or cresols,

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

[0286] 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.

[0287] 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.

[0288] The concentration of a DPP-IV 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 a DPP-IV 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.

[0289] 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 know and practiced in the art.

[0290] 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 DPP-IV inhibitor to the treated tissue(s). The DPP-IV 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.

[0291] The DPP-IV 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.

C. Lyophilized powders

[0292] The DPP-IV inhibitors 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.

[0293] 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 DPP-IV inhibitor is added to the resulting mixture, preferably above room temperature, more preferably at about 30-35 °C, 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 DPP-IV inhibitor.

D. Topical administration

[0294] The DPP-IV inhibitors 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.

[0295] The DPP-IV 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 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.

[0296] The DPP-IV 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 DPP-IV inhibitor alone or in combination with other pharmaceutically acceptable excipients can also be administered.

E. Formulations for other routes of administration

[0297] 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.

F. Examples of Formulations

[0298] 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%.

5. KITS COMPRISING DPP-IV INHIBITORS

[0299] The invention is also directed to kits and other articles of manufacture for treating diseases associated with DPP-IV. It is noted that diseases are intended to cover all conditions for which the DPP-IV possesses activity that contributes to the pathology and/or symptomology of the condition.

[0300] In one embodiment, a kit is provided that comprises a composition comprising at least one DPP-IV 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.

[0301] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one DPP-IV 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.

[0302] 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.

[0303] 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.

[0304] 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.

EXAMPLES

1. Preparation Of DPP-IV Inhibitors

[0305] 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.

[0306] 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 (enantiomers, diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

[0307] 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).

[0308] 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.

[0309] 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).

[0310] 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.

[0311] 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 °C.

[0312] 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).

[0313] 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.

[0314] 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.

[0315] 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 diasteromeric 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).

[0316] 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:

g (grams); mg (milligrams);
L (liters); mL (milliliters);
μL (microliters); psi (pounds per square inch);
M (molar); mM (millimolar);
i.v. (intravenous); Hz (Hertz);
MHz (megahertz); mol (moles);
mmol (millimoles); RT (ambient temperature);
min (minutes); h (hours);
mp (melting point); TLC (thin layer chromatography);
Tr (retention time); RP (reverse phase);
MeOH (methanol); i-PrOH (isopropanol);
TEA (triethylamine); TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride); THF (tetrahydrofuran);
DMSO (dimethylsulfoxide); EtOAc (ethyl acetate);
DME (1,2-dimethoxyethane); DCM (dichloromethane);
DCE (dichloroethane); DMF (N,N-dimethylformamide);
DMPU (N,N'-dimethylpropyleneurea); CDI (1,1-carbonyldiimidazole);
IBCF (isobutyl chloroformate); HOAc (acetic acid);
HOSu (N-hydroxysuccinimino); HOBT (1-hydroxybenzotriazole);
Et_2O (diethyl ether); EDCI (ethylcarbodiimino hydrochloride);
BOC (tert-butyloxycarbonyl); FMOC (9-fluorenylmethoxycarbonyl);
DCC (dicyclohexylcarbodiimino); CBZ (benzyloxycarbonyl);
Ac (acetyl); atm (atmosphere);
TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl);
TIPS (triisopropylsilyl); TBS (t-butyldimethylsilyl);
DMAP (4-dimethylaminopyridine); Me (methyl);
OMe (methoxy); Et (ethyl);
Et (ethyl); tBu (tert-butyl);
HPLC (high pressure liquid chomatography);
BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);

TBAF (tetra-n-butylammonium fluoride);

mCPBA (meta-chloroperbenzoic acid.

[0317] All references to ether or Et_2O are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted under an inert atmosphere at RT unless otherwise noted.

[0318] ^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).

[0319] 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).

2. Synthetic Schemes For DPP-IV Inhibitors Of The Present Invention

[0320] DPP-IV inhibitors according to the present invention may be synthesized according to a variety of reaction schemes. Some illustrative schemes are provided herein in the examples. Other reaction schemes could be readily devised by those skilled in the art.

[0321] 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.

[0322] By varying the Q^1 and Q^2, R_1, R_2, and R_3 groups, a wide variety of different DPP-IV inhibitors according to the present invention may be synthesized.

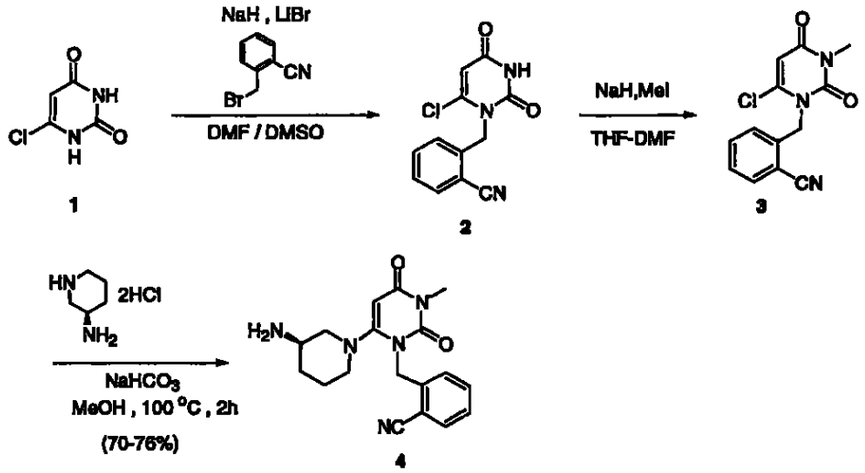
[0323] In each of the above reaction schemes, the various substituents may be selected from among the various substituents otherwise taught herein.

[0324] Descriptions of the syntheses of particular compounds according to the present invention based on the above reaction schemes are set forth herein.

3. Examples Of DPP-IV Inhibitors

[0325] The present invention is further exemplified, but not limited by, the following examples that describe the synthesis of particular compounds according to the invention.

Experimental Methods



[0326] **2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (2).** To a solution of 6-chlorouracil (20 g, 122 mmol) in a mixture of DMF-DMSO (6:1, 600 mL) under nitrogen at 0 °C, was added sodium hydride (60%, 5.5 g, 137 mmol) in portions. After 0.5h, lithium bromide (8 g, 96 mmol) was added into the mixture and stirred for 15 min at 0 °C. A solution of *α*-Bromo-*o*-tolunitrile (25.1 g, 128 mmol) in DMF (30 mL) was added dropwise, and stirred at this temperature for 1 h, and then RT overnight. It will be understood that alkylation of the amine may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH or the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may be used, including LiBr, LiI, NaI and the like. The mixture was evaporated and co-evaporated with water *in vacuo*

to remove most of the DMF, and then poured into ice water (1L). The precipitate was collected by filtration. The crude product was suspended in hot AcOEt-$CHCl_3$ and sonicated for 5 min, allowed to stand at 0 °C for 1h, and then filtered to give a white solid of the title compound (19 g) in 54% yield. It will also be understood by those skilled in the art that purification may be accomplished using various methods known in the art, including washing with an aqueous/organic solvent or mixture of solvents, recrystallization and/or column chromatography. Non-limiting examples of organic solvents and solvent mixtures may include ethyl acetate, isopropyl acetate, acetone, THF and the like. ^{1}H-NMR (400 MHz, DMSO): δ 11.82 (s, 1H), 7.87 (d, 1H, J = 7.6 Hz), 7.71 (t, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.37 (d, 1H, J = 8 Hz), 6.06 (s, 1H), 5.31 (s, 2H). MS (ES) [m+H] calc'd for $C_{12}H_9ClN_3O_2$, 262.0; found 262.0.

[0327] 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (3). To a cold (0 °C) solution of benzylated 6-chlorouracil 2 (10 g, 38 mmol) in DMF-THF (1:1, 300 mL) under nitrogen, was added NaH (60%, 1.6 g, 39.9 mmol) in portions, followed by adding LiBr (2g). The mixture was stirred at r.t for 20 min. After adding iodomethane (5.4 mL, 76 mmol), the flask was sealed and stirred at this temperature for 10 min, rt for 2h, and 35 °C overnight, and then concentrated *in vacuo*. It will be understood that alkylation of the amine may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH or the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may be used, including LiBr, LiI, NaI and the like. For example, the alkylation can be performed using methyliodide and K_2CO_3 in acetone. The reaction may be performed at about 15-45 °C, preferably at about 20-43 °C, and more preferably at about 35-41 °C until the reaction is complete. The residue was dissolved in $CHCl_3$ and washed with water and brine, dried (Na_2SO_4), and filtered then concentrated *in vacuo*. The crude product was crystallized from THF-Hexanes to give 7.6 g (72%) of the title compound 3. It will also be understood by those skilled in the art that the benzonitrile may be purified in a variety of organic solvents or solvent mixtures. For example, the benzonitrile can be purified by adding a mixture of dichloromethane and heptane. Optionally, the benzonitrile may be further purified in an organic solvent or mixture of solvents such as dichloromethane, chloroform, acetonitrile, THF, ethyl acetate,

isopropyl acetate and the like. Preferably, the product is purified and washed with ethyl acetate. ^{1}H NMR (400 MHz, DMSO): δ 7.87 (d, 1H, J = 7.6 Hz), 7.70 (t, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.40 (d, 1H, J = 8 Hz), 6.21 (s, 1H), 5.38 (s, 2H), 3.28 (s, 3H). MS (ES) [m+H] calc'd for $C_{13}H_{11}ClN_3O_2$, 276.1; found 276.1.

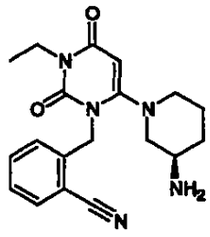
[0328] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (4). 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2-H-pyrimidin-1-ylmethyl)-benzonitrile (330 mg, 1.08 mmol), (*R*)-3-amino-piperidine dihydrochloride (246 mg, 1.4 mmol) and sodium bicarbonate (500mg, 5.4 mmol) were stirred with 200 mg activated molecular sieves (4A) in dry MeOH (5 mL) at 100 °C for 2 h. The reaction was filtered through Celite, concentrated *in vacuo*, and then diluted with $CHCl_3$, and washed with water. The water phase was extracted with $CHCl_3$ and the combined organic phases were washed with water, dried (Na_2SO_4), and filtered. TFA (1mL) was added into the solution which was then concentrated *in vacuo*. The residue was dissolved in a small amount of MeOH, and Et_2O was added to force precipitation. The mixture was allowed to stand at RT overnight. It will be understood by those skilled in the art that condensation with the amine or amine hydrochloride may be performed in a solvent or mixture of solvents with a base, such as potassium carbonate, sodium bicarbonate and the like, or mixtures thereof. The solvent may comprise both protic and aprotic solvents, or mixtures thereof. For example, the solvent may comprise a mixture of isopropyl alcohol and water. Further, the reaction may be heated to about 30-100 °C, preferably about 35-55 °C, and more preferably about 45-50 °C until the reaction is complete. Solvents were decanted, and the solid was washed with Et_2O two times to give 270 mg product as off-white powder. It will also be understood that the product may be further purified by washing with an organic solvent or mixture of solvents. Non-limiting examples of solvent or solvent mixtures include isopropyl acetate, ethyl acetate, dichloromethane, heptane, and the like. Further, the product may optionally be purified by column chromatography.

[0329] The benzonitrile product may be isolated as the free base if desired, but preferably, the product may be further converted to the corresponding acid addition salt, such as the benzoic acid salt. Preferably, the benzonitrile product is treated with benzoic acid to form 2-[6-(3-amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-

1-ylmethyl]-benzonitrile benzoate (4). Preparation and isolation of the benzoate salt may be performed by conventional methods for the formation of acid addition salts. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.82 (d, 1H, J = 7.6 Hz), 7.65 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 8.0 Hz), 5.42 (s, 1H), 5.50-5.00 (ABq, 2H, J = 41.6, 15.2 Hz), 3.30 (m, 2H), 3.16 (s, 3H), 2.91 (m, 1H), 2.76 (m, 2H), 1.93 (m, 1H), 1.79 (m, 1H), 1.51 (m, 2H). MS (ES) [m+H] calc'd for $C_{18}H_{22}N_5O_2$, 340.2; found, 340.2.

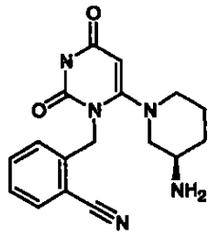
[0330] In each of the above steps, the isolation and/or purification steps of the intermediate compounds may be avoided if the intermediates from the reaction mixture are obtained as relatively pure compounds and the by-products or impurities of the reaction mixture do not interfere with the subsequent reaction steps. Where feasible, one or more isolation steps may be eliminated to provide shorter processing times, and the elimination of further processing may also afford higher overall reaction yields.

Compound 5



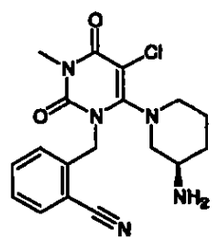
[0331] **2-{6-[3(R)-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile TFA salt (5).** The title compound, 5, was prepared from sample 2 using the procedures described in the preparation of samples 3 and 4, except that ethyl bromide was used in place of iodomethane. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.66 (d, *J*=7.8 Hz, 1 H), 7.59 (td, *J*=7.8, 1.4 Hz, 1 H), 7.40 (t, *J*=7.6 Hz, 1 H), 7.26 (d, *J*=7.6 Hz, 1 H), 5.41 (s, 1 H), 5.13 - 5.23 (ABq, 2H, J = 41.6, 15.2 Hz), 3.91 (q, *J*=7.1 Hz, 2 H), 3.37 (m, 2 H), 2.87 - 2.98 (m, 2 H), 2.70 (m, 1 H), 2.12 (m, 1 H), 1.88 (m, 1 H), 1.67 (m, 2 H), 1.15 (t, *J*=6.9 Hz, 3 H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

Compound 6



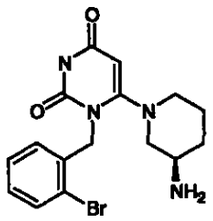
[0332] 2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (6). The title compound 6 was prepared from compound 2 by the procedure used in preparation of compound 4. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.65 (d, *J*=7.5 Hz, 1 H), 7.58 (t, *J*=7.8 Hz, 1 H), 7.39 (t, *J*=7.5 Hz, 1 H), 7.27 (d, *J*=7.8 Hz, 1 H), 5.32 (s, 1 H), 5.13 - 5.13 (ABq, 2H, J = 30.0, 15.0 Hz), 3.39 (m, 2 H), 2.95 (m, 2 H), 2.69 (m, 1 H), 2.12 (m, 1 H), 1.85 (m, 1 H), 1.64 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{20}N_5O_2$, 326.2; found, 326.2.

Compound 7



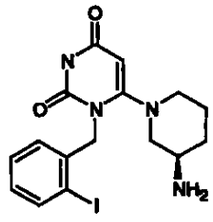
[0333] 2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (7). Compound 4 (40 mg, 0.1 mmol) in $CHCl_3$ (2 mL) was treated with $SOCl_2$ (200μL) at 100 °C for 30 min, concentrated, and then purified by LC-MS to give the title compound 7. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.73 (d, *J*=7.6 Hz, 1 H), 7.64 (t, *J*=7.6 Hz, 1 H), 7.45 (t, *J*=7.6 Hz, 1 H), 7.14 (d, *J*=8.1 Hz, 1 H), 5.32 - 5.42 (m, 2 H), 3.43 (s, 3 H), 3.33 - 3.40 (m, 2 H), 3.17 (m, 2 H), 2.87 (s, 1 H), 2.08 (m, 1 H), 1.70 (m, 1 H), 1.32 - 1.43 (m, 2 H). MS (ES) [m+H] calc'd for $C_{18}H_{21}ClN_5O_2$, 374.1; found, 374.1.

Compound 8



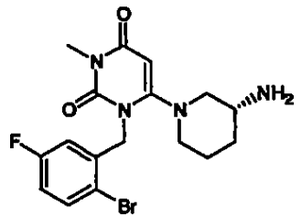
[0334] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione (8). The title compound was prepared in two steps. The first step was accomplished using the procedure for the preparation of compound 2, except that 2-bromobenzylbromide was used in the place of α-Bromo-*o*-tolunitrile. The crude product was then converted to the title compound by the method used in the preparation of compound 4. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.52 (d, *J*=8.1Hz, 1 H), 7.24 (t, *J*=7.8 Hz, 1 H), 7.10 (t, *J*=7.8 Hz, 1 H), 6.89 (d, *J*=7.579 Hz, 1 H), 5.27 (s, 1 H), 4.92 - 5.04 (ABq, *J* = 34.1, 15.0 Hz, 2H), 3.27 (bd, *J*=10.4Hz, 1 H), 3.09 - 3.18 (m, 1 H), 2.89 (m, 1 H), 2.70 (t, *J*=10.9Hz, 1 H), 2.48 (t, *J*=12.0 Hz, 1 H), 2.03 (m, 1 H), 1.60 - 1.71 (m, 1 H), 1.42 - 1.53 (m, 2 H). MS (ES) [m+H] calc'd for $C_{16}H_{20}BrN_4O_2$, 379.1; found, 379.1.

Compound 9



[0335] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione (9). The title compound was prepared by the procedure described in the preparation of compound 8, except that 2-iodobenzyl chloride was used as the benzylating reagent. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.76 (d, *J*=7.6Hz, 1 H), 7.21 (t, *J*=7.3 Hz, 1 H), 6.89 (t, *J*=7.2 Hz, 1 H), 6.79 (d, *J*=7.3 Hz, 1 H), 5.26 (s, 1H), 4.79 – 4.92 (ABq, *J* = 34.1, 6.7.0 Hz, 2H), 3.27 (m, 1 H), 3.13 (s, 1 H), 2.85 (d, *J*=11.6 Hz, 1 H), 2.70 (m, 1 H), 2.41 (m, 1 H), 2.02 (m, 1 H), 1.60 (m, 1 H), 1.45 (m, 2 H). MS (ES) [m+H] calc'd for $C_{16}H_{20}IN_4O_2$, 427.1; found, 427.1.

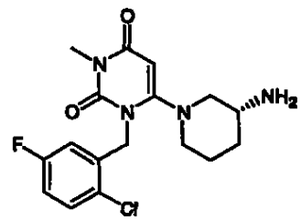
Compound 10



[0336] **6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (10).** To a solution of 6-chlorouracil (220 mg, 1.5 mmol) in a mixture of dry DMF-DMSO (6:1, 5 mL) under nitrogen at 0 °C, was added sodium hydride (60%, 61 mg, 1.8 mmol) in portions. After 0.5h, lithium bromide (83 mg, 1 mmol) was added and the mixture was stirred for 15 min at 0 °C. A solution of 2-bromo-5-fluoro-benzyl bromide (497 mg, 1.8 mmol) in DMF (30 mL) was added dropwise, and stirred at this temperature for 1 h, and then RT overnight. The mixture was evaporated and co-evaporated with water *in vacuo* to remove most of the DMF, and then poured into ice-water. The precipitate was collected by filtration, and then suspended in cold MeOH and filtered. The solution was concentrated to give the crude monobenzylated product.

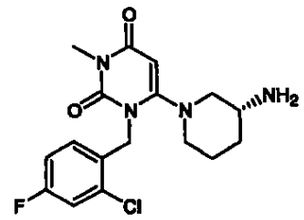
[0337] The crude product was treated with NaH and MeI using the procedure described in the preparation of compound 3, followed by the procedure used in the preparation of compound 4 to give the title compound. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.46 (dd, *J*=8.7, 5.2 Hz, 1 H), 6.82 (td, *J*=8.3, 2.9Hz, 1 H), 6.59 (dd, *J*=9.1, 3.0 Hz, 1 H), 5.28 (s, 1H), 4.99 - 5.06 (ABq, *J* = 41.7, 16.7 Hz, 2H), 3.28 (m, 1H), 3.23 (s, 3 H), 3.13 - 3.21 (m, 1 H), 2.86 (bd, *J*=12.6 Hz, 1 H), 2.71 (t, *J*=10.5 Hz, 1 H), 2.47 (t, *J*=11.0 Hz, 1 H), 2.00 - 2.08 (m, 1 H), 1.65 - 1.74 (m, 1 H), 1.42 - 1.53 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}BrFN_4O_2$, 411.1; found, 411.1.

Compound 11



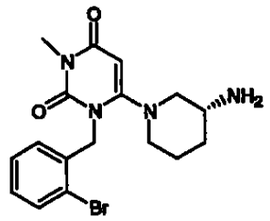
[0338] **6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (11).** The title compound was prepared from compound 1 using the same procedures as the preparation of compound 10, except that 2-chloro-5-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.34 - 7.40 (dd, *J*=8.5, 5.1 Hz, 1 H), 6.97 (td, *J*=8.3, 2.9 Hz, 1 H), 6.72 (dd, *J*=9.0, 2.9 Hz, 1 H), 5.41 (s, 1 H), 5.11 - 5.19 (ABq, *J* = 41.7, 16.7 Hz, 2H), 3.37 (s, 1 H), 3.32 (s, 3H), 3.23 - 3.30 (m, 1 H), 2.96 (d, *J*=12.1 Hz, 1 H), 2.81 (t, *J*=10.2 Hz, 1 H), 2.59 (t, *J*=11.1 Hz, 1 H), 2.13 (d, *J*=10.4 Hz, 1 H), 1.76 - 1.86 (m, 1 H), 1.52 - 1.63 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}ClFN_4O_2$, 367.1; found 367.1.

Compound 12



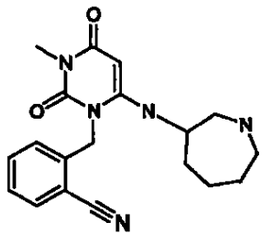
[0339] **6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (12).** The title compound was prepared from compound 1 using the same procedures as described the preparation of compound 10, except that 2-chloro-4-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.15 (dd, *J*=8.211, 2.400 Hz, 1 H), 6.95 - 7.06 (m, 2 H), 5.40 (s, 1 H), 5.09 - 5.18 (ABq, *J* = 37.7, 15.9 Hz, 2H), 3.33 - 3.39 (m, 1 H), 3.30 (s, 3 H), 3.23 - 3.29 (m, 1 H), 2.98 (bd, *J*=12.9 Hz, 1 H), 2.79 (t, *J*=10.4 Hz, 1 H), 2.55 - 2.66 (t, *J*=11.2 Hz, 1 H), 2.13 (m, 1 H), 1.78 - 1.88 (m, 1 H), 1.55 - 1.65 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}ClFN_4O_2$, 367.1; found 367.1.

Compound 13

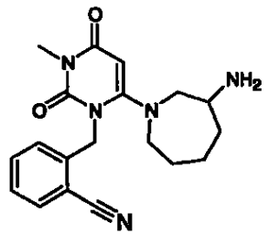


[0340] **6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (13).** The title compound was prepared from compound **1** used the procedures described in the synthesis of compound **10**, except that 2-bromo benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.45 (d, *J*=7.8 Hz, 1 H), 7.16 (t, *J*=7.5 Hz, 1 H), 7.03 (t, *J*=7.2 Hz, 1 H), 6.80 (d, *J*=7.3 Hz, 1 H), 5.28 (s, 1 H), 4.93 - 5.05 (ABq, 2H, J = 36.4, 16.4 Hz), 3.22 (m, 1H), 3.19 (m, 3 H), 3.09 (m, 1 H), 2.84 (d, *J*=12.6 Hz, 1 H), 2.63 (t, *J*=10.5 Hz, 1 H), 2.42 (t, *J*=10.9 Hz, 1 H), 1.97 (d, *J*=11.1 Hz, 1 H), 1.58 - 1.69 (m, 1 H), 1.38 - 1.48 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{22}BrN_4O_2$, 393.1; found, 393.1.

Compound 14



Compound 15



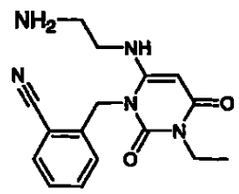
[0341] **2-{6-[Azepan-3(±)-ylamino]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (14) and 2-{6-[3(±)-Amino-azepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (15).** Title compounds 14 and 15 were prepared from compound 3 (70 mg, 0.27 mmol) and azepan-3-ylamine (70 mg, 0.61 mg) using the procedure for the preparation of compound 4. Both compounds were purified by LC-MS.

[0342] **14:** ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.77 (d, *J*=7.8 Hz, 1 H), 7.66 (t, *J*=7.6 Hz, 1 H), 7.47 (t, *J*=8.0 Hz, 1 H), 7.36 (d, *J*=8.1 Hz, 1 H), 5.54 (s, 1 H), 5.49 (s, 1 H), 5.27 - 5.36 (ABq, *J* = 26.0, 16.4 Hz, 2H), 3.50 (m, 2 H), 3.37 (s, 2 H), 3.26 (s, 3 H), 3.12 (m, 1H), 3.04 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.60 - 1.71 (m, 3H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

[0343] **15:** ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.77 (d, *J*=8.1 Hz, 1 H), 7.63 (t, *J*=7.6 Hz, 1 H), 7.46 (t, *J*=8.0 Hz, 1 H), 7.19 (d, *J*=7.6 Hz, 1 H), 5.48 (s, 1H), 5.44 - 5.52 (ABq, *J* = 61.9, 18.4 Hz, 2H), 3.80 (s, 1 H), 3.58-3.50 (m, 1 H), 3.39-3.39 (m, 1 H), 3.26 (s, 3 H), 3.13 (m, 1 H), 2.89 (t, *J* =12.4 Hz, 1 H), 2.04 (m, 1 H), 1.93 (m, 1 H), 1.86

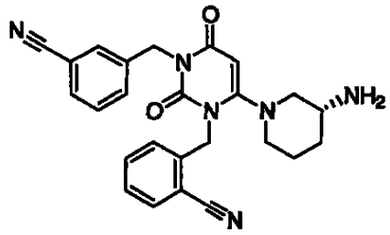
(m, 2 H), 1.59 - 1.70 (m, 2 H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

Compound 16



[0344] 2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (16). Compound 2 (150 mg, 0.57 mmol) in THF–DMSO (6:1, 4mL) was treated with 60% NaH (26 mg, 0.65 mmol), followed by adding ethyl bromide (300uL). In a sealed tube, ~20% crude product in dry MeOH (3 mL) was treated $NaHCO_3$ and ethane-1,2-diamine (200μL) at 120 °C for 2h, and purified by LC-MS to give the title compound 16. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.70 (d, *J*=7.8 Hz, 1 H), 7.58 (t, *J*=7.7 Hz, 1 H), 7.40 (t, *J*=7.4 Hz, 1 H), 7.12 (d, *J*=8.1 Hz, 1 H), 5.37 (s, 2 H), 3.95 (q, *J*=6.8 Hz, 2 H), 3.45 (t, *J*=5.9 Hz, 2 H), 3.11 (t, *J*=6.1 Hz, 2 H), 1.19 (t, *J*=6.8 Hz, 3 H). MS (ES) [m+H] calc'd for $C_{16}H_{20}N_5O_2$, 314.2; found 314.2.

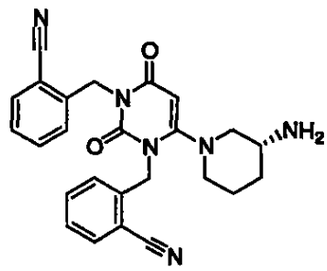
Compound 17



[0345] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (17). Compound 2 (65 mg, 0.25 mmol) in DME-DMF (2:1, 2.5 mL) was treated with 60% NaH (15 mg, 0.38 mmol) at 0 °C for 20 min, and then LiBr (25 mg) was added. 10 min later, *m*-cyano-benzyl bromide (55mg, 0.28 mg) was added, and the mixture was stirred at RT for 5h, and concentrated. The crude residue was dissolved in MeOH (3 mL). (*R*)-3-Amino-piperidine dihydrochloride (52 mg, 0.3 mmol) and sodium bicarbonate (100 mg) were added. The mixture was heated in a sealed tube at 120 °C for 2h, and then filtered and concentrated. LC-MS purification

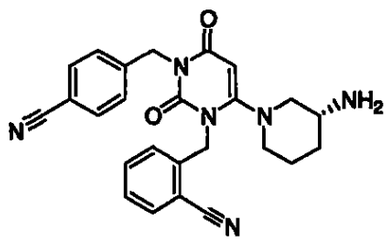
gave the title compound 17 in 84% yield. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.67 (d, *J*=7.8 Hz, 1 H), 7.52 - 7.62 (m, 4 H), 7.35 - 7.46 (m, 2 H), 7.27 (d, *J*=7.8 Hz, 1 H), 5.43 (s, 1 H), 5.15 - 5.31 (ABq, *J*=40.9, 13.7 Hz, 2 H), 5.04 (s, 2 H), 3.40 (s, 1 H), 3.40 (m 1 H), 3.03 (m,1 H), 2.91 (m, 1 H), 2.76 (s, 1 H), 2.13 (s, 1 H), 1.92 (m, 1 H), 1.63 - 1.74 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

Compound 18



[0346] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (18). Title compound 18 was prepared by the methods used in the preparation of compound 17, except that *α*-bromo-*o*-tolunitrile was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.64 (d, *J*=6.8Hz, 1H), 7.60 (d, *J*=7.8Hz, 1H), 7.55 (t, *J*=7.8Hz, 2 H), 7.44 (t, *J*=7.6Hz, 1 H), 7.38 (t, *J*=7.5 Hz, 1 H), 7.31 (t, *J*=7.6Hz, 1H), 7.27 (d, *J*=7.8 Hz, 1H), 7.12 (d, *J*=7.8 Hz, 1 H), 5.45 (s, 1 H), 5.15 - 5.32 (m, 4 H), 3.36 - 3.47 (m, 2 H), 2.98 (m, 2 H), 2.10 (m, 1 H), 1.91 (m, 1 H), 1.68 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

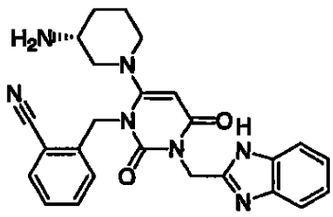
Compound 19



[0347] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (19). Title compound 19 was prepared by the methods used in the preparation of compound 17, except that *p*-cyano-benzyl bromide was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1)

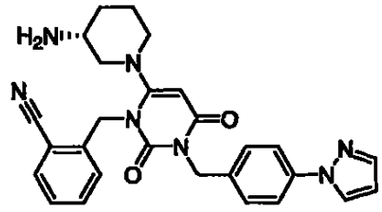
δ 7.70 (d, *J*=7.8 Hz, 1 H), 7.56 - 7.63 (m, 3 H), 7.46 (m, 3 H), 7.29 (d, *J*=7.8 Hz, 1 H), 5.47 (s, 1 H), 5.16 - 5.36 (ABq, *J*= 51.1, 14.7 Hz, 2 H), 5.11 (s, 2 H), 3.36 - 3.47 (m, 2 H), 2.90-3.07 (m, 2 H), 2.79 (s, 1 H), 2.15 (s, 1 H), 1.95 (s, 1 H), 1.73 (s, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

Compound 20



[0348] 2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (20). Title compound 20 was prepared by the methods used in the preparation of compound 17, except that 2-chloromethyl benzimidazole was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.67(d, *J*=3.0Hz, 1H), 7.65-7.56(m, 2 H), 7.47 (d, *J*=3.3 Hz, 2 H), 7.46 (d, *J*=3.3 Hz, 1 H), 7.37-7.40 (m, 2 H), 5.52 (s, 3 H), 5.23 (s, 2 H), 3.51 (d, *J*=9.6 Hz, 1 H), 3.36 (m, 1 H), 2.87 - 2.92 (m, 2 H), 2.64 - 2.72 (m, 1 H), 2.09 (m, 1 H), 1.76 (m, 1 H), 1.52-1.64 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{26}N_7O_2$, 456.2; found 456.2.

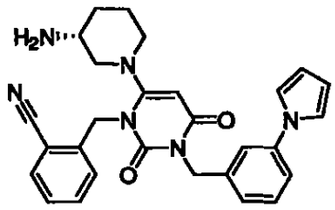
Compound 21



[0349] 2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (21). Title compound 21 was prepared by the methods used in the preparation of compound 17, except that 1-(4-bromomethyl-phenyl)-1H-pyrazole was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.90 (d, *J*=2.5 Hz, 1 H), 7.71 (d, *J*=1.8 Hz, 1 H), 7.65 (d, *J*=7.6 Hz, 1 H), 7.51 - 7.58 (m, 3 H), 7.43-7.37(m, 3 H), 7.22 (d, *J*=7.8 Hz, 1 H), 6.47 (t, *J*=2.1 Hz, 1 H), 5.43 (s, 1H), 5.14 - 5.30 (ABq, *J*=41.2, 16.4 Hz, 2 H), 5.05 (s, 2 H), 3.32-

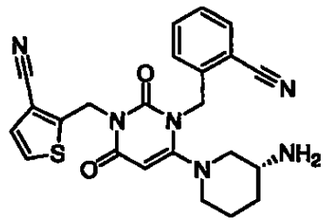
3.40 (m, 2H), 2.96 (m,1 H), 2.89 (m, 1 H), 2.70 (m, 1 H), 2.10 (m, 1 H), 1.88 (m, 1 H), 1.66 (s, 2 H). MS (ES) [m+H] calc'd for $C_{27}H_{28}N_7O_2$, 482.2; found 482.2.

Compound 22



[0350] 2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (22). Title compound 22 was prepared by the methods used in the preparation of compound 17, except that 1-(3-bromomethyl-phenyl)-1H-pyrrole was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.59 (d, *J*=7.3 Hz, 1 H), 7.48 (t, *J*=7.7 Hz, 1 H), 7.24 - 7.36 (m, 4 H), 7.21 (t, *J*=7.6 Hz, 2 H), 7.02 (t, *J* = 2.1 Hz, 2 H), 6.32 (t, *J* = 2.0 Hz, 2 H), 5.42 (s, 1H), 5.11 - 5.20 (ABq, *J*= 44.7, 15.9 Hz, 2 H), 5.06 (s, 2 H), 3.36 (m, 2 H), 2.98 (m, 1 H), 2.89 (m, 1 H), 2.70 (m, 1 H), 2.10 (m, 1 H), 1.88 (m, 1 H), 1.73-1.58 (m, 2 H). MS (ES) [m+H] calc'd for $C_{28}H_{29}N_6O_2$, 481.2; found 481.2.

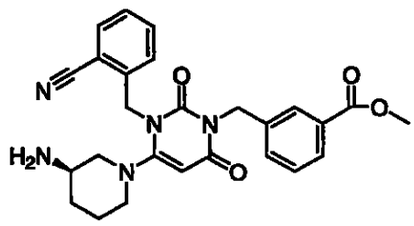
Compound 23



[0351] 6-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile (23). Title compound 23 was prepared by the methods used in the preparation of compound 17, except that 2-bromomethyl-thiophene-3-carbonitrile was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.65 (d, *J*=7.6 Hz, 1 H), 7.57 (t, *J*=7.8 Hz, 1 H), 7.40 (t, *J*=7.7 Hz, 1 H), 7.29 (d, *J*=7.8 Hz, 1 H), 7.25 (dd, *J*=5.3, 1.3 Hz, 1 H), 7.11 (dd, *J*=5.3, 1.0 Hz, 1 H), 5.45 (s, 1 H), 5.35 (s, 2 H), 5.15 - 5.33 (ABq, *J*=45.0, 15.5 Hz, 2 H), 3.38 (bd, *J*=10.1 Hz, 2 H), 2.98 (m, 2 H), 2.72 (s, 1 H), 2.12 (d, *J*=7.3 Hz, 1 H), 1.83 -

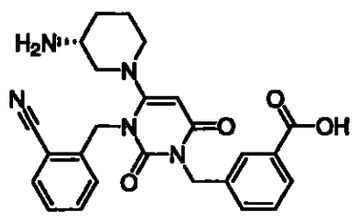
1.93 (m, 1 H), 1.61 - 1.72 (m, 2 H). MS (ES) [m+H] calc'd for $C_{23}H_{23}N_6O_4$, 447.1; found 447.1.

Compound 24



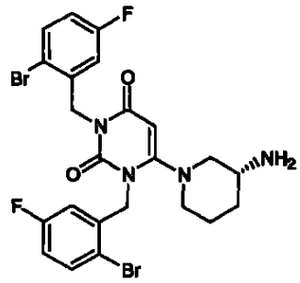
[0352] 3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester (24). Title compound 24 was prepared by the methods used in the preparation of compound 17, except that 3-bromomethyl-benzoic acid methyl ester was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.99 (s, 1 H), 7.91 (d, *J*=7.8 Hz, 1 H), 7.65 (d, *J*=7.6 Hz, 1 H), 7.56 (d, *J*=7.9 Hz, 1 H), 7.52 (d, *J*=7.6 Hz, 1 H), 7.39 (t, *J*=7.6 Hz, 1 H), 7.34 (t, *J*=7.6 Hz, 1 H), 7.23 (d, *J*=8.1 Hz, 1 H), 5.44 (s, 1 H), 5.12 - 5.31 (ABq, *J*=43.7, 15.9 Hz, 2 H), 5.08 (s, 2 H), 3.90 (s, 3 H), 3.31 - 3.39 (m, 2 H), 2.98 (d, *J*=11.9 Hz, 1 H), 2.87 (m, 1 H), 2.71 (m, 1 H), 2.11 (m, 1 H), 1.89 (m, 1 H), 1.73-1.59 (m, 2 H). MS (ES) [m+H] calc'd for $C_{26}H_{28}N_5O_4$, 474.2; found 474.2.

Compound 25



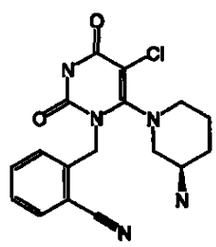
[0353] 3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid (25). A crude mixture of compound 24 (~50 mg) was treated with LiOH in THF-water (10:1) to give the title compound 25. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.90 (s, 1 H), 7.86 (d, *J*=7.6 Hz, 1 H), 7.60 (d, *J*=7.6 Hz, 1 H), 7.50 (t, *J*=8.2 Hz, 1 H), 7.45 (d, *J*=7.3 Hz, 1 H), 7.26 - 7.36 (m, 2H), 7.17 (d, *J*=8.1Hz, 1 H), 5.39 (s, 1 H), 5.10- 5.25 (ABq, *J*=36.9, 15.5 Hz, 2 H), 5.03 (s, 2 H), 3.31 (m,2H), 2.95 (m, 1 H), 2.81 (m, 1 H), 2.64 (m, 1 H), 2.07 (m, 1 H), 1.82 (m, 1 H), 1.51-1.68 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{26}N_5O_4$, 460.2; found 460.2.

Compound 26



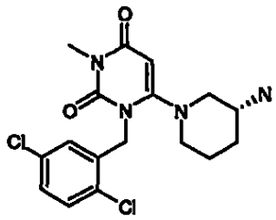
[0354] 6-[3 (R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione (26). The title compound was prepared from 1 by di-benzylation, using the procedure for the preparation of 2, except that 2-bromo-5-fluoro-benzyl bromide was used in the place of *α*-bromo-*o*-tolunitrile, followed by treatment with 3-(R)-amino-piperidine under the conditions described in the preparation of compound 4. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.42 (dd, *J*=8.6, 5.3 Hz, 2 H), 7.11 - 7.08 (dd, *J*=9.1, 2.2 Hz, 1 H), 7.06 (dd, *J*=9.3, 2.8 Hz, 1 H), 6.78 - 6.84 (m, 2 H), 5.71 (s, 1H), 5.29 (s, 4 H), 4.22 (d, *J*=11.1 Hz, 1 H), 3.82 (d, *J*=13.4 Hz, 1 H), 3.07 - 3.24 (m, 3 H), 2.06 (m, 1 H), 1.75 - 1.83 (m, 1 H), 1.63 - 1.72 (m, 1 H), 1.50 - 1.59 (m, 1 H). MS (ES) [m+H] calc'd for $C_{23}H_{23}Br_2F_2N_3O_2$, 583.01; found 583.01.

Compound 27



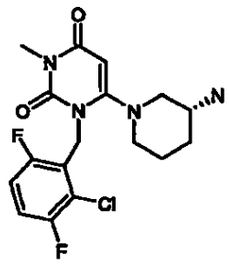
[0355] 2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (27). Compound 4 (100 mg) in THF (2 mL) was treated with 4M HCl *in* dioxane (1mL) at rt for 1 h, concentrated, and then purified by LC-MS to give the title compound. ^{1}H-NMR (400 MHz, DMSO-D6): δ ppm 12.0 (s, 1 H), 7.88 (d, *J*=7.6 Hz, 1 H), 7.68 (t, *J*=7.7 Hz, 1 H), 7.49 (t, *J*=7.7 Hz, 1 H), 7.36 (d, *J*=7.8 Hz, 1 H), 5.09 - 5.21 (m, 2 H), 3.17 (m, 2 H), 2.96 (t, *J*=11.1 Hz, 1 H), 2.86 (d, *J*=10.6 Hz, 1 H), 2.65 (m, 1 H), 1.90 (d, *J*=11.6 Hz, 1 H), 1.57 (d, *J*=13.1 Hz, 1 H), 1.19 - 1.31 (m, 1 H), 1.03 - 1.15 (m, 1 H). MS (ES) [m+H] calc'd for $C_{17}H_{19}ClN_5O_2$, 360.1; found, 360.1.

Compound 28



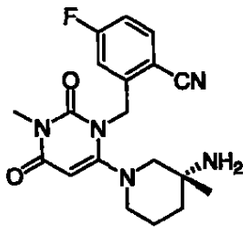
[0356] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-*di*-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (28). The title compound was prepared from compound 1 using the same procedures as in the preparation of compound 10, except that 2,5-di-chloro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ ppm 7.50 (d, *J*=8.6 Hz, 1 H), 7.39 (dd, *J*=8.3, 2.526 Hz, 1 H), 7.22 (d, *J*=2.5 Hz, 1 H), 5.41 (s, 1 H), 5.01 – 4.93 (ABq, *J* = 41.9, 16.2 Hz, 2H), 3.25 (m, 2 H), 3.10 (s, 3H), 2.85 (m, 1 H), 2.76 (m, 1 H), 2.67 (m, 1 H), 1.91 (m, 1 H), 1.75 (m, 1 H), 1.45 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}Cl_2N_4O_2$, 383.1; found 383.1.

Compound 29



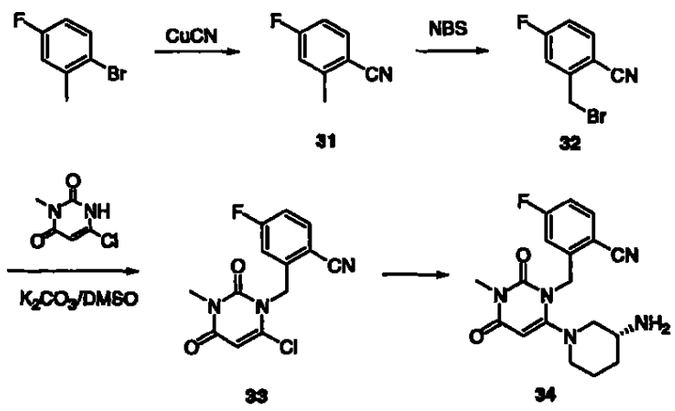
[0357] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-*di*-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (29). The title compound was prepared from compound 1 using the same procedures as in the preparation of compound 10, except that 2-chloro-3,6-*di*-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. 1H NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ ppm 6.98 - 7.06 (m, 2 H), 6.90 (m, 2 H), 5.31 (s, 1 H), 5.01 – 5.20 (ABq, *J* = 24.2, 14.4 Hz, 2H), 3.28 - 3.37 (m, 2 H) 3.13 (s,3H), 3.01 - 2.94 (m, 1 H), 2.6-2.9 (m, 2 H), 2.10 (m, 1 H), 1.92 (m, 2 H), 1.73 (s, 1 H), 1.6-1.75 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{20}ClF_2N_4O_2$, 385.1; found 385.1.

Compound 30



[0358] **(R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile (30).** 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (300 mg, 1.0 mmol), (R)-3-amino-3-methyl-piperidine dihydrochloride (266 mg, 1.4 mmol) and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100 °C for 2 hrs. The final compound was obtained as TFA salt after HPLC purification. 1H-NMR (400 MHz, CD3OD): δ. 7.78-7.83 (m, 1H), 7.14-7.26 (m, 2H), 5.47 (s, 1H), 5.12-5.36 (ABq, 2H, J = 105.2, 15.6 Hz), 3.21 (s, 1H), 2.72-3.15 (m, 4H), 1.75-1.95 (m, 4H), 1.39 (s, 3H). MS (ES) [m+H] calc'd for C19H22FN5O2, 372.41; found, 372.41.

Compound 34



[0359] **4-Fluoro-2-methylbenzonitrile (31).** A mixture of 2-bromo-5fluorotoluene (3.5 g, 18.5 mmol) and CuCN (2 g, 22 mmol) in DMF (100 mL) was refluxed for 24 hours. The reaction was diluted with water and extracted with hexane. The organics were dried over $MgSO_4$ and the solvent removed to give product 31 (yield 60%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, J=5.6, 8.8 Hz, 1H), 6.93-7.06 (m, 2H), 2.55 (s, 3H).

[0360] **2-Bromomethyl-4-fluorobenzonitrile (32).** A mixture of 4-fluoro-2-methylbenzonitrile (2 g, 14.8 mmol), NBS (2.64 g, 15 mmol) and AIBN (100 mg) in CCl_4 was refluxed under nitrogen for 2 hours. The reaction was cooled to room temperature. The solid was removed by filtration. The organic solution was concentrated to give crude product as an oil, which was used in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, J= 5.2, 8.4 Hz, 1H), 7.28 (dd, J= 2.4, 8.8 Hz, 1H), 7.12 (m, 1H), 4.6 (s, 2H).

[0361] **2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (33).** A mixture of crude 3-methyl-6-chlorouracil (0.6 g, 3.8 mmol), 2-bromomethyl-4-fluorobenzonitrile (0.86 g, 4 mmol) and K_2CO_3 (0.5 g, 4 mmol) in DMSO (10 mL) was stirred at 60 °C for 2 hours. The reaction was diluted with water and extracted with EtOAc. The organics were dried over $MgSO_4$ and the solvent removed. The residue was purified by column chromatography. 0.66 g of the product was obtained (yield: 60%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, J=7.2, 8.4Hz, 1H), 7.26 (d, J-4.0Hz, 1H), 7.11-7.17 (m, 1H), 6.94 (dd, J=2.0, 9.0 Hz, 1H), 6.034 (s, 2H), 3.39 (s, 3H). MS (ES) [m+H] calc'd for $C_{13}H_9ClFN_3O_2$, 293.68; found 293.68.

[0362] **2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile (34).** 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (300 mg, 1.0 mmol), (*R*)-3-amino-piperidine dihydrochloride (266 mg, 1.5 mmol) and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100 °C for 2 hrs. The final compound was obtained as TFA salt after HPLC purification. ^{1}H-NMR (400 MHz, CD_3OD): δ. 7.77-7.84 (m, 1H), 7.16-7.27 (m, 2H), 5.46 (s, 1H), 5.17-5.34 (ABq, 2H, J = 35.2, 15.6 Hz), 3.33-3.47 (m, 2H), 3.22 (s, 3H), 2.98-3.08 (m, 1H), 2.67-2.92 (m, 2H), 2.07-2.17 (m, 1H), 1.82-1.92 (m, 1H), 1.51-1.79 (m, 2H). MS (ES) [m+H] calc'd for $C_{18}H_{20}FN_5O_2$, 357.38; found, 357.38.

4. Examples Of *In vitro* Assays

[0363] The protease inhibitory activities of DPP-IV inhibitors can be readily determined by methods known to those of ordinary skill in the art since suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are

known. Examples of assays that may be used for measuring protease inhibitory activity and selectivity are set forth below.

DPP-IV Assay

[0364] Solutions of test compounds in varying concentrations (≤10mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 20mM Tris, pH 7.4; 20mM KCl; and 0.1mg/mL BSA. Human DPP-IV (0.1 nM final concentration) was added to the dilutions and pre-incubated for 10 minutes at ambient temperature before the reaction was initiated with A-P-7-amido-4-trifluoromethylcoumarin (AP-AFC; 10 μM final concentration). The total volume of the reaction mixture was 10-100 μL depending on assay formats used (384 or 96 well plates). The reaction was followed kinetically (excitation λ=400 nm; emission λ=505 nm) for 5-10 minutes or an end-point was measured after 10 minutes. Inhibition constants (IC_{50}) were calculated from the enzyme progress curves using standard mathematical models.

FAPα Assay

[0365] Solutions of test compounds in varying concentrations (≤10mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 20mM Tris, pH 7.4; 20mM KCl; and 0.1mg/mL BSA. Human FAPα (2 nM final concentration) was added to the dilutions and pre-incubated for 10 minutes at ambient temperature before the reaction was initiated with A-P-7-amido-4-trifluoromethylcoumarin (AP-AFC; 40 μM final concentration). The total volume of the reaction mixture was 10-100μL depending on assay formats used (384 or 96 well plates). The reaction was followed kinetically (excitation λ=400 nm; emission λ=505 nm) for 5-10 minutes or an end-point was measured after 10 minutes. Inhibition constants (IC_{50}) were calculated from the enzyme progress curves using standard mathematical models.

PREP Assay

[0366] Solutions of test compounds in varying concentrations (≤10mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 20mM Sodium Phosphate, pH 7.4; 0.5mM EDTA; 0.5mM DTT; and 0.1mg/mL BSA. PREP (EC3.4.21.26 from Flavobacterium meningosepticum; 0.2 nM

final concentration) was added to the dilutions. The PREP and compound were pre-incubated for 10 minutes at ambient temperature before the reaction was initiated with Z-G-P-AMC (10 μM final concentration). The total volume of the reaction mixture was 10-100 μL depending on assay formats used (384 or 96 well plates). The reaction was followed kinetically (excitation λ=375 nm; emission λ=460 nm) for 10 minutes or an end-point was measured after 10 minutes. Inhibition constants (IC_{50}) were calculated from the enzyme progress curves using standard mathematical models.

Tryptase Assay

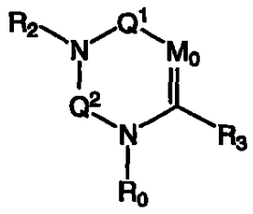
[0367] Solutions of test compounds in varying concentrations (≤10mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 100mM Hepes, pH 7.4; 0.01% Brij35; and 10% glycerol. Tryptase (rhLung beta; 0.1 nM final concentration) was added to the dilutions and pre-incubated with compound for 10 minutes at ambient temperature. The enzymatic reaction was initiated with 25 μM Z-lys-SBzl and 400μM DTNB. The total volume of the reaction mixture was 100μL in Costar A/2 96 well plates. The reaction was followed colorimetrically (λ=405 nm) for 10 minutes. Inhibition constants (IC_{50}) were calculated from the enzyme progress curves using standard mathematical models.

[0368] Compounds of the invention were tested according to the above-described assays for protease inhibition and observed to exhibit selective DPP-IV inhibitory activity. For example, compounds of the invention were found to inhibit DPP-IV activity at concentrations that are at least 50 fold less than those concentrations required to produce an equiactive inhibition of protease activity for FAPα. The apparent inhibition constants (K_i) for compounds of the invention, against DPP-IV, were in the range from about 10^{-9}M to about 10^{-5}M.

[0369] It will be apparent to those skilled in the art that various modifications and variations can be made to 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

M_0 is –C–LX, N or CR_4;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

R_0 is R_1 or –LX, with the proviso that only one of R_0 and M_0 is -LX;

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl

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group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

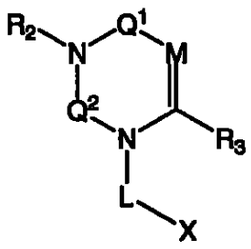
R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

2. A compound according to claim 1 comprising:



wherein

M is N or CR_4;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and $C{=}NR_9$;

group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

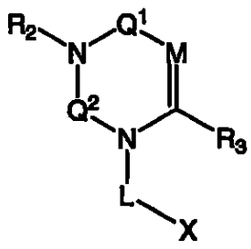
R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

2. A compound according to claim 1 comprising:



wherein

M is N or CR_4;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

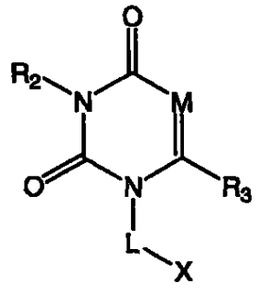
R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

3. A compound according to claim 2 comprising:



wherein

M is N or CR_4;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

4. The compound according to any one of claims 1-3, wherein the 1, 2 or 3 atoms of L providing the separation consist of carbon atoms.

5. The compound according to any one of claims 1-3, wherein the 1, 2 or 3 atoms of L providing the separation are selected from the group of linkers consisting of at least one oxygen or at least one nitrogen atom.

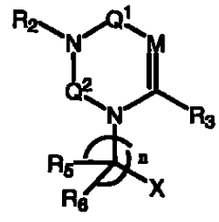
6. The compound according to any one of claims 1-3, wherein L separates X from the ring atom by one atom.

7. The compound according to any one of claims 1-3, wherein L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, $-NH-C(O)-$, $-NCH_3-C(O)-$, $-C(O)NH-$, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, $-S-$, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, $-C(O)S-$, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, and $-CH_2SC(O)-$, each substituted or unsubstituted.

8. The compound according to any one of claims 1-3, wherein L is selected from the group consisting of $-CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, and $-CH_2CH_2C(O)-$, each substituted or unsubstituted.

9. The compound according to any one of claims 1-3, wherein -L-X taken together is selected from the group consisting of -(CH_2)-(2-cyano)phenyl; -(CH_2)-(3-cyano)phenyl; -(CH_2)-(2-hydroxy)phenyl; -(CH_2)-(3-hydroxy)phenyl; -(CH_2)-(2-alkenyl)phenyl; -(CH_2)-(3-alkenyl)phenyl; -(CH_2)-(2-alkynyl)phenyl; -(CH_2)-(3-alkynyl)phenyl; -(CH_2)-(2-methoxy)phenyl; -(CH_2)-(3-methoxy)phenyl; -(CH_2)-(2-nitro)phenyl; -(CH_2)-(3-nitro)phenyl; -(CH_2)-(2-carboxy)phenyl; -(CH_2)-(3-carboxy)phenyl; -(CH_2)-(2-carboxamido)phenyl; -(CH_2)-(3-carboxamido)phenyl; -(CH_2)-(2-sulfonamido)phenyl; -(CH_2)-(3-sulfonamido)phenyl; -(CH_2)-(2-tetrazolyl)phenyl; -(CH_2)-(3-tetrazolyl)phenyl; -(CH_2)-(2-aminomethyl)phenyl; -(CH_2)-(3-aminomethyl)phenyl; -(CH_2)-(2-hydroxymethyl)phenyl; -(CH_2)-(3-hydroxymethyl)phenyl; -(CH_2)-(2-phenyl)phenyl; -(CH_2)-(3-phenyl)phenyl; -(CH_2)-(2-halo)phenyl; -(CH_2)-(3-halo)phenyl; -(CH_2)-(2-$CONH_2$)phenyl; -(CH_2)-(3-$CONH_2$)phenyl; -(CH_2)-(2-$CONH(C_{1-7})$alkyl)phenyl; -(CH_2)-(3-$CONH(C_{1-7})$alkyl)phenyl; -(CH_2)-(2-$CO_2(C_{1-7})$alkyl)phenyl; -(CH_2)-(3-$CO_2(C_{1-7})$alkyl)phenyl; -(CH_2)-(2-NH_2)phenyl; -(CH_2)-(3-NH_2)phenyl; -(CH_2)-(2-(C_{3-7})alkyl)phenyl; -(CH_2)-(3-(C_{3-7})alkyl)phenyl; -(CH_2)-(2-(C_{3-7})cycloalkyl)phenyl; -(CH_2)-(3-(C_{3-7})cycloalkyl)phenyl; -(CH_2)-(2-aryl)phenyl; -(CH_2)-(3-aryl)phenyl; -(CH_2)-(2-heteroaryl)phenyl; -(CH_2)-(3-heteroaryl)phenyl; -(CH_2)-2-bromo-5-fluoro phenyl; -(CH_2)-2-chloro-5-fluoro phenyl; -(CH_2)-2-cyano-5-fluoro phenyl; -(CH_2)-2,5-dichloro phenyl; -(CH_2)-2,5-difluoro phenyl; -(CH_2)-2,5-dibromo phenyl; -(CH_2)-2-bromo-3,5-difluoro phenyl; -(CH_2)-2-chloro-3,5-difluoro phenyl; -(CH_2)-2,3,5-trifluoro phenyl; -(CH_2)-2,3,5,6-tetrafluorophenyl; -(CH_2)-2-bromo-3,5,6-trifluoro phenyl; -(CH_2)-2-chloro-3,5,6-trifluoro phenyl; -(CH_2)-2-cyano-3,5-difluoro phenyl; -(CH_2)-2-cyano-3,5,6-trifluoro phenyl; -(CH_2)-(2-heterocycloalkyl)phenyl; and -(CH_2)-(3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

10. A compound according to claim 2 comprising:



wherein

n is 1, 2, or 3;

M is N or CR_4;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and $C=NR_9$;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl,

sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

11. The compound according to any one of claims 1-10, wherein X is a substituted or unsubstituted (C_{3-7})cycloalkyl, (C_{3-7})heterocycloalkyl, aryl, phenyl, heteroaryl, halophenyl, dihalophenyl, haloaryl, haloheteroaryl, dihaloaryl, dihaloheteroaryl, or a ring-bearing or cyclic group having a non-hydrogen substituent at a 2 or 3 position of the ring, each substituted or unsubstituted.

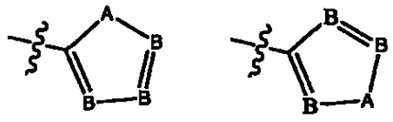
12. The compound according to any one of claims 1-10, wherein X is a ring-bearing or cyclic group having a non-hydrogen substituent at a 2 or 3 position of the ring selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, cyano, nitro, halo, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

13.

14. The compound according to any one of claims 1-10, wherein X is selected from the group consisting of (2-cyano)phenyl; (3-cyano)phenyl; (2-hydroxy)phenyl; (3-hydroxy)phenyl; (2-alkenyl)phenyl; (3-alkenyl)phenyl; (2-alkynyl)phenyl; (3-alkynyl)phenyl; (2-methoxy)phenyl; (3-methoxy)phenyl; (2-nitro)phenyl; (3-nitro)phenyl; (2-carboxy)phenyl; (3-carboxy)phenyl; -(CH_2)-(2-carboxamido)phenyl; (3-carboxamido)phenyl; (2-sulfonamido)phenyl; (3-sulfonamido)phenyl; (2-tetrazolyl)phenyl; (3-tetrazolyl)phenyl; (2-aminomethyl)phenyl; (3-aminomethyl)phenyl; (2-hydroxymethyl)phenyl; (3-hydroxymethyl)phenyl; (2-phenyl)phenyl; (3-phenyl)phenyl; (2-halo)phenyl; (3-halo)phenyl; (2-$CONH_2$)phenyl; (3-$CONH_2$)phenyl; (2-CONH(C_{1-7})alkyl)phenyl; (3-CONH(C_{1-7})alkyl)phenyl; (2-CO_2(C_{1-7})alkyl)phenyl; (3-CO_2(C_{1-7})alkyl)phenyl; (2-

NH_2)phenyl; (3-NH_2)phenyl; (2-(C_{3-7})alkyl)phenyl; (3-(C_{3-7})alkyl)phenyl; (2-(C_{3-7})cycloalkyl)phenyl; (3-(C_{3-7})cycloalkyl)phenyl; (2-aryl)phenyl; (3-aryl)phenyl; (2-heteroaryl)phenyl; (3-heteroaryl)phenyl; 2-bromo-5-fluoro phenyl; 2-chloro-5-fluoro phenyl; 2-cyano-5-fluoro phenyl; 2,5-dichloro phenyl; 2,5-difluoro phenyl; 2,5-dibromo phenyl; 2-bromo-3,5-difluoro phenyl; 2-chloro-3,5-difluoro phenyl; 2,3,5-trifluoro phenyl; 2,3,5,6-tetrafluorophenyl; 2-bromo-3,5,6-trifluoro phenyl; 2-chloro-3,5,6-trifluoro phenyl; 2-cyano-3,5-difluoro phenyl; 2-cyano-3,5,6-trifluoro phenyl; (2-heterocycloalkyl)phenyl; and (3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

15. The compound according to any one of claims 1-10, wherein X is selected from the group consisting of



wherein

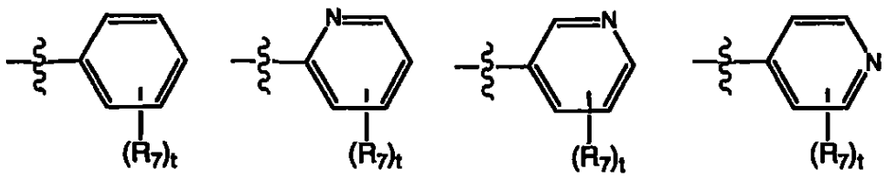
A is S, O or NR_{24};

B is CR_{23} or N;

R_{23} is independently selected from the group consisting of hydrogen, halo, perhalo(C_{1-10})alkyl, amino, thio, cyano, CF_3, nitro, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and

R_{24} is independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

16. The compound according to any one of claims 1-10, wherein X is selected from the group consisting of

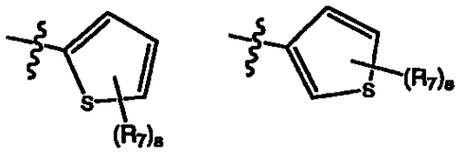


wherein

t is 0, 1, 2, 3, 4 or 5; and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

17. The compound according to any one of claims 1-10, wherein X is selected from the group consisting of



wherein

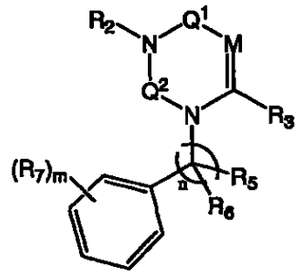
s is 0, 1, 2, or 3; and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

18. The compound according to claim 16 or 17 wherein R_7 is independently selected from the group consisting of -cyano, -methoxy, -nitro, -carboxy, -sulfonamido, -tetrazolyl,

-aminomethyl, -hydroxymethyl, -phenyl, -halo, $-CONH_2$, $-CONH(C_{1-7})alkyl$, $-CO_2(C_{1-7})alkyl$, $-NH_2$, -OH, $-(C_{1-5})alkyl$, -alkenyl, -alkynyl, $(C_{1-5})cycloalkyl$, aryl, heteroaryl, and heterocycloalkyl, each substituted or unsubstituted.

19. A compound according to claim 10 comprising:



wherein

m is 0, 1, 2, 3, 4, or 5;

n is 1, 2, or 3;

M is N or CR_4;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and $C=NR_9$;

R_2 is hydrogen or selected from the group consisting of $(C_{1-10})alkyl$, $(C_{3-12})cycloalkyl$, $(C_{3-12})cycloalkyl(C_{1-5})alkyl$, $hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl$, $hetero(C_{3-12})cycloalkyl$, $aryl(C_{1-10})alkyl$, $heteroaryl(C_{1-5})alkyl$, $(C_{9-12})bicycloaryl$, $hetero(C_{4-12})bicycloaryl$, $hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl$, carbonyl $(C_{1-3})alkyl$, thiocarbonyl $(C_{1-3})alkyl$, sulfonyl $(C_{1-3})alkyl$, sulfinyl $(C_{1-3})alkyl$, imino $(C_{1-3})alkyl$, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of $perhalo(C_{1-10})alkyl$, amino, $(C_{1-10})alkyl$, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl $(C_{1-3})alkyl$, thiocarbonyl $(C_{1-3})alkyl$, sulfonyl $(C_{1-3})alkyl$, sulfinyl $(C_{1-3})alkyl$, imino $(C_{1-3})alkyl$, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

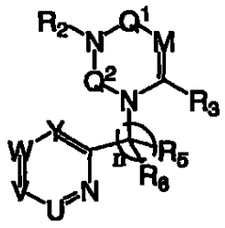
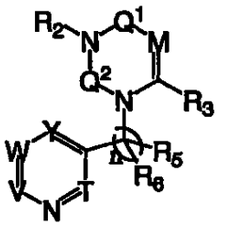
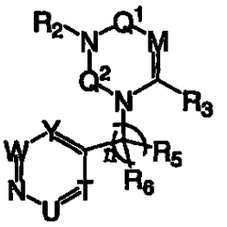
each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; and

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted.

20. A compound according to claim 10 comprising:

a member selected from the group consisting of

wherein

n is 1, 2, or 3;

M is N or CR_4;

each of T, U, V, W and Y is independently nitrogen or CR_{16}, provided that no more than two of T, U, V, W and Y are nitrogen;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

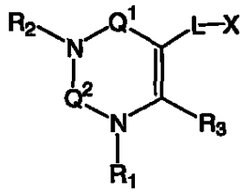
each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

each R_{16} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy,

carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

21. A compound according to claim 1 comprising:



wherein

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and $C{=}NR_9$;

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

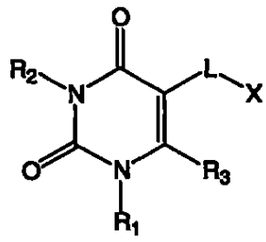
R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

22. A compound according to claim 21 comprising:



wherein

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy,

aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

23. The compound according to claim 21 or 22, wherein the 1, 2 or 3 atoms of L providing the separation consist of carbon atoms.

24. The compound according to claim 21 or 22, wherein the 1, 2 or 3 atoms of L providing the separation are selected from the group of linkers consisting of at least one oxygen or at least one nitrogen atom.

25. The compound according to claim 21 or 22, wherein L separates X from the ring atom by one atom.

26. The compound according to claim 21 or 22, wherein L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$,

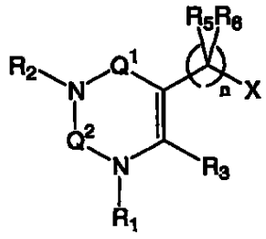
$-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, -NH-C(O)-, $-NCH_3-C(O)-$, -C(O)NH-, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, -S-, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, -C(O)S-, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, and $-CH_2SC(O)-$, each substituted or unsubstituted.

27. The compound according to claim 21 or 22, wherein L is selected from the group consisting of $-CH_2-$, -C(O)-, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, and $-CH_2CH_2C(O)-$, each substituted or unsubstituted.

28. The compound according to claim 21 or 22, wherein -L-X taken together is selected from the group consisting of $-(CH_2)$-(2-cyano)phenyl; $-(CH_2)$-(3-cyano)phenyl; $-(CH_2)$-(2-hydroxy)phenyl; $-(CH_2)$-(3-hydroxy)phenyl; $-(CH_2)$-(2-alkenyl)phenyl; $-(CH_2)$-(3-alkenyl)phenyl; $-(CH_2)$-(2-alkynyl)phenyl; $-(CH_2)$-(3-alkynyl)phenyl; $-(CH_2)$-(2-methoxy)phenyl; $-(CH_2)$-(3-methoxy)phenyl; $-(CH_2)$-(2-nitro)phenyl; $-(CH_2)$-(3-nitro)phenyl; $-(CH_2)$-(2-carboxy)phenyl; $-(CH_2)$-(3-carboxy)phenyl; $-(CH_2)$-(2-carboxamido)phenyl; $-(CH_2)$-(3-carboxamido)phenyl; $-(CH_2)$-(2-sulfonamido)phenyl; $-(CH_2)$-(3-sulfonamido)phenyl; $-(CH_2)$-(2-tetrazolyl)phenyl; $-(CH_2)$-(3-tetrazolyl)phenyl; $-(CH_2)$-(2-aminomethyl)phenyl; $-(CH_2)$-(3-aminomethyl)phenyl; $-(CH_2)$-(2-hydroxymethyl)phenyl; $-(CH_2)$-(3-hydroxymethyl)phenyl; $-(CH_2)$-(2-phenyl)phenyl; $-(CH_2)$-(3-phenyl)phenyl; $-(CH_2)$-(2-halo)phenyl; $-(CH_2)$-(3-halo)phenyl; $-(CH_2)$-(2-$CONH_2$)phenyl; $-(CH_2)$-(3-$CONH_2$)phenyl; $-(CH_2)$-(2-$CONH(C_{1-7})$alkyl)phenyl; $-(CH_2)$-(3-$CONH(C_{1-7})$alkyl)phenyl; $-(CH_2)$-(2-$CO_2(C_{1-7})$alkyl)phenyl; $-(CH_2)$-(3-$CO_2(C_{1-7})$alkyl)phenyl; $-(CH_2)$-(2-NH_2)phenyl; $-(CH_2)$-(3-NH_2)phenyl; $-(CH_2)$-(2-(C_{3-7})alkyl)phenyl; $-(CH_2)$-(3-(C_{3-7})alkyl)phenyl; $-(CH_2)$-(2-(C_{3-7})cycloalkyl)phenyl; $-(CH_2)$-(3-(C_{3-7})cycloalkyl)phenyl; $-(CH_2)$-(2-aryl)phenyl; $-(CH_2)$-(3-aryl)phenyl; $-(CH_2)$-(2-heteroaryl)phenyl; $-(CH_2)$-(3-heteroaryl)phenyl; $-(CH_2)$-2-bromo-5-fluoro phenyl; $-(CH_2)$-2-chloro-5-fluoro phenyl; $-(CH_2)$-2-cyano-5-fluoro phenyl; $-(CH_2)$-2,5-dichloro phenyl; $-(CH_2)$-2,5-difluoro phenyl; $-(CH_2)$-2,5-dibromo phenyl; $-(CH_2)$-2-bromo-3,5-difluoro phenyl; $-(CH_2)$-2-chloro-3,5-difluoro phenyl; $-(CH_2)$-2,3,5-trifluoro phenyl; $-(CH_2)$-2,3,5,6-tetrafluorophenyl; $-(CH_2)$-2-bromo-3,5,6-trifluoro phenyl; $-(CH_2)$-2-chloro-3,5,6-trifluoro phenyl; $-(CH_2)$-2-cyano-3,5-difluoro phenyl; $-(CH_2)$-2-cyano-3,5,6-trifluoro

phenyl; -(CH_2)-(2-heterocycloalkyl)phenyl; and -(CH_2)-(3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

29. A compound according to claim 21 comprising:



wherein

n is 1, 2, or 3;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

30. The compound according to any one of claims 22-29, wherein X is a substituted or unsubstituted (C_{3-7})cycloalkyl.

31. The compound according to any one of claims 22-29, wherein X is a substituted or unsubstituted (C_{3-7})heterocycloalkyl.

32. The compound according to any one of claims 22-29, wherein X is a substituted or unsubstituted aryl.

33. The compound according to any one of claims 22-29, wherein X is a substituted or unsubstituted phenyl.

34. The compound according to any one of claims 22-29, wherein X is a substituted or unsubstituted heteroaryl.

35. The compound according to any one of claims 22-29, wherein X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring.

36. The compound according to any one of claims 22-29, wherein X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, cyano, nitro, halo, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

37. The compound according to any one of claims 22-29, wherein X is a substituted or unsubstituted halophenyl or dihalophenyl.

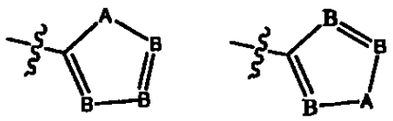
38. The compound according to any one of claims 22-29, wherein X is a substituted or unsubstituted haloaryl, haloheteroaryl, dihaloaryl or dihaloheteroaryl.

39. The compound according to any one of claims 22-29, wherein X is selected from the group consisting of (2-cyano)phenyl; (3-cyano)phenyl; (2-hydroxy)phenyl; (3-hydroxy)phenyl; (2-alkenyl)phenyl; (3-alkenyl)phenyl; (2-alkynyl)phenyl; (3-alkynyl)phenyl; (2-methoxy)phenyl; (3-methoxy)phenyl; (2-nitro)phenyl; (3-nitro)phenyl; (2-carboxy)phenyl; (3-carboxy)phenyl; -(CH_2)-(2-carboxamido)phenyl; (3-carboxamido)phenyl; (2-sulfonamido)phenyl; (3-sulfonamido)phenyl; (2-tetrazolyl)phenyl; (3-tetrazolyl)phenyl; (2-aminomethyl)phenyl; (3-aminomethyl)phenyl; (2-hydroxymethyl)phenyl; (3-hydroxymethyl)phenyl; (2-phenyl)phenyl; (3-phenyl)phenyl; (2-halo)phenyl; (3-halo)phenyl; (2-$CONH_2$)phenyl; (3-$CONH_2$)phenyl; (2-CONH(C_{1-7})alkyl)phenyl; (3-CONH(C_{1-7})alkyl)phenyl; (2-$CO_2(C_{1-7})$alkyl)phenyl; (3-$CO_2(C_{1-7})$alkyl)phenyl; (2-NH_2)phenyl; (3-NH_2)phenyl; (2-(C_{3-7})alkyl)phenyl; (3-(C_{3-7})alkyl)phenyl; (2-(C_{3-7})cycloalkyl)phenyl; (3-(C_{3-7})cycloalkyl)phenyl; (2-aryl)phenyl; (3-aryl)phenyl; (2-heteroaryl)phenyl; (3-heteroaryl)phenyl; 2-bromo-5-fluoro phenyl; 2-chloro-5-fluoro phenyl; 2-cyano-5-fluoro phenyl; 2,5-dichloro phenyl; 2,5-difluoro phenyl; 2,5-dibromo phenyl; 2-bromo-3,5-difluoro phenyl; 2-chloro-3,5-difluoro phenyl; 2,3,5-trifluoro phenyl; 2,3,5,6-tetrafluorophenyl; 2-bromo-3,5,6-trifluoro phenyl; 2-chloro-3,5,6-trifluoro phenyl; 2-

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cyano-3,5-difluoro phenyl; 2-cyano-3,5,6-trifluoro phenyl; (2-heterocycloalkyl)phenyl; and (3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

40. The compound according to any one of claims 22-29, wherein X is selected from the group consisting of



wherein

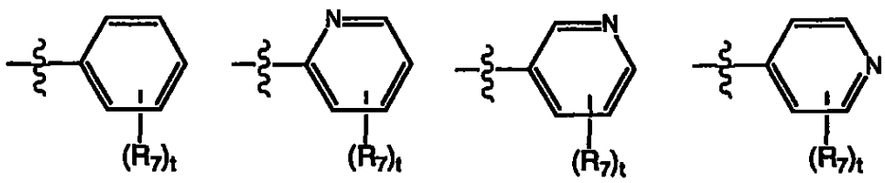
A is S, O or NR_{24};

B is CR_{23} or N;

R_{23} is independently selected from the group consisting of hydrogen, halo, perhalo(C_{1-10})alkyl, amino, thio, cyano, CF_3, nitro, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and

R_{24} is independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

41. The compound according to any one of claims 22-29, wherein X is selected from the group consisting of

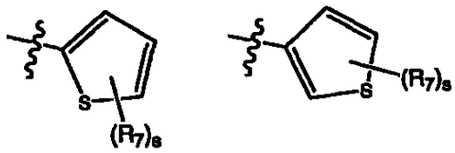


wherein

t is 0, 1, 2, 3, 4, or 5; and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

42. A compound according to any one of claims 22-29, wherein X is selected from the group consisting of



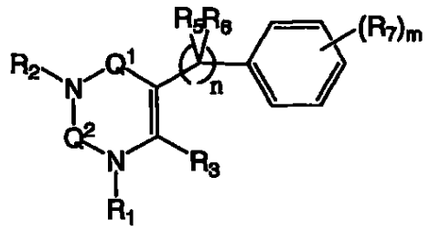
wherein

s is 0, 1, 2, or 3; and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

43. The compound according to claims 41 or 42 wherein R_7 is independently selected from the group consisting of -cyano, -methoxy, -nitro, -carboxy, -sulfonamido, -tetrazolyl, -aminomethyl, -hydroxymethyl, -phenyl, -halo, -$CONH_2$, -CONH(C_{1-7})alkyl, -CO_2(C_{1-7})alkyl, -NH_2, -OH, -(C_{1-5})alkyl, -alkenyl, -alkynyl, (C_{1-5})cycloalkyl, aryl, heteroaryl, and heterocycloalkyl, each substituted or unsubstituted.

44. A compound according to claim 29 comprising:



wherein

m is 0, 1, 2, 3, 4 or 5;

n is 1, 2, or 3;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

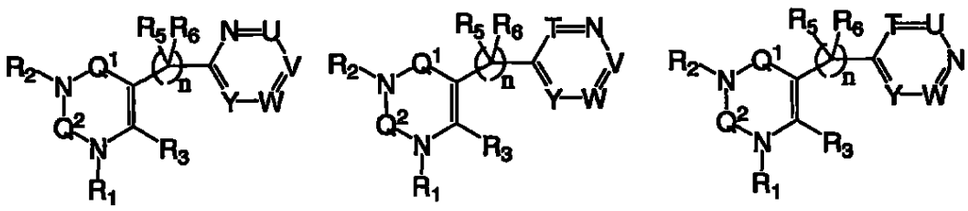
each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; and

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted.

45. A compound according to claim 29 comprising:

a member selected from the group consisting of



wherein

n is 1, 2, or 3;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2, and C=NR_9;

each of T, U, V, W and Y is independently nitrogen or CR_{16}, provided that no more than two of T, U, V, W and Y are nitrogen;

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl

(C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

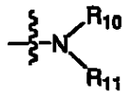
each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

each R_{16} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

46. The compound according to any one of claims 1-45 wherein R_3 is selected from the group consisting of amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring.

47. The compound according to any one of claims 1-45 wherein R_3 comprises the formula



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wherein R_{10} and R_{11} are each independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, and sulfinyl group, each substituted or unsubstituted, or R_{10} and R_{11} are taken together to form a 4, 5, 6, or 7 membered ring, each substituted or unsubstituted.

48. The compound according to any one of claims 1-45 wherein R_3 is a substituted or unsubstituted 3, 4, 5, 6, or 7 membered ring.

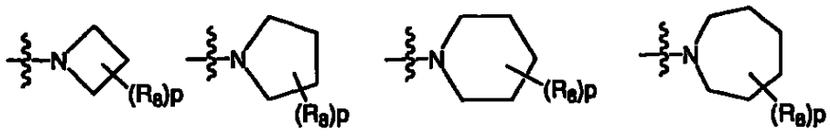
49. The compound according to any one of claims 1-45 wherein R_3 is a substituted or unsubstituted 3, 4, 5, 6, or 7 membered cycloalkyl.

50. The compound according to any one of claims 1-45 wherein R_3 is a substituted or unsubstituted 4, 5, 6, or 7 membered heterocycloalkyl.

51. The compound according to any one of claims 1-45 wherein R_3 is a substituted or unsubstituted aryl.

52. The compound according to any one of claims 1-45 wherein R_3 is a substituted or unsubstituted heteroaryl.

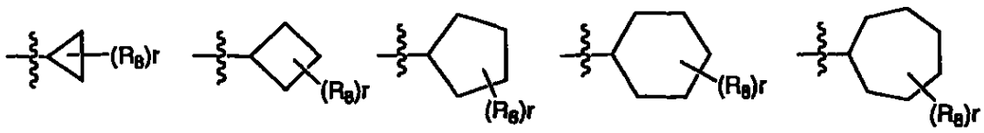
53. The compound according to any one of claims 1-45 wherein R_3 is selected from the group consisting of



wherein p is 0-12 and each R_8 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl,

alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

54. The compound according to any one of claims 1-45 wherein R_3 is selected from the group consisting of



wherein r is 0-13 and each R_8 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

55. The compound according to any one of claims 1-45, wherein R_3 is a substituted or unsubstituted heteroaryl selected from the group consisting of furan, thiophene, pyrrole, pyrazole, triazole, isoxazole, oxazole, thiazole, isothiazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, imidazole, benzimidazole, indole, isoindole, quinoline, isoquinoline, cinnoline, quinazoline, naphthyridine, pyridopyridine, quinoxaline, phthalazine, and benzothiazole, each substituted or unsubstituted.

56. The compound according to any one of claims 1-45, wherein R_3 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

57. The compound according to any one of claims 1-45, wherein R_3 is a substituted or unsubstituted (C_{3-7})cycloalkyl ring, optionally comprising O, N(O), N, S, SO, SO_2 or a carbonyl group in the ring.

58. The compound according to any one of claims 1-57 wherein R_3 is substituted such that R_3 comprises a substituent selected from the group consisting of a primary, secondary or tertiary amine, a heterocycloalkyl comprising a nitrogen ring atom, and a heteroaryl comprising a nitrogen ring atom.

59. The compound according to any one of claims 1-57 wherein R_3 comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein.

60. The compound of claim 59 wherein the basic nitrogen of R_3 is separated from the ring atom to which R_3 is attached by between 1-5 atoms.

61. The compound of claim 59 wherein the basic nitrogen atom forms part of a primary, secondary or tertiary amine.

62. The compound of claim 59 wherein the basic nitrogen atom is a nitrogen ring atom of a heterocycloalkyl or a heteroaryl.

63. The compound according to claim 53 or 54 wherein at least one R_8 comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein.

64. The compound of claim 63 wherein the basic nitrogen atom forms part of a primary, secondary or tertiary amine.

65. The compound of claim 63 wherein the basic nitrogen atom is a nitrogen ring atom of a heterocycloalkyl comprising a nitrogen ring atom or a heteroaryl comprising a nitrogen ring atom.

66. The compound according to claim 53 or 54 wherein at least one R_8 is a primary, secondary or tertiary amine.

67. The compound according to claim 53 or 54 wherein at least one R_8 is a substituted or unsubstituted heterocycloalkyl comprising a nitrogen ring atom or a substituted or unsubstituted heteroaryl comprising a nitrogen ring atom.

68. The compound according to claim 53 or 54 wherein at least one R_8 is selected from the group consisting of $-NH_2$, $-NH(C_{1-5}$ alkyl), $-N(C_{1-5}$ alkyl) $_2$, piperazine, imidazole, and pyridine.

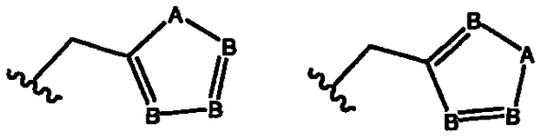
69. The compound according to any one of claims 1-45, wherein R_3 is selected from the group consisting of 3-amino-piperidinyl-1-yl, 3-aminomethyl-pyrrolidin-1-yl, 3-aminoazetidin-1-yl, 3-amino-3-methylpiperidin-1-yl, 3-aminocyclopent-1-yl, 3-aminomethylcyclopent-1-yl, 3-aminomethylcyclohex-1-yl, 3-aminohexahydroazepin-1-yl, 3-amino-cyclohex-1-yl, piperazin-1-yl, homopiperazin-1-yl, 3-amino-pyrrolidin-1-yl, R-3-aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, 3-amino-cyclohex-1-yl, 3-amino-cyclopent-1-yl, and 3-amino-pyrrolidin-1-yl, each substituted or unsubstituted.

70. The compound according to any one of claims 1, 2, 4-22, and 23-69, wherein at least one of Q^1 and Q^2 is CO.

71. The compound according to any one of claims 1, 2, 4-22, and 23-69, wherein Q^1 and Q^2 are CO.

72. The compound according to any one of claims 1-20, wherein M is nitrogen.

73. The compound according to any one of claims 1-20, wherein M is CR_4 and where R_4 is selected from the group consisting of



wherein

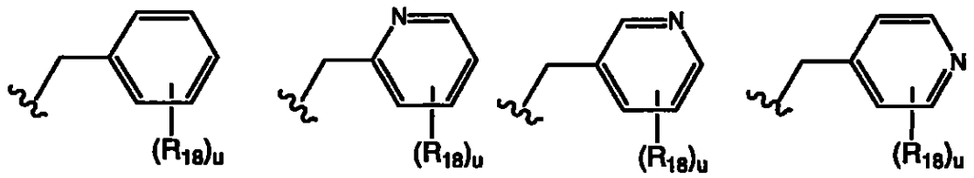
A is S, O or NR_{24};

B is CR_{23} or N;

R_{23} is independently selected from the group consisting of hydrogen, halo, perhalo(C_{1-10})alkyl, amino, thio, cyano, CF_3, nitro, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and

R_{24} is independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

74. The compound according to any one of claims 1-20, wherein M is CR_4 and where R_4 is selected from the group consisting of



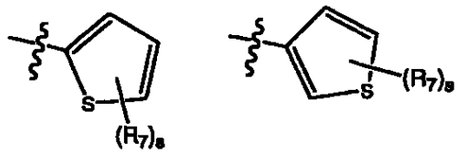
wherein

u is 0, 1, 2, 3, 4, or 5; and

each R_{18} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imine group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

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75. The compound according to any one of claims 1-20, wherein M is CR_4 and where R_4 is selected from the group consisting of



wherein

s is 0, 1, 2, or 3; and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

76. The compound according to any one of claims 10, 19, 20, 29, 44 and 45, wherein R_5 and R_6 are hydrogen.

77. The compound according to any one of claims 10, 19, 20, 29, 44 and 45, wherein R_5 and R_6 are halogen.

78. The compound according to any one of claims 10, 19, 20, 29, 44 and 45, wherein R_5 and R_6 are taken together to form a ring.

79. The compound according to any one of claims 10, 19, 20, 29, 44 and 45, wherein at least one of R_5 and R_6 is a substituted or unsubstituted -(C_{1-8})alkyleneR_{13}, wherein R_{13} is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{4-12})cycloalkyl, (C_{6-12})aryl, hetero(C_{5-12})aryl, (C_{9-12})bicycloalkyl, hetero(C_{9-12})bicycloalkyl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

80. The compound according to any one of claims 19 and 44, wherein R_5 and R_6 are hydrogen, m is 1 or 2, and each R_7 is independently selected from the group consisting of

halo, perhalo(C_{1-10})alkyl, CF_3, cyano, nitro, hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

81. The compound according to any one of claims 19 and 44, wherein two R_7 are taken together to form a substituted or unsubstituted fused or bridged ring.

82. The compound according to any one of claims 10, 19, 20, 29, 44 and 45, wherein:

n is 1, 2 or 3; and

R_5 and R_6 are hydrogen.

83. The compound according to any one of claims 10, 19, 20, 29, 44 and 45, wherein:

n is 1 or 2;

R_3 is selected from the group consisting of amino, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, and a substituted or unsubstituted 4, 5, 6 or 7 membered ring; and

R_5 and R_6 are hydrogen.

84. The compound according to any one of claims 19 and 44, wherein: R_5 and R_6 are hydrogen and R_7 is 2-cyano.

85. The compound of claim 84, wherein n is 1.

86. The compound according to any one of claims 10, 19, 20, 29, 44 and 45, wherein:

n is 1, 2 or 3;

R_5 and R_6 are hydrogen; and

R_3 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

87. The compound according to any one of claims 19 and 44, wherein:

n is 1, 2 or 3;

R_5 and R_6 are hydrogen; and

each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, alkenyl, alkynyl, CF_3, cyano, nitro, hydroxy, heteroaryl, aryloxy, heteroaryloxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

88. The compound according to any one of claims 16, 17, 19 and 41-44, wherein: two R_7 are taken together to form a substituted or unsubstituted fused ring.

89. The compound according to any one of claims 16, 17, 19 and 41-44, wherein: two R_7 are taken together to form a substituted or unsubstituted bridged ring.

90. The compound according to any one of claims 20 and 45, wherein two of T, U, V, W and Y are taken together and substituted through available valencies to form a substituted or unsubstituted ring fused or bridged to the ring formed by T U, V, W and Y.

91. The compound according to any one of claims 1-90, wherein R_2 is a substituted or unsubstituted (C_{1-10})alkyl.

92. The compound according to any one of claims 1-90, wherein R_2 is a substituted or unsubstituted (C_{1-4})alkyl.

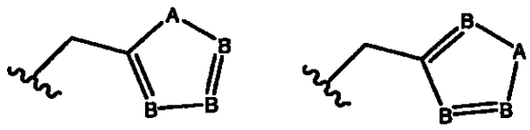
93. The compound according to any one of claims 1-90, wherein R_2 is -Y-Z wherein

Y a linker providing 1, 2 or 3 atom separation between Z and the ring to which Y is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

Z is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl,

sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

94. The compound according to any one of claims 1-90, wherein R_2 is selected from the group consisting of



wherein

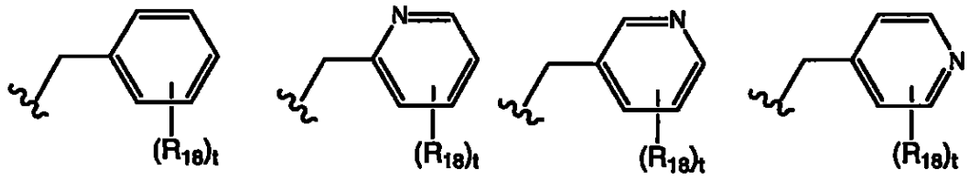
A is S, O or NR_{24};

B is CR_{23} or N;

R_{23} is independently selected from the group consisting of hydrogen, halo, perhalo(C_{1-10})alkyl, amino, thio, cyano, CF_3, nitro, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and

R_{24} is independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

95. The compound according to any one of claims 1-90, wherein R_2 is selected from the group consisting of



wherein

t is 0, 1, 2, 3, 4, or 5; and

each R_{18} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imine group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

96. A compound according to any one of claims 1-95 selected from the group consisting of:

2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

2-{6-[Azepan-3(±)-ylamino]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (14);

2-{6-[3(±)-Amino-azepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;

3-{4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester;

3-{4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid;

6-[3-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione;

2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-*di*-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-*di*-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

(R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile; and

2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile.

97. A compound according to any one of claims 1-95 selected from the group consisting of:

2-{6-[3(R)-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;

3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester;

3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid;

6-[3(R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione; and

2-{6-(3(R)-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile.

98. The compound according to any one of claims 1-97, wherein the compound is in the form of a pharmaceutically acceptable salt.

99. The compound according to any one of claims 1-98, wherein the compound is present in a mixture of stereoisomers.

100. The compound according to any one of claims 1-98, wherein the compound comprises a single stereoisomer.

101. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of claims 1-100.

102. The pharmaceutical composition according to claim 101, wherein the composition is a solid formulation adapted for oral administration.

103. The pharmaceutical composition according to claim 101, wherein the composition is a tablet.

104. The pharmaceutical composition according to claim 101, wherein the composition is a liquid formulation adapted for oral administration.

105. The pharmaceutical composition according to claim 101, wherein the composition is a liquid formulation adapted for parenteral administration.

106. The pharmaceutical composition comprising a compound according to any one of claims 1-100, 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.

107. A kit comprising:

a compound according to any one of claims 1-100 or a composition according to any one of claims 101-106; 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.

108. The kit according to claim 107, wherein the kit comprises the compound in a multiple dose form.

109. An article of manufacture comprising:

a compound according to any one of claims 1-100; and

packaging materials.

110. The article of manufacture of claim 109, wherein the packaging material comprises a container for housing the compound.

111. The article of manufacture of claim 110, 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 composition.

112. The article of manufacture of claim 109, wherein the article of manufacture comprises the compound in a multiple dose form.

113. A method of inhibiting DPP-IV comprising:

contacting DPP-IV with a compound according to any one of claims 1-100.

114. A method of inhibiting DPP-IV comprising:

causing a compound according to any one of claims 1-100 to be present in a subject in order to inhibit DPP-IV *in vivo*.

115. A method of inhibiting DPP-IV comprising:

administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits DPP-IV *in vivo*, the second compound being a compound according to any one of claims 1-100.

116. A therapeutic method comprising:

administering a compound according to any one of claims 1-100 to a subject.

117. A method of treating a disease state for which DPP-IV 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 1-100 to be present in a subject in a therapeutically effective amount for the disease state.

118. The method according to claim 117, wherein the disease is type I or type II diabetes.

119. A method of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to any one of claims 1-100.

120. The method of claim 119, wherein the cancer treated is colorectal, prostate, breast, thyroid, skin, lung, or head and neck.

121. A method of treating autoimmune disorders such as, but not limited to, rheumatoid arthritis, psoriasis, and multiple sclerosis in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to any one of claims 1-100.

122. A method of treating HIV infection in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to any one of claims 1-100.

123. A method of treating a condition characterized by inadequate lymphocyte or hemapoietic cell activation or concentration in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to any one of claims 1-100.

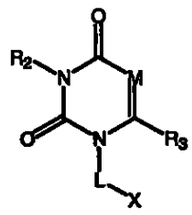
123. The method of claim 123, wherein said condition is a side effect of chemotherapy or radiation therapy.

125. The method of claim 123, wherein said condition is a result of kidney failure.

126. The method of claim 123, wherein said condition is a result of a bone marrow disorder.

127. A method of treating a condition characterized by immunodeficiency symptoms in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to any one of claims 1-100.

128. A process for producing a pyrimidin-dione of the formula:



wherein

M is N or CR_4;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino $(C_{1-}$

$_3$)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

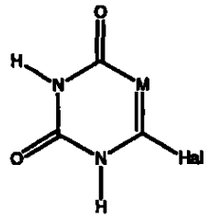
R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

the process comprising the steps of:

(i) contacting a compound of the formula **A**



A

wherein Hal is halogen;

with a compound of the formula **B**

X—L—LG **B**

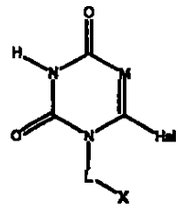
wherein LG is a leaving group;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the

separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

under conditions sufficient to produce a compound of the formula C



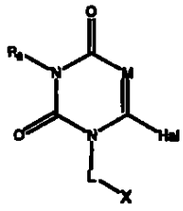
C

(ii) contacting the compound of formula C with a compound of formula D

$$R_2—LG' \qquad D$$

wherein LG' is a leaving group;

under conditions sufficient to produce a compound of the formula E;



E

wherein R_2 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; and

(iii) contacting the compound of formula E with a compound of formula R_3-H under conditions sufficient to produce the pyrimidin-dione.

129. The process of Claim 128, wherein the pyrimidin-dione product is further converted to an acid addition salt.

130. The process of Claim 129, wherein the acid addition salt is selected from the group consisting of acetate, citrate, hydrochloride, L-lactate, succinate, sulfate, p-toluenesulfonate, benzenesulfonate, benzoate, methanesulfonate, naphthylene-2-sulfonate, propionate, p-toluenesulfonate, hydrobromate, hydroiodate, R-mandelate, and L-tartrate.

131. The process of Claim 128, wherein Hal is selected from the group consisting of Br, Cl and F in the compound of formula A.

132. The process of Claim 128, wherein the leaving group LG is selected from the group consisting of Br, Cl and I.

133. The process of Claim 128, wherein step (ii) further comprises the addition of a base.

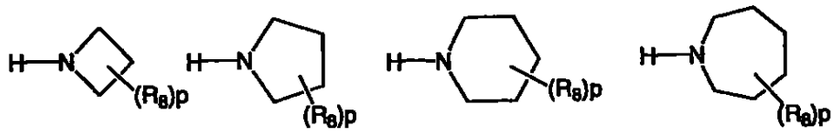
134. The process of Claim 133, wherein the base is potassium carbonate.

135. The process of Claim 128, wherein product E is further purified before subjecting to step (iii).

136. The process of Claim 135, wherein the purification of product E is performed by solvent washes and/or by chromatography.

137. The process of Claim 128, wherein R_3-H is a secondary amine or an amine hydrochloride.

138. The process of Claim 128, wherein R_3-H is selected from the group consisting of



wherein p is 0-12 and each R_8 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, or the mono- or di-hydrochloride salt.

139. The process of Claim 128, wherein step iii) further comprises a purification step of washing of the product with organic solvents or mixture of solvents and/or by column chromatography.

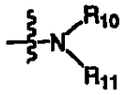
140. The process of Claim 128, wherein L is selected from the group consisting of –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -C(O)-, -$CH_2C(O)$-, -$C(O)CH_2$-, -CH_2-$C(O)CH_2$-, -$C(O)CH_2CH_2$-, -$CH_2CH_2C(O)$-, -O-, -OCH_2-, -CH_2O-, -CH_2OCH_2-, -OCH_2CH_2-, -CH_2CH_2O-, -$N(CH_3)$-, -$NHCH_2$-, -CH_2NH-, -CH_2NHCH_2-, -$NHCH_2CH_2$-, -CH_2CH_2NH-, -NH-C(O)-, -NCH_3-C(O)-, -C(O)NH-, -$C(O)NCH_3$-, -$NHC(O)CH_2$-, -$C(O)NHCH_2$-, -$C(O)CH_2NH$-, -$CH_2NHC(O)$-, -$CH_2C(O)NH$-, -$NHCH_2C(O)$-, -S-, -SCH_2-, -CH_2S-, -SCH_2CH_2-, -CH_2SCH_2-, -CH_2CH_2S-, -C(O)S-, -$C(O)SCH_2$-, -$CH_2C(O)S$-, -$C(O)CH_2S$-, and -$CH_2SC(O)$-, each substituted or unsubstituted.

141. The process of Claim 140, wherein L is selected from the group consisting of -CH_2-, -C(O)-, -$CH_2C(O)$-, -$C(O)CH_2$-, -CH_2-$C(O)CH_2$-, -$C(O)CH_2CH_2$-, and -$CH_2CH_2C(O)$-, each substituted or unsubstituted.

142. The process of Claim 128, wherein -L-X taken together is selected from the group consisting of -(CH_2)-(2-cyano)phenyl; -(CH_2)-(3-cyano)phenyl; -(CH_2)-(2-hydroxy)phenyl; -(CH_2)-(3-hydroxy)phenyl; -(CH_2)-(2-alkenyl)phenyl; -(CH_2)-(3-alkenyl)phenyl; -(CH_2)-

(2-alkynyl)phenyl; -(CH_2)-(3-alkynyl)phenyl; -(CH_2)-(2-methoxy)phenyl; -(CH_2)-(3-methoxy)phenyl; -(CH_2)-(2-nitro)phenyl; -(CH_2)-(3-nitro)phenyl; -(CH_2)-(2-carboxy)phenyl; -(CH_2)-(3-carboxy)phenyl; -(CH_2)-(2-carboxamido)phenyl; -(CH_2)-(3-carboxamido)phenyl; -(CH_2)-(2-sulfonamido)phenyl; -(CH_2)-(3-sulfonamido)phenyl; -(CH_2)-(2-tetrazolyl)phenyl; -(CH_2)-(3-tetrazolyl)phenyl; -(CH_2)-(2-aminomethyl)phenyl; -(CH_2)-(3-aminomethyl)phenyl; -(CH_2)-(2-hydroxymethyl)phenyl; -(CH_2)-(3-hydroxymethyl)phenyl; -(CH_2)-(2-phenyl)phenyl; -(CH_2)-(3-phenyl)phenyl; -(CH_2)-(2-halo)phenyl; -(CH_2)-(3-halo)phenyl; -(CH_2)-(2-$CONH_2$)phenyl; -(CH_2)-(3-$CONH_2$)phenyl; -(CH_2)-(2-$CONH(C_{1-7})$alkyl)phenyl; -(CH_2)-(3-$CONH(C_{1-7})$alkyl)phenyl; -(CH_2)-(2-$CO_2(C_{1-7})$alkyl)phenyl; -(CH_2)-(3-$CO_2(C_{1-7})$alkyl)phenyl; -(CH_2)-(2-NH_2)phenyl; -(CH_2)-(3-NH_2)phenyl; -(CH_2)-(2-(C_{3-7})alkyl)phenyl; -(CH_2)-(3-(C_{3-7})alkyl)phenyl; -(CH_2)-(2-(C_{3-7})cycloalkyl)phenyl; -(CH_2)-(3-(C_{3-7})cycloalkyl)phenyl; -(CH_2)-(2-aryl)phenyl; -(CH_2)-(3-aryl)phenyl; -(CH_2)-(2-heteroaryl)phenyl; -(CH_2)-(3-heteroaryl)phenyl; -(CH_2)-2-bromo-5-fluoro phenyl; -(CH_2)-2-chloro-5-fluoro phenyl; -(CH_2)-2-cyano-5-fluoro phenyl; -(CH_2)-2,5-dichloro phenyl; -(CH_2)-2,5-difluoro phenyl; -(CH_2)-2,5-dibromo phenyl; -(CH_2)-2-bromo-3,5-difluoro phenyl; -(CH_2)-2-chloro-3,5-difluoro phenyl; -(CH_2)-2,3,5-trifluoro phenyl; -(CH_2)-2,3,5,6-tetrafluorophenyl; -(CH_2)-2-bromo-3,5,6-trifluoro phenyl; -(CH_2)-2-chloro-3,5,6-trifluoro phenyl; -(CH_2)-2-cyano-3,5-difluoro phenyl; -(CH_2)-2-cyano-3,5,6-trifluoro phenyl; -(CH_2)-(2-heterocycloalkyl)phenyl; and -(CH_2)-(3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

143. The process of Claim 128, wherein M is CH, and R_3 comprises the formula

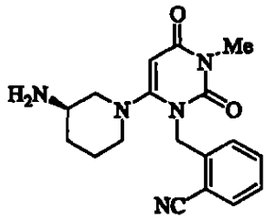


wherein R_{10} and R_{11} are each independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, and sulfinyl group, each substituted or unsubstituted, or R_{10} and R_{11} are taken together to form a 4, 5, 6, or 7 membered ring, each substituted or unsubstituted.

144. The process of Claim 128, wherein M is CH, and wherein R_3 is selected from the group consisting of 3-amino-piperidinyl-1-yl, 3-aminomethyl-pyrrolidin-1-yl, 2-aminoazetidin-1-yl, 3-amino-3-methylpiperidin-1-yl, 3-aminocyclopent-1-yl, 3-aminomethylcyclopent-1-yl, 3-aminomethylcyclohex-1-yl, 3-aminohexahydroazepin-1-yl, 3-amino-cyclohex-1-yl, piperazin-1-yl, homopiperazin-1-yl, 3-amino-pyrrolidin-1-yl, R-3-aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, 3-amino-cyclohex-1-yl, 3-amino-cyclopent-1-yl, and 3-amino-pyrrolidin-1-yl, each substituted or unsubstituted.

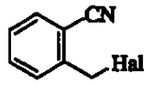
145. The process of Claim 128, wherein M is CH, and wherein R_2 is a substituted or unsubstituted (C_{1-10})alkyl.

146. The process of claim 128 for producing a pyrimidin-dione of the formula

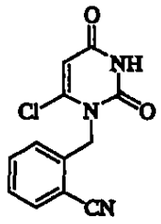


comprising:

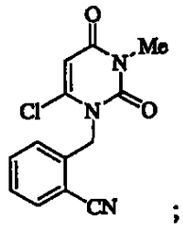
(i) admixing 6-chloro-1H-pyrimidine-2,4-dione with an aryl halide of the formula



where Hal is Br, Cl, or I, under condition sufficient to produce a compound of the formula

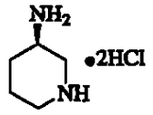


(ii) alkylating the above product with a methyl halide under conditions sufficient to form a compound of the formula



; and

(iii) condensing the above product with a compound of the formula



147. The process for producing a pyrimidin-dione of Claim 146, further comprising the formation of the acid addition salt.

148. The process of Claim 147, wherein the acid addition salt is the benzoate salt.

149. The process of claim 128 wherein the pyrimidin-dione is selected from the group consisting of:

2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

2-{6-[Azepan-3(±)-ylamino]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (14);

2-{6-[3(±)-Amino-azepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;

3-{4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester;

3-{4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid;

2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-*di*-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-*di*-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

(R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile; and

6-[3-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione.

150. The process of claim 128, wherein the pyrimidin-dione is selected from the group consisting of:

2-{6-[3(R)-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile;

6-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;

3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester;

3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid; and

6-[3(R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione.

151. The process of claim 128, wherein the pyrimidin-dione is present in a mixture of stereoisomers.

152. The process of claim 128, wherein the pyrimidin-dione comprises a single stereoisomer.

153. A compound according to any one of claims 1-100 for use as a medicament.

154. Use of a compound according to any one of claims 1-100 in the manufacture of a medicament for inhibiting DPP-IV.

155. Use of a compound according to any one of claims 1-100 in the manufacture of a medicament for treating a disease state for which DPP-IV possess activity that contributes to the pathology and/or symptomology of the disease state.

156. Use of a compound according to any one of claims 1-100 in the manufacture of a medicament for treating cancer.

157. Use of a compound according to any one of claims 1-100 in the manufacture of a medicament for treating type I or type II diabetes.

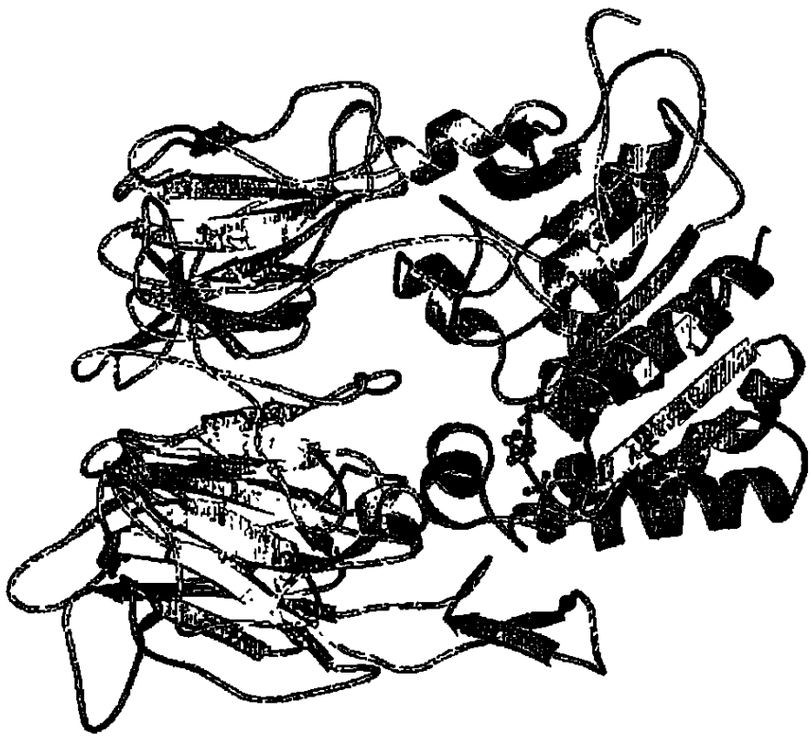
158. Use of a compound according to any one of claims 1-100 in the manufacture of a medicament for treating autoimmune disorders.

159. Use of a compound according to any one of claims 1-100 in the manufacture of a medicament for treating a condition characterized by inadequate lymphocyte or hemapoietic cell activation or concentration.

160. Use of a compound according to any one of claims 1-100 in the manufacture of a medicament for treating HIV infection.

161. Use of a compound according to any one of claims 1-100 in the manufacture of a medicament for treating a condition characterized by immunodeficiency symptoms.

FIGURE 1



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/042209

912

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 C07D401/12 C07D401/14 A61K31/506 A61P3/10 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)
IPC 7 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, PAJ, WPI Data, 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.
P,A	WEBER, A.E.: "DIPEPTIDYL PEPTIDASE IV INHIBITORS FOR THE TREATMENT OF DIABETES" JOURNAL OF MEDICINAL CHEMISTRY, vol. 47, 2004, pages 4135-4141, XP002329845 figure 2	1-161
A	WO 03/035057 A (FERRING B.V; EVANS, DAVID, MICHAEL; ASHWORTH, DOREEN, MARY) 1 May 2003 (2003-05-01) the whole document	1-161
X	PATENT ABSTRACTS OF JAPAN vol. 2003, no. 12, 5 December 2003 (2003-12-05) & JP 2003 300977 A (SUMITOMO PHARMACEUT CO LTD), 21 October 2003 (2003-10-21) abstract	1-161
	-/—	

[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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"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 May 2005	14/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Baston, E

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/042209

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DE 21 50 686 A1 (BADISCHE ANILIN- & SODA-FABRIK AG) 19 April 1973 (1973-04-19) claim 1	1-161
X	EP 0 442 473 A (TAKEDA CHEMICAL INDUSTRIES, LTD) 21 August 1991 (1991-08-21) tables 1a-4a,5	1-161
X	BOTTA, M., SALADINO, R., LAMBA, D., NICOLETTI, R.: "Researches on Antiviral Agents. 31. Synthesis and Transformations of Racemic and Chiral 6-Oxiranyl Pyrimidinones" TETRAHEDRON, vol. 49, 1993, pages 6053-6070, XP002329846 examples 3,6	1
X	FRAISSE, L. ET AL.: "Long-Chain-Substituted Uric Acid and 5,6-Diaminouracil Derivatives as Novel Agents against Free Radical Processes: Synthesis and in Vitro Activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, 1993, pages 1465-1473, XP002329847 example 4k	1
X	KIM, H.O. ET AL.: "Structure-Activity Relationships of 1,3-Dialkylxanthine Derivatives at Rat A3 adenosine Receptors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, 1994, pages 3373-3382, XP002329848 example 38b	1

INTERNATIONAL SEARCH REPORT

information on patent family members

Interna[redacted]al Application No
PCT/US2004/042209

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03035057 A	01-05-2003	CA 2464254 A1	01-05-2003
		CN 1571667 A	26-01-2005
		EP 1446116 A1	18-08-2004
		WO 03035057 A1	01-05-2003
		HU 0401738 A2	28-12-2004
		JP 2005511541 T	28-04-2005
		MX PA04003829 A	16-07-2004
		NZ 532048 A	29-10-2004
		US 2005043299 A1	24-02-2005
JP 2003300977 A	21-10-2003	NONE	
DE 2150686 A1	19-04-1973	NONE	
EP 0442473 A	21-08-1991	AT 169915 T	15-09-1998
		CA 2036304 A1	16-08-1991
		DE 69129998 D1	24-09-1998
		DE 69129998 T2	24-12-1998
		EP 0442473 A1	21-08-1991
		JP 3032844 B2	17-04-2000
		JP 4330072 A	18-11-1992
		US 5162326 A	10-11-1992

INHIBIDORES DE DIPEPTIDIL PEPTIDASA

CAMPO DE LA INVENCIÓN

La invención se relaciona con compuestos que pueden usarse para inhibir dipeptidil peptidasas, así como composiciones y equipos que comprenden estos compuestos. La presente invención también se relaciona con métodos para inhibir dipeptidil peptidasas, así como métodos de tratamiento que usan compuestos de acuerdo con la presente invención.

DESCRIPCIÓN DE LA TÉCNICA RELACIONADA

La dipeptidil peptidasa IV (Nomenclatura Enzimática de la IUBMB EC,3,4,14,5) es una proteína de membrana tipo II, conocida en la literatura a través de una variedad de nombres, incluyendo DPP4, DP4, DAP-IV, FAPβ, proteína formadora de complejos de adenosina deaminasa 2, proteína de unión a adenosina deaminasa (ADAbp), dipeptidil aminopeptidasa IV; Xaa-Pro-dipeptidil-aminopeptidasa; Gly-Pro naftilamidasa; postprolina dipeptidil aminopeptidasa IV; antígeno de linfocitos CD26; glicoproteína GP110; dipeptidil peptidasa IV; glicilprolina aminopeptidasa; glicilprolina aminopeptidasa; X-prolil dipeptidil aminopeptidasa; pep X; antígeno de leucocitos CD26; glicilprolil dipeptidilaminopeptidasa; dipeptidil-péptido hidrolasa; glicilprolil aminopeptidasa; dipeptidil-aminopeptidasa IV; DPP IV/CD26; amino acil-prolil dipeptidil aminopeptidasa; molécula activadora de células T Tp103; X-PDAP. En la presente documentación, se conoce la dipeptidil peptidasa IV como "DPP-IV".

La DPP-IV es una serina aminodipeptidasa no clásica que retira dipéptidos Xaa-Pro del extremo amino (extremo N) de los polipéptidos y las proteínas. También se ha descripto la liberación lenta de péptidos del tipo X-Gly o X-Ser dependiente de DPP-IV para algunos péptidos de°Currencia natural.

La DPP-IV se expresa en forma constitutiva en las células epiteliales y endoteliales de una variedad de tejidos (intestino, hígado, pulmón, riñón y placenta), y también se halla en fluidos corporales. La DPP-IV también se expresa en los linfocitos T en circulación, y se ha demostrado que es sinónimo del antígeno superficial celular CD-26. También se ha implicado la DPP-IV en una cantidad de estados de enfermedad, algunos de los cuales se describirán más adelante.

La DPP-IV es responsable del corte metabólico de determinados péptidos endógenos (GLP-I (7-36), glucagon) in vivo, y ha demostrado poseer actividad proteolítica contra una variedad de otros péptidos (GHRH, NPY, GLP-2, VIP) in vitro.

GLP-I (7-36) es un péptido de 29 aminoácidos derivado del procesamiento post-traduccional del proglucagon en el intestino delgado. GLP-I (7-36) tiene diversas funciones in vivo, incluyendo la estimulación de la secreción de insulina, la inhibición de la secreción de glucagon, la promoción de la saciedad y la disminución de la velocidad de la evacuación gástrica. Sobre la base de su perfil fisiológico, se cree que las acciones de GLP-I (7-36) son beneficiosas para la prevención y el tratamiento de la diabetes tipo II y la obesidad potencial. Por ejemplo, se ha descubierto que la administración exógena de GLP-I (7-36) (infusión continua) es eficaz en la población de pacientes diabéticos. Desafortunadamente, GLP-I (7-36) se degrada rápidamente in vivo, y se ha demostrado que presenta una vida media corta in vivo ($t_{1/2}$ = 1,5 minutos).

Sobre la base de un estudio en ratones knock out para DPP-IV desarrollados genéticamente, y estudios in vivo/in vitro con inhibidores selectivos de DPP-IV, se ha demostrado que DPP-IV es la enzima primaria de degradación

de GLP-I (7-36) in vivo. GLP-I (7-36) es degradado por DPP-IV en forma eficiente para formar GLP-I (9-36), del que se ha especulado que actúa como antagonista fisiológico de GLP-I (7-36). Por ende, se cree que la inhibición de DPP-IV in vivo es útil para potenciar los niveles endógenos de GLP-I (7-36) y atenuar la formación de su antagonista, GLP-I (9-36). Por consiguiente, se cree que los inhibidores de DPP-IV son agentes útiles para prevenir, demorar la progresión y/o tratar condiciones mediadas por DPP-IV, en particular la diabetes, y más particularmente la diabetes mellitus tipo 2, la dislipidemia diabética, condiciones de tolerancia alterada a la glucosa (IGT), condiciones de glucosa en plasma en ayuno alterada (IFG), la acidosis metabólica, la cetosis, la regulación del apetito y la obesidad.

La expresión de DPP-IV aumenta en las células T al presentarse una estimulación mitogénica o antigénica (Mattem, T., et al., Scand. J. Immunol., 1991, 33, 737). Se ha informado que los inhibidores de DPP-IV y los anticuerpos de DPP-IV suprimen la proliferación de las células T estimuladas por mitógenos y estimuladas por antígeno, de una manera dependiente de la dosis (Schon, E., et al., Biol. Chem., 1991, 372, 305). Se ha demostrado que varias otras funciones de los linfocitos T, tales como la producción de citoquina, la proliferación celular mediada por IL-2 y la actividad de las células B ayudantes depende de la actividad de DPP-IV (Schon, E., et al., Scand. J. Immunol., 1989, 29, 127). Los inhibidores de DPP-IV, basados en boroProlina, (Flentke, G. R., et al., Proc. Nat. Acad. Sci. USA, 1991, 88, 1556), aunque resultaron inestables, fueron efectivos para inhibir la proliferación de linfocitos inducida por antígenos y la producción de IL-2 en células T CD4+ ayudantes murinas. Se ha demostrado que dichos inhibidores del ácido borónico presentan un efecto in vivo en ratones, provocando la supresión de

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la producción de anticuerpos inducida por ataques al sistema inmune (Kubota, T. et al., Clin. Exp. Immun., 1992, 89, 192). La función de DPP-IV en la regulación de la activación de los linfocitos T también puede atribuirse, en parte, a su asociación en la superficie celular con la fosfatasa transmembrana, CD45. Los inhibidores de DPP-IV, o los ligandos para sitios no activos, pueden alterar posiblemente la asociación CD45-DPP-IV Se sabe que CD45 es un componente integral del aparato de señalización de las células T. Se ha informado que DPP-IV es esencial para la penetración y la infectividad de los virus HIV-1 y HIV-2 en células T CD4+ (Wakselman, M., Nguyen, C., Mazaleyrat, J.-P., Callebaut, C., Krust, B., Hovanessian, A. G., Inhibition de HIV-1 infection de CD 26+ but not CD 26-cells by a potent ciclopeptidic inhibitor of the DPP-IV activity of CD 26. Resumen en la P,44 del 24° Simposio Europeo de Péptidos de 1996). Adicionalmente, se ha demostrado que DPP-IV se asocia con la enzima adenosina deaminasa (ADA) sobre la superficie de las células T (Kameoka, J., et al., Science, 193, 26 466). La deficiencia de ADA provoca una enfermedad de inmunodeficiencia severa combinada (SCID) en seres humanos. Esta interacción ADA-CD26 puede proporcionar datos sobre la patofisiología SCID. Puede concluirse que los inhibidores de DPP-IV pueden ser útiles como inmunosupresores (o drogas supresoras de la liberación de citoquinas) para el tratamiento, entre otras cosas, del rechazo a los transplantaes de órganos, enfermedades autoinmunes, tales como la enfermedad intestinal inflamatoria, la esclerosis múltiple y la artritis reumatoide, y el tratamiento del SIDA.

Se ha demostrado que la DPP-IV de las células endoteliales pulmonares es una molécula de adhesión para las células de carcinoma metatstásico de pulmón en mama y próstata de rata (Johnson, R. C., et al., J. Cell. Biol., 1993, 121, 1423).

Se sabe que la DPP-IV se une a la fibronectina, y se sabe que algunas células tumorales metastásicas contienen grandes cantidades de fibronectina en su superficie. Los inhibidores potentes de DPP-IV pueden ser útiles como drogas para prevenir la metástasis, por ejemplo, de tumores de mama y próstata, en los pulmones.

También se han hallado niveles elevados de expresión de DPP-IV en fibroblastos de piel humana en pacientes con psoriasis, artritis reumatoide (RA) y liquen plano (Raynaud, F., et al., J. Cell. Physiol., 1992, 151, 378). Entonces, los inhibidores de DPP-IV pueden ser útiles como agentes para tratar enfermedades dermatológicas, tales como psoriasis y liquen plano.

Se ha descubierto actividad elevada de DPP-IV en homogenatos de tejido de pacientes con hipertrofia prostática benigna y en prostatosomas. Éstos son organelas derivadas de la próstata, importantes para mejorar la motilidad de desplazamiento del esperma (Vanhoof, G., et al., Eur. J. Clin. Chem. Clin. Biochem., 1992, 30, 333). Los inhibidores de DPP-IV también pueden actuar para suprimir la motilidad del esperma y, por lo tanto, pueden actuar como agentes anticonceptivos masculinos. Del mismo modo, se han implicado los inhibidores de DPP-IV como agentes novedosos para el tratamiento de la infertilidad, y particularmente la infertilidad femenina humana debida al síndrome de ovarios poliquísticos (PCOS, síndrome de Stein-Leventhal), que es una condición caracterizada por el engrosamiento de la cápsula del ovario y la formación de múltiples quistes foliculares, que resulta en infertilidad y amenorrea.

Se cree que DPP-IV participa en el corte de varias citoquinas (estimulando las células hematopoyéticas), factores de crecimiento y neuropéptidos.

Las células hematopoyéticas estimuladas son útiles para tratar trastornos

caracterizados por una cantidad reducida de células hematopoyéticas o sus precursores in vivo. Dichas condiciones°Curren frecuentemente en pacientes inmunosuprimidos, por ejemplo, como consecuencia de la quimioterapia y/o la terapia con radiación para tratar el cáncer. Se descubrió que los inhibidores de la dipeptidil peptidasa tipo IV son útiles para estimular el crecimiento y la diferenciación de las células hematopoyéticas, en ausencia de citoquinas, factores de crecimiento o células estromáticas agregadas en forma exógena. Este descubrimiento contradice el dogma en el campo de la estimulación de las células hematopoyéticas, que establece que la adición de citoquinas, o células que producen citoquinas (células estromáticas), es un elemento esencial para mantener y estimular el crecimiento y la diferenciación de las células hematopoyéticas en cultivo (véase, por ejemplo, la Solicitud Internacional PCT N° PCT /US93/017173, publicada como WO 94/03055).

Se ha demostrado que la DPP-IV en plasma humano corta el fragmento Tyr-Ala N-terminal del factor liberador de hormona de crecimiento, y provoca la inactivación de esta hormona. Por lo tanto, los inhibidores de DPP-IV pueden ser útiles en el tratamiento de la estatura baja debida a deficiencias de hormonas de crecimiento (enanismo), y en la promoción del crecimiento o la regeneración tisular dependiente de GH.

La DPP-IV también puede cortar neuropéptidos, y se ha demostrado que modula la actividad de la sustancia peptídica neuroactiva P, el neuropéptido e Y CLIP (Mentlein, R., Dahms, P., Grandt, D., Kruger, R., Proteolytic processing de neuropeptide e Y peptide YY by dipeptidyl peptidase IV, Regul. Pept., 49, 133, 1993; Wetzel, W., Wagner, T., Vogel, D., Demuth, H.-U., Balschun, D., Effects of the CLIP fragment ACTH 20-24 on the duration of REM sleep episodes,

Neuropeptides, 31, 41, 1997). Por consiguiente, los inhibidores de DPP-IV también pueden ser útiles como agentes para regular o normalizar trastornos neurológicos.

Se ha demostrado que varios compuestos inhiben la DPP-IV. Sin embargo, aún subsiste la necesidad de nuevos inhibidores de DPP-IV que tengan una potencia, una estabilidad, una selectividad, una toxicidad y/o propiedades farmacodinámicas ventajosas. En este caso, se provee una nueva clase de inhibidores de DPP-IV en la presente documentación.

RESUMEN DE LA INVENCIÓN

La presente invención se relaciona con compuestos que tienen actividad de inhibición de DPP-IV. Puede destacarse que estos compuestos también pueden tener actividad de inhibición de otras proteasas S9, y, por consiguiente, pueden usarse contra estas proteasas S9, tal como contra DPP-IV. La presente invención también provee composiciones, artículos de manufactura y equipos que comprenden estos compuestos.

En una realización, se proporciona una composición farmacéutica que comprende un inhibidor de DPP-IV, 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 DPP-IV de esta invención. Estas composiciones farmacéuticas pueden administrarse o coadministrarse empleando una variedad de rutas, incluyendo, por ejemplo, vía oral, parenteral, intrapentoneal, 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. Las composiciones también pueden administrarse o coadministrarse en formas de dosificación de liberación lenta.

La invención también se relaciona con equipos y otros artículos de manufactura para tratar estados de enfermedad asociados con DPP-IV.

En una realización, se proporciona un equipo que comprende una composición que comprende al menos un inhibidor de DPP-IV 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 DPP-IV 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.

También se proporcionan métodos para usar los compuestos, las composiciones, los equipos y artículos de manufactura de acuerdo con la presente invención.

En una realización, se usan los compuestos, las composiciones, los equipos y los artículos de manufactura para inhibir DPP-IV.

En otra realización, se usan los compuestos, las composiciones, los equipos y los artículos de manufactura para tratar una enfermedad, donde DPP-IV 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 DPP-IV 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 DPP-IV.

En otra realización, se proporciona un método para inhibir DPP-IV, que comprende poner en contacto DPP-IV con un compuesto de acuerdo con la presente invención.

En otra realización, se proporciona un método para inhibir DPP-IV, que comprende administrar un compuesto de acuerdo con la presente invención a un sujeto, con el fin de inhibir DPP-IV.

En otra realización, se proporciona un método para inhibir DPP-IV, que

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comprende administrar un primer compuesto a un sujeto, que se convierte in vivo en un segundo compuesto, donde el segundo compuesto inhibe DPP-IV 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 inhibir la proliferación celular, que comprende poner en contacto una cantidad con una cantidad efectiva de un compuesto de acuerdo con la presente invención.

En otra realización, se proporciona un método para inhibir la proliferación celular en un paciente, que comprende administrar al paciente una cantidad efectiva para el uso terapéutico de 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 DPP-IV, o de la que se sabe que puede tratarse con inhibidores de DPP-IV, que comprende administrar al paciente una cantidad efectiva para el uso terapéutico de un compuesto de acuerdo con la presente invención.

En otra realización, se proporciona un método para usar un compuesto de acuerdo con la presente invención para fabricar un medicamento para usar en el tratamiento de un estado de enfermedad del que se sabe que es mediado por DPP-IV, o del que se sabe que puede tratarse empleando inhibidores de DPP-IV.

En otra realización, se proporciona un método para tratar un estado de enfermedad, donde la actividad de DPP-IV 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 efectiva 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 DPP-IV 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 efectiva 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 DPP-IV 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 efectiva para el uso terapéutico en el tratamiento del estado de enfermedad.

En otra realización, se proporciona un método para tratar un estado de enfermedad relacionado con la proliferación celular con un compuesto de acuerdo con la presente invención, en combinación con un agente anti-proliferativo, donde se tratan las células con el compuesto de acuerdo con la presente invención antes, al mismo tiempo y/o después de tratarlas con el agente anti-proliferativo, lo que se conoce en la presente documentación como terapia de combinación. Puede destacarse que el tratamiento con un agente antes que otro se conoce en la presente documentación como terapia consecutiva, aún si también se

administran los agentes juntos. Puede destacarse que la terapia de combinación está dirigida a abarcar las situaciones en las que se administra un agente antes o después del otro (terapia consecutiva), así como cuando se administran los agentes al mismo tiempo.

Los ejemplos de enfermedades que pueden tratarse administrando los compuestos y las composiciones de acuerdo con la presente invención incluyen, sin limitaciones, condiciones mediadas por DPP-IV, en particular la diabetes, más particularmente la diabetes mellitus tipo 2, la dislipidemia diabética, condiciones de tolerancia alterada a la glucosa (IGT), condiciones de glucosa en plasma en ayuno alterada (IFG), la acidosis metabólica, la cetosis, la regulación del apetito, la obesidad, la regulación de la liberación de inmunosupresores o citoquinas, enfermedades autoinmunes, tales como la enfermedad intestinal inflamatoria, la esclerosis múltiple y la artritis reumatoide, el SIDA, cánceres (prevención de metástasis, por ejemplo, tumores de mama y próstata en los pulmones), enfermedades dermatológicas, tales como psoriasis y liquen plano, el tratamiento de la infertilidad femenina, la osteoporosis, la anticoncepción masculina y los trastornos neurológicos.

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 éstereoquímica particular, la mención de un compuesto abarca todos los éstereoisómeros 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 éstereoisómeros 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 DPP-IV, 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 DPP-IV.

BREVE DESCRIPCIÓN DE LA FIGURA

La Figura 1 ilustra un diagrama de cintas de la estructura de DPP-IV, donde se detallan los elementos estructurales secundarios de la proteína.

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-C_8, tales como ciclopropilo, ciclohexano, ciclopentano, ciclopenteno, ciclopentadieno, ciclohexano, ciclohexeno, ciclohexadieno, cicloheptano, cicloheptano, 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.

"Alquenilo" representa un radical alifático recto o ramificado, insaturado, que tiene una cadena de átomos de carbono con al menos un enlace doble entre átomos de carbono adyacentes. Se usa C_X alquenilo y C_{X-Y} alquenilo típicamente cuando X e Y indican la cantidad de átomos de carbono en la cadena. Por ejemplo, C_{2-6} alquenilo incluye los alquenilos que tienen una cadena de entre 2 y 6 carbonos.

"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 "oxaalquilo") 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).

"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).

"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).

"Alquinilo" representa un radical alifático, recto o ramificado, saturado o insaturado, que tiene una cadena de carbonos que tiene al menos un enlace triple entre carbonos adyacentes. Se usa C_X alquinilo y C_{X-Y} alquinilo típicamente cuando X e Y indican la cantidad de átomos en la cadena. Por ejemplo, C_{2-6} alquinilo incluye aquellos alquinilos que tienen una cadena con entre 2 y 6 carbonos.

"Amino" representa una porción de nitrógeno que tiene otros dos sustituyentes, donde 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_{1-3}-alquilo, -$N(C_{1-3}$-alquil$)_2$ y semejantes. 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 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.

"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.

"Heterobiciclcloalquilo" 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]pindina, tieno[3,2-b]pindina, 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]pirıdina, 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]pirıdina, pirrolo[3,2-c]piridina, pirrolo[3,2-b]pirıdina, pirrolo[2,3-d]pirimidina, pirrolo[3,2-d]pirimidina, pirrolo[2,3-b]pirazina, pirazolo[1,5-a]pirıdina, pirrolo[1,2-b]pirıdazina, 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.

"Heterobiciclоarilo" representa un biciclоarilo, como se lo define en esta Solicitud, donde uno o más de los átomos en el anillo es un heteroátomo. Por ejemplo, hetero(C_{4-10})biciclоarilo, 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.

"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 "éstereoisómeros". Los éstereoisómeros que no son imágenes especulares uno del otro se denominan "diastereómeros", y los éstereoisómeros 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 éstereoisómero 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 éstereoqímica y

separar éstereoisómeros son bien conocidos en la técnica (por ejemplo, véase "Advanced Organic Chemistry", 4ª edición, Marzo, Jerry, John Wiley & Sons, Nueva York, 1992).

"Nitro" representa el radical $-NO_2$

"Oxaalquilo" 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})oxaalquilo 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 inhibidores 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 DPP-IV, 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 Groups in Organic Synthesis*, 3ª edición, John Wiley & Sons, Inc. 1999.

"Sustituido o insustituido" significa que una porción dada puede comprender solamente sustituyentes hidrógeno en todas las valencias disponibles (insustituido), 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 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 efectiva 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:

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,

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

mejorar la enfermedad en el animal que está presentando la patología o la

síntomatología de la enfermedad (es decir, invertir la patología y/o la síntomatología).

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 de manufactura que pueden usarse para inhibir dipeptidil peptidasas IV (conocidas en la presente documentación como DPP-IV).

La DPP-IV (EC,3,4,14,5 también conocida como DPP4, DP4, DAP-IV, proteína formadora de complejos de adenosina deaminasa 2, proteína de unión a adenosina deaminasa (ADAbp) o CD26), es una proteína con 766 residuos, de 240 kDa, que es una serina aminodipeptidasa no clásica de membrana, altamente específica. La DPP-IV tiene un mecanismo tipo serina de actividad de proteasa, y corta dipéptidos del extremo amino de péptidos con prolina o alanina en la penúltima posición. Además, se informa la liberación lenta de dipéptidos del tipo X-Gly o X-Ser para algunos péptidos de°Currencia natural. DPP-IV se expresa en forma constitutiva en las células epiteliales y endoteliales de una variedad de tejidos (intestino, hígado, pulmón, riñón y placenta), y también se halla en fluidos

corporales. La DPP-IV también se expresa en los linfocitos T en circulación, y se ha demostrado que es sinónimo del antígeno superficial celular CD-26. Se describe la forma tipo salvaje completa de DPP-IV en el Número de Acceso GenBank NM_001935 ("Dipeptidyl peptidase IV (CD 26) gene expression in enterocyte-like colon cancer cell lines HT-29 y Caco-2. Cloning of the complete human coding sequence and changes of dipeptidyl peptidase IV mRNA levels during cell differentiation", Darmoul, D., Lacasa, M., Baricault, L , Marguet, D , Sapin, C., Trotot, P., Barbat, A. y Trugnan, G., J. Biol. Chem., 267 (7), 4824-4833, 1992).

La DPP-IV es un miembro de la familia S9 de proteasas de serina, más particularmente, la familia S9B. Otros miembros de la familia S9 incluyen, sin limitaciones:

Subfamilia S9A: Dipeptidil-peptidasa; Oligopeptidasa B (EC 3,4,21,83); Oligopeptidasa B; Prolil oligopeptidasa (EC 3,4,21,26);

Subfamilia S9B: Dipeptidil aminopeptidasa A; Dipeptidil aminopeptidasa B

Dipeptidil-peptidasa IV (EC 3,4,14,5); Dipeptidil-peptidasa V

Subunidad alfa de la proteína activadora de fibroblastos; Seprasa

Subfamilia S9C: Acilaminoacil-peptidasa (EC 3,4,19,1)

Debe destacarse que los compuestos de la presente invención pueden presentar también la actividad de inhibición de otros miembros de la familia S9, y, por consiguiente, pueden usarse para tratar estados de enfermedad asociados con estos y otros miembros de la familia.

1 - Estructura cristalina de DPP-IV

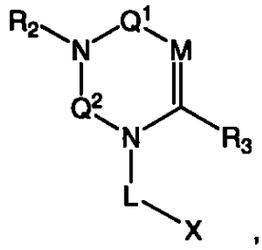
Syrrx, Inc. (San Diego, California) descubrió recientemente la estructura cristalina de DPP-IV. Se usó el conocimiento de la estructura cristalina para guiar

el diseño de los inhibidores de DPP-IV proporcionados en la presente documentación.

La Figura 1 ilustra un diagrama de cintas de la estructura de DPP-IV, donde se detallan los elementos estructurales secundarios de la proteína. DPP-IV es una molécula con forma cilíndrica, que tiene una altura aproximada de 70 Å y un diámetro de 60 Å. La tríada catalítica de DPP-IV (Ser642, Asp720 y His752) se ilustra en el centro de la figura a través de una representación de "esferas y palillos". Esta tríada de aminoácidos se localiza en el dominio de peptidasa o el dominio catalítico de DPP-IV. El dominio catalítico está unido en forma covalente al dominio β-propelente. El dominio catalítico de DPP-IV incluye los residuos 1-67 y 511-778. El dominio catalítico de DPP-IV adopta un plegamiento característico de α/β hidrolasa. El núcleo de este dominio contiene una lámina β con 8 cadenas, donde todas las cadenas son paralelas, excepto una. La lámina α está significativamente torcida, y está rodeada por tres hélices α en un lado y cinco hélices α en el otro. La trilogía de cadenas β es 1, 2, -1x, 2x y (1x) (J. S. Richardson: The anatomy and taxonomy of protein structure; (1981) *Adv. Protein Chem.* 269, 15076-15084.). Se ha identificado una cantidad de residuos que contribuyen a las características de forma y carga del sitio activo. El conocimiento de estos residuos ha sido una contribución importante al diseño de los inhibidores de DPP-IV de la presente invención.

2 - INHIBIDORES DE DPP-IV

En una realización, los inhibidores de DPP-IV de la presente invención incluyen compuestos que comprenden:



donde

M es N o CR_4,

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo,

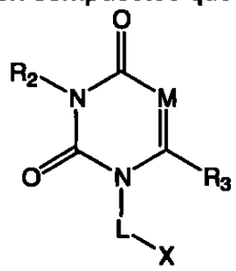
heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

En otra realización, los inhibidores de DPP-IV de la presente invención incluyen compuestos que comprenden:



donde

M es N o CR_4;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono,

oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

Sustituyente L:

En una variación de las realizaciones anteriores, los inhibidores de DPP-IV de la presente invención comprenden compuestos donde los 1, 2 ó 3 átomos de L que proporcionan la separación consisten en átomos de carbono. En otra variación, los 1, 2 ó 3 átomos de L que proporcionan la separación se seleccionan del grupo de conectores que consiste en al menos un átomo de oxígeno o al menos un átomo de nitrógeno. En aún otra variación, L separa X del átomo del anillo por un átomo.

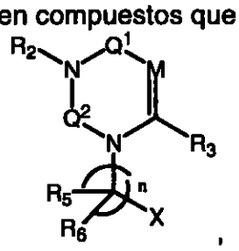
En una variación particular de las realizaciones anteriores, L se selecciona del grupo que consiste en –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -C(O)-, -CH_2C(O)-, -C(O)CH_2-, -CH_2-C(O)CH_2-, -C(O)CH_2CH_2-, -CH_2CH_2C(O)-, -O-, -OCH_2-, -CH_2O-, -CH_2OCH_2-, -OCH_2CH_2-, -CH_2CH_2O-, -N(CH_3)-, -NHCH_2-, -CH_2NH-, -CH_2NHCH_2-, -NHCH_2CH_2-, -CH_2CH_2NH-, -NH-C(O)-, -NCH_3-C(O)-, -C(O)NH-, -C(O)NCH_3-, -NHC(O)CH_2-, -C(O)NHCH_2-, -C(O)CH_2NH-, -CH_2NHC(O)-, -CH_2C(O)NH-, -NHCH_2C(O)-, -S-, -SCH_2-, -CH_2S-, -SCH_2CH_2-, -CH_2SCH_2-, -CH_2CH_2S-, -C(O)S-, -C(O)SCH_2-, -CH_2C(O)S-, -C(O)CH_2S-, y -CH_2SC(O)-, cada uno sustituido o no sustituido.

En otra variación particular de las realizaciones anteriores, L se selecciona del grupo que consiste en $-CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, y $-CH_2CH_2C(O)-$, cada uno sustituido o no sustituido.

En otra variación de las realizaciones anteriores, -L-X, tomados juntos, se seleccionan del grupo que consiste en $-(CH_2)$-(2-ciano)fenilo; $-(CH_2)$-(3-ciano)fenilo; $-(CH_2)$-(2-hidroxi)fenilo; $-(CH_2)$-(3-hidroxi)fenilo; $-(CH_2)$-(2-alquenil)fenilo; $-(CH_2)$-(3-alquenil)fenilo; $-(CH_2)$-(2-alquinil)fenilo; $-(CH_2)$-(3-alquinil)fenilo; $-(CH_2)$-(2-metoxi)fenilo; $-(CH_2)$-(3-metoxi)fenilo; $-(CH_2)$-(2-nitro)fenilo, $-(CH_2)$-(3-nitro)fenilo; $-(CH_2)$-(2-carboxi)fenilo; $-(CH_2)$-(3-carboxi)fenilo; $-(CH_2)$-(2-carboxamido)fenilo; $-(CH_2)$-(3-carboxamido)fenilo; $-(CH_2)$-(2-sulfonamido)fenilo; $-(CH_2)$-(3-sulfonamido)fenilo; $-(CH_2)$-(2-tetrazolil)fenilo; $-(CH_2)$-(3-tetrazolil)fenilo; $-(CH_2)$-(2-aminometil)fenilo; $-(CH_2)$-(3-aminometil)fenilo; $-(CH_2)$-(2-hidroximetil)fenilo; $-(CH_2)$-(3-hidroximetil)fenilo; $-(CH_2)$-(2-fenil)fenilo; $-(CH_2)$-(3-fenil)fenilo; $-(CH_2)$-(2-halo)fenilo; $-(CH_2)$-(3-halo)fenilo; $-(CH_2)$-(2-$CONH_2$)fenilo; $-(CH_2)$-(3-$CONH_2$)fenilo; $-(CH_2)$-(2-$CONH(C_{1-7})$alquil)fenilo; $-(CH_2)$-(3-$CONH(C_{1-7})$alquil)fenilo; $-(CH_2)$-(2-$CO_2(C_{1-7})$alquil)fenilo; $-(CH_2)$-(3-$CO_2(C_{1-7})$alquil)fenilo; $-(CH_2)$-(2-NH_2)fenilo; $-(CH_2)$-(3-NH_2)fenilo; $-(CH_2)$-(2-(C_{3-7})alquil)fenilo; $-(CH_2)$-(3-(C_{3-7})alquil)fenilo; $-(CH_2)$-(2-(C_{3-7})cicloalquil)fenilo; $-(CH_2)$-(3-(C_{3-7})cicloalquil)fenilo; $-(CH_2)$-(2-aril)fenilo; $-(CH_2)$-(3-aril)fenilo; $-(CH_2)$-(2-heteroaril)fenilo; $-(CH_2)$-(3-heteroaril)fenilo; $-(CH_2)$-2-bromo-5-fluoro fenilo; $-(CH_2)$-2-cloro-5-fluoro fenilo; $-(CH_2)$-2-ciano-5-fluoro fenilo; $-(CH_2)$-2,5-dicloro fenilo; $-(CH_2)$-2,5-difluoro fenilo; $-(CH_2)$-2,5-dibromo fenilo; $-(CH_2)$-2-bromo-3,5-difluoro fenilo; $-(CH_2)$-2-cloro-3,5-difluoro fenilo; $-(CH_2)$-2,3,5-trifluoro fenilo; $-(CH_2)$-2,3,5,6-tetrafluorofenilo; $-(CH_2)$-2-bromo-3,5,6-trifluoro fenilo; $-(CH_2)$-2-cloro-3,5,6-trifluoro fenilo; $-(CH_2)$-2-ciano-3,5-difluoro fenilo; $-(CH_2)$-2-ciano-3,5,6-trifluoro fenilo; $-(CH_2)$-(2-

heterocicloalquil)fenilo; y -(CH_2)-(3-heterocicloalquil)fenilo, cada uno sustituido o no sustituido

En otra realización, los inhibidores de DPP-IV de la presente invención incluyen compuestos que comprenden:



donde

n es 1, 2 ó 3;

M es N o CR_4;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un

grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

cada R_5 y R_6 es independientemente hidrógeno, o se selecciona del grupo que consiste en un (C_{1-10})alquilo sustituido o no sustituido, un (C_{1-10})alcoxilo sustituido o no sustituido, ciano, y halo, o donde R_5 y R_6 se toman juntos para formar un anillo;

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

Sustituyente X:

Respecto de las variaciones particulares de la presente invención, se

proporcionan compuestos donde X es un (C_{3-7})cicloalquilo sustituido o no sustituido. De acuerdo con cada una de las variaciones anteriores, la invención provee compuestos donde X es un (C_{3-7})heterocicloalquilo sustituido o no sustituido, o donde X es un arilo sustituido o no sustituido.

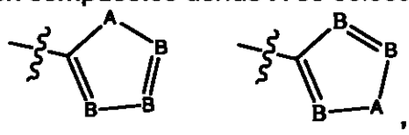
Además, de acuerdo con cada una de las variaciones anteriores, la invención provee compuestos donde X es un fenilo sustituido o no sustituido, o donde X es un heteroarilo sustituido o no sustituido. En otra variación de acuerdo con la variación anterior, X es un anillo que tiene un sustituyente distinto de hidrógeno en la posición 2 ó 3 del anillo.

De acuerdo con las variaciones anteriores, se proporcionan compuestos donde X es un anillo que tiene un sustituyente distinto de hidrógeno en la posición 2 ó 3 del anillo, que se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, ciano, nitro, halo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido. En otra variación de lo anterior, X es un halofenilo o dihalofenilo sustituido o no sustituido. En aún otra variación, X es un haloarilo, haloheteroarilo, dihaloarilo o dihaloheteroarilo sustituido o no sustituido.

De acuerdo con las variaciones anteriores, X se selecciona del grupo que consiste en (2-ciano)fenilo; (3-ciano)fenilo; (2-hidroxi)fenilo; (3-hidroxi)fenilo; (2-alquenil)fenilo; (3-alquenil)fenilo; (2-alquinil)fenilo; (3-alquinil)fenilo; (2-metoxi)fenilo; (3-metoxi)fenilo; (2-nitro)fenilo; (3-nitro)fenilo; (2-carboxi)fenilo; (3-carboxi)fenilo; -(CH_2)-(2-carboxamido)fenilo; (3-carboxamido)fenilo; (2-

sulfonamido)fenilo; (3-sulfonamido)fenilo; (2-tetrazolil)fenilo; (3-tetrazolil)fenilo; (2-aminometil)fenilo; (3-aminometil)fenilo; (2-hidroximetil)fenilo; (3-hidroximetil)fenilo; (2-fenil)fenilo; (3-fenil)fenilo; (2-halo)fenilo; (3-halo)fenilo; (2-$CONH_2$)fenilo; (3-$CONH_2$)fenilo; (2-$CONH(C_{1-7})$alquil)fenilo; (3-$CONH(C_{1-7})$alquil)fenilo; (2-$CO_2(C_{1-7})$alquil)fenilo; (3-$CO_2(C_{1-7})$alquil)fenilo; (2-NH_2)fenilo; (3-NH_2)fenilo; (2-(C_{3-7})alquil)fenilo; (3-(C_{3-7})alquil)fenilo; (2-(C_{3-7})cicloalquil)fenilo; (3-(C_{3-7})cicloalquil)fenilo, (2-aril)fenilo; (3-aril)fenilo, (2-heteroaril)fenilo; (3-heteroaril)fenilo; 2-bromo-5-fluoro fenilo; 2-cloro-5-fluoro fenilo; 2-ciano-5-fluoro fenilo, 2,5-dicloro fenilo; 2,5-difluoro fenilo; 2,5-dibromo fenilo; 2-bromo-3,5-difluoro fenilo; 2-cloro-3,5-difluoro fenilo; 2,3,5-trifluoro fenilo; 2,3,5,6-tetrafluorofenilo; 2-bromo-3,5,6-trifluoro fenilo; 2-cloro-3,5,6-trifluoro fenilo; 2-ciano-3,5-difluoro fenilo; 2-ciano-3,5,6-trifluoro fenilo; (2-heterocicloalquil)fenilo; y (3-heterocicloalquil)fenilo, cada uno sustituido o no sustituido.

Respecto de las variaciones particulares anteriores, la invención también incluyen compuestos donde X se selecciona del grupo que consiste en



donde

A es S, O o NR_{24};

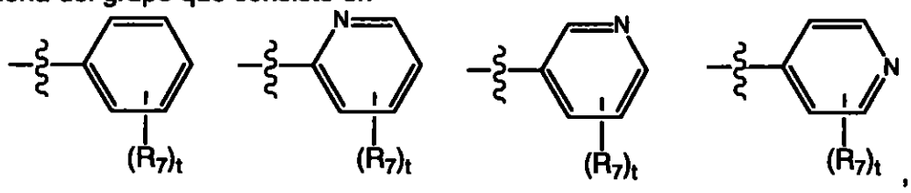
B es CR_{23} o N;

R_{23} se selecciona independientemente del grupo que consiste en hidrógeno, halo, perhalo(C_{1-10})alquilo, amino, tiol, ciano, CF_3, nitro, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo

imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido; y

R_{24} se selecciona independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloanlo, hetero(C_{8-12})bicicloanlo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, anlo, heteroanlo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido.

En una variación de las realizaciones y variaciones anteriores, X se selecciona del grupo que consiste en

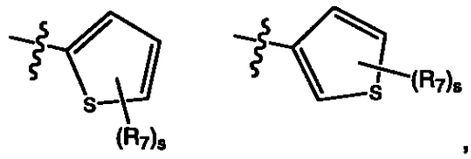


donde

t es 0, 1, 2, 3, 4 o 5; y

cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

En otra variación de los compuestos anteriores, X se selecciona del grupo que consiste en



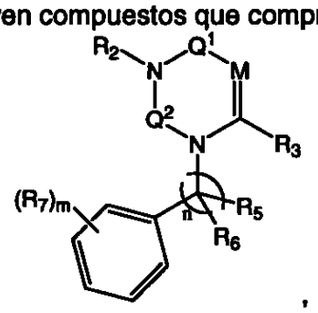
donde

s es 0, 1, 2 ó 3; y

cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

En una variación particular de los compuestos anteriores, R_7 se selecciona independientemente del grupo que consiste en -ciano, -metoxilo, -nitro, -carboxilo, -sulfonamido, -tetrazolilo, -aminometilo, -hidroximetilo, -fenilo, -halo, $-CONH_2$, -CONH(C_{1-7})alquilo, $-CO_2$(C_{1-7})alquilo, $-NH_2$, -OH, -(C_{1-5})alquilo, -alquenilo, -alquinilo, (C_{1-5})cicloalquilo, arilo, heteroarilo, y heterocicloalquilo, cada uno sustituido o no sustituido.

En otra realización, los inhibidores de DPP-IV de la presente invención incluyen compuestos que comprenden:



donde

M es 0, 1, 2, 3, 4 ó 5;

n es 1, 2 ó 3;

M es N o CR_4;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоarilo, hetero(C_{4-12})biciclоarilo, hetero(C_{4-12})biciclоaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

cada R_5 y R_6 es independientemente hidrógeno, o se selecciona del grupo que consiste en a sustituido o no sustituido (C_{1-10})alquilo, a sustituido o no sustituido (C_{1-10})alcoxilo, ciano, y halo, o donde R_5 y R_6 se toman juntos para formar un anillo;

cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido; y

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido.

En otra realización, los inhibidores de DPP-IV de la presente invención incluyen compuestos que comprenden:

un miembro que se selecciona del grupo que consiste en



donde

n es 1, 2 ó 3;

M es N o CR_4;

cada de T, U, V, W e Y es independientemente nitrógeno o CR_{16}, teniendo en cuenta que no más de dos de T, U, V, W e Y son nitrógeno;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоarilo, hetero(C_{4-12})biciclоarilo, hetero(C_{4-12})biciclоaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

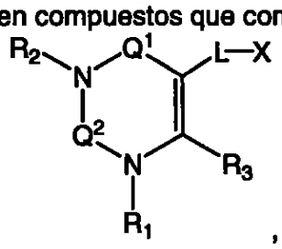
cada R_5 y R_6 es independientemente hidrógeno, o se selecciona del grupo que consiste en a sustituido o no sustituido (C_{1-10})alquilo, a sustituido o no

sustituido (C_{1-10})alcoxilo, ciano, y halo, o donde R_5 y R_6 se toman juntos para formar un anillo;

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido; y

cada R_{16} se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

En otra realización, los inhibidores de DPP-IV de la presente invención incluyen compuestos que comprenden:



,

donde

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_1 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, arioxilo, heteroariloxilo, un grupo carbonilo, un grupo

imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

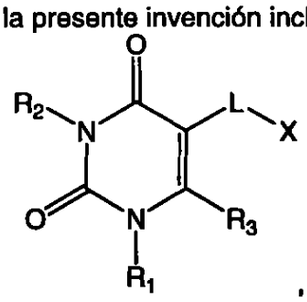
R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo,

hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido

En otra realización, los inhibidores otra realización, los inhibidores de DPP-IV de la presente invención incluyen compuestos que comprenden:



donde

R_1 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroarioxilo, un grupo

carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

Sustituyente L:

En una variación de la presente invención, se proporcionan compuestos donde los 1, 2 ó 3 átomos de L que proporcionan la separación consisten en átomos de carbono. En otra variación, los 1, 2 ó 3 átomos de L que proporcionan la separación se seleccionan del grupo de conectores que consisten en al menos

un átomo de oxígeno o al menos un átomo de nitrógeno. En una variación particular, L separa X del anillo por un átomo.

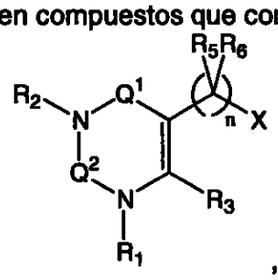
Respecto de una variación particular de la presente invención, L se selecciona del grupo que consiste en $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, $-NH-C(O)-$, $-NCH_3-C(O)-$, $-C(O)NH-$, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, $-S-$, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, $-C(O)S-$, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, y $-CH_2SC(O)-$, cada uno sustituido o no sustituido.

Respecto de otra variación de los compuestos anteriores, L se selecciona del grupo que consiste en $-CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, y $-CH_2CH_2C(O)-$, cada uno sustituido o no sustituido.

En otra variación de los compuestos anteriores, -L-X, tomados juntos, se seleccionan del grupo que consiste en $-(CH_2)-$(2-ciano)fenilo; $-(CH_2)-$(3-ciano)fenilo; $-(CH_2)-$(2-hidroxi)fenilo; $-(CH_2)-$(3-hidroxi)fenilo; $-(CH_2)-$(2-alquenil)fenilo; $-(CH_2)-$(3-alquenil)fenilo; $-(CH_2)-$(2-alquinil)fenilo; $-(CH_2)-$(3-alquinil)fenilo; $-(CH_2)-$(2-metoxi)fenilo; $-(CH_2)-$(3-metoxi)fenilo; $-(CH_2)-$(2-nitro)fenilo; $-(CH_2)-$(3-nitro)fenilo; $-(CH_2)-$(2-carboxi)fenilo; $-(CH_2)-$(3-carboxi)fenilo; $-(CH_2)-$(2-carboxamido)fenilo; $-(CH_2)-$(3-carboxamido)fenilo; $-(CH_2)-$(2-sulfonamido)fenilo; $-(CH_2)-$(3-sulfonamido)fenilo; $-(CH_2)-$(2-tetrazolil)fenilo; $-(CH_2)-$(3-tetrazolil)fenilo; $-(CH_2)-$(2-aminometil)fenilo; $-(CH_2)-$(3-aminometil)fenilo; $-(CH_2)-$(2-hidroximetil)fenilo; $-(CH_2)-$(3-hidroximetil)fenilo; $-(CH_2)-$(2-fenil)fenilo; $-(CH_2)-$(3-fenil)fenilo; $-(CH_2)-$(2-halo)fenilo; $-(CH_2)-$(3-halo)fenilo; $-(CH_2)-$(2-$CONH_2$)fenilo; -

(CH_2)-(3-$CONH_2$)fenilo; -(CH_2)-(2-$CONH(C_{1-7})$alquil)fenilo; -(CH_2)-(3-$CONH(C_{1-7})$alquil)fenilo; -(CH_2)-(2-$CO_2(C_{1-7})$alquil)fenilo; -(CH_2)-(3-$CO_2(C_{1-7})$alquil)fenilo; -(CH_2)-(2-NH_2)fenilo; -(CH_2)-(3-NH_2)fenilo; -(CH_2)-(2-(C_{3-7})alquil)fenilo; -(CH_2)-(3-(C_{3-7})alquil)fenilo; -(CH_2)-(2-(C_{3-7})cicloalquil)fenilo; -(CH_2)-(3-(C_{3-7})cicloalquil)fenilo; -(CH_2)-(2-aril)fenilo; -(CH_2)-(3-aril)fenilo; -(CH_2)-(2-heteroaril)fenilo; -(CH_2)-(3-heteroaril)fenilo; -(CH_2)-2-bromo-5-fluoro fenilo; -(CH_2)-2-cloro-5-fluoro fenilo; -(CH_2)-2-ciano-5-fluoro fenilo; -(CH_2)-2,5-dicloro fenilo; -(CH_2)-2,5-difluoro fenilo; -(CH_2)-2,5-dibromo fenilo; -(CH_2)-2-bromo-3,5-difluoro fenilo; -(CH_2)-2-cloro-3,5-difluoro fenilo; -(CH_2)-2,3,5-trifluoro fenilo; -(CH_2)-2,3,5,6-tetrafluorofenilo; -(CH_2)-2-bromo-3,5,6-trifluoro fenilo; -(CH_2)-2-cloro-3,5,6-trifluoro fenilo; -(CH_2)-2-ciano-3,5-difluoro fenilo; -(CH_2)-2-ciano-3,5,6-trifluoro fenilo; -(CH_2)-(2-heterocicloalquil)fenilo; y -(CH_2)-(3-heterocicloalquil)fenilo, cada uno sustituido o no sustituido.

En otra realización, los inhibidores de DPP-IV de la presente invención incluyen compuestos que comprenden:



,

donde

n es 1, 2 ó 3;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_8$;

R_1 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo,

heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

cada R_5 y R_6 es independientemente hidrógeno, o se selecciona del grupo que consiste en a sustituido o no sustituido (C_{1-10})alquilo, a sustituido o no sustituido (C_{1-10})alcoxilo, ciano, y halo, o donde R_5 y R_6 se toman juntos para formar un anillo;

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y

heterobicicloarilo, cada uno sustituido o no sustituido; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

Sustituyente X:

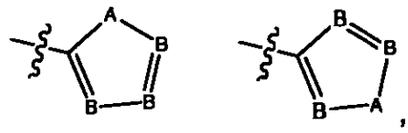
De acuerdo con las variaciones anteriores, la invención provee compuestos donde X es un (C3-7)cicloalquilo sustituido o no sustituido. En otra variación particular de los compuestos anteriores, X es un (C3-7)heterocicloalquilo sustituido o no sustituido, X es un arilo sustituido o no sustituido, o X es un fenilo sustituido o no sustituido. En otra variación particular, X es un heteroarilo sustituido o no sustituido.

En una variación particular de los compuestos anteriores, X es un anillo que tiene un sustituyente distinto de hidrógeno en la posición 2 ó 3 del anillo. En una variación de los compuestos anteriores, X es un anillo que tiene un sustituyente distinto de hidrógeno en la posición 2 ó 3 del anillo, seleccionado del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, ciano, nitro, halo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

En otra variación particular, X es un halofenilo o dihalofenilo sustituido o no sustituido. En aún otra variación particular, se proporcionan compuestos donde X es un haloarilo, haloheteroarilo, dihaloarilo o dihaloheteroarilo sustituido o no sustituido.

Respecto de una variación particular, la presente invención provee compuestos donde X se selecciona del grupo que consiste en (2-ciano)fenilo; (3-ciano)fenilo; (2-hidroxi)fenilo; (3-hidroxi)fenilo; (2-alquenil)fenilo; (3-alquenil)fenilo; (2-alquinil)fenilo; (3-alquinil)fenilo; (2-metoxi)fenilo; (3-metoxi)fenilo; (2-nitro)fenilo; (3-nitro)fenilo; (2-carboxi)fenilo; (3-carboxi)fenilo; -(CH_2)-(2-carboxamido)fenilo; (3-carboxamido)fenilo; (2-sulfonamido)fenilo; (3-sulfonamido)fenilo; (2-tetrazolil)fenilo; (3-tetrazolil)fenilo; (2-aminometil)fenilo; (3-aminometil)fenilo; (2-hidroximetil)fenilo; (3-hidroximetil)fenilo; (2-fenil)fenilo; (3-fenil)fenilo; (2-halo)fenilo; (3-halo)fenilo; (2-$CONH_2$)fenilo; (3-$CONH_2$)fenilo; (2-CONH(C_{1-7})alquil)fenilo; (3-CONH(C_{1-7})alquil)fenilo; (2-CO_2(C_{1-7})alquil)fenilo; (3-CO_2(C_{1-7})alquil)fenilo; (2-NH_2)fenilo; (3-NH_2)fenilo; (2-(C_{3-7})alquil)fenilo; (3-(C_{3-7})alquil)fenilo; (2-(C_{3-7})cicloalquil)fenilo; (3-(C_{3-7})cicloalquil)fenilo; (2-aril)fenilo; (3-aril)fenilo; (2-heteroaril)fenilo; (3-heteroaril)fenilo; 2-bromo-5-fluoro fenilo; 2-cloro-5-fluoro fenilo; 2-ciano-5-fluoro fenilo; 2,5-dicloro fenilo; 2,5-difluoro fenilo; 2,5-dibromo fenilo; 2-bromo-3,5-difluoro fenilo; 2-cloro-3,5-difluoro fenilo; 2,3,5-trifluoro fenilo; 2,3,5,6-tetrafluorofenilo; 2-bromo-3,5,6-trifluoro fenilo; 2-cloro-3,5,6-trifluoro fenilo; 2-ciano-3,5-difluoro fenilo; 2-ciano-3,5,6-trifluoro fenilo; (2-heterocicloalquil)fenilo; y (3-heterocicloalquil)fenilo, cada uno sustituido o no sustituido.

En una variación de los compuestos anteriores, X se selecciona del grupo que consiste en



donde

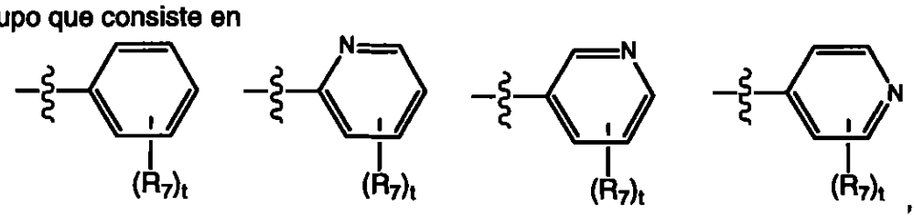
A es S, O o NR_{24};

B es CR_{23} o N;

R_{23} se selecciona independientemente del grupo que consiste en hidrógeno, halo, perhalo(C_{1-10})alquilo, amino, tiol, ciano, CF_3, nitro, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido; y

R_{24} se selecciona independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido.

En otra variación particular de los compuestos anteriores, X se selecciona del grupo que consiste en

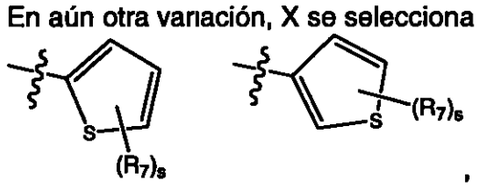


donde

t es 0, 1, 2, 3, 4 ó 5; y

cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

En aún otra variación, X se selecciona del grupo que consiste en



donde

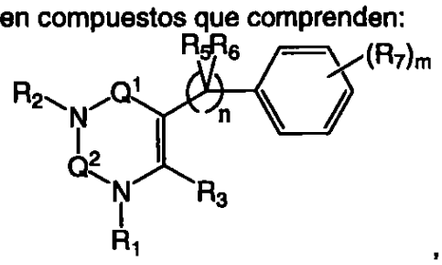
s es 0, 1, 2 ó 3; y

cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

En una variación particular de los compuestos anteriores, R_7 se selecciona independientemente del grupo que consiste en -ciano, -metoxilo, -nitro, -carboxilo, -sulfonamido, -tetrazolilo, -aminometilo, -hidroximetilo, -fenilo, -halo, $-CONH_2$, -CONH(C_{1-7})alquilo, $-CO_2$(C_{1-7})alquilo, $-NH_2$, -OH, -(C_{1-5})alquilo, -alquenilo, -alquinilo, (C_{1-5})cicloalquilo, arilo, heteroarilo, y heterocicloalquilo, cada uno sustituido o no sustituido.

En otra realización, los inhibidores de DPP-IV de la presente invención

incluyen compuestos que comprenden:



donde

M es 0, 1, 2, 3, 4 o 5;

n es 1, 2 ó 3;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_8$;

R_1 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino,

(C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

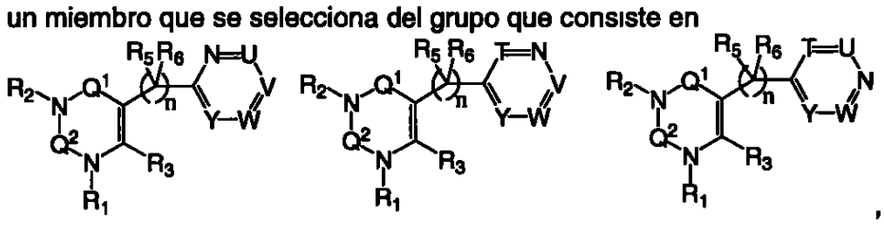
cada R_5 y R_6 es independientemente hidrógeno, o se selecciona del grupo que consiste en a sustituido o no sustituido (C_{1-10})alquilo, a sustituido o no sustituido (C_{1-10})alcoxilo, ciano, y halo, o donde R_5 y R_6 se toman juntos para formar un anillo;

cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido; y

R_8 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido.

En otra realización, los inhibidores de DPP-IV de la presente invención incluyen compuestos que comprenden:

un miembro que se selecciona del grupo que consiste en



,

donde

n es 1, 2 ó 3;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

cada de T, U, V, W e Y es independientemente nitrógeno o CR_{16}, teniendo en cuenta que no más de dos de T, U, V, W e Y son nitrógeno;

R_1 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоanlo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno

sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

cada R_5 y R_6 es independientemente hidrógeno, o se selecciona del grupo que consiste en a sustituido o no sustituido (C_{1-10})alquilo, a sustituido o no sustituido (C_{1-10})alcoxilo, ciano, y halo, o donde R_5 y R_6 se toman juntos para formar un anillo;

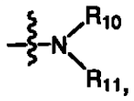
R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido; y

cada R_{16} se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

Sustituyente R_3:

Respecto de cada una de las realizaciones y variaciones anteriores, la presente invención provee compuestos donde R_3 se selecciona del grupo que consiste en amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, y heteroarilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros.

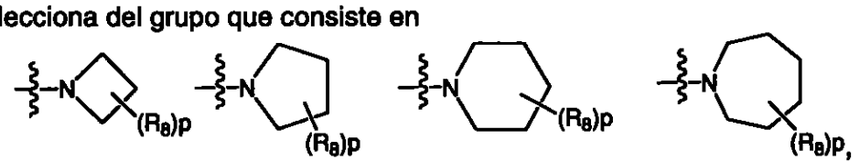
Además, de acuerdo con cada una de las realizaciones y variaciones anteriores, la presente invención también provee compuestos donde R_3 comprende la fórmula



donde R_{10} y R_{11} se seleccionan cada uno independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo sulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido, o R_{10} y R_{11} se toman juntos para formar un anillo de 4, 5, 6 ó 7 miembros, cada uno sustituido o no sustituido.

De acuerdo con otra variación de cada una de las realizaciones y variaciones anteriores, R_3 es un anillo de 3, 4, 5, 6 ó 7 miembros sustituido o no sustituido, donde R_3 es un cicloalquilo de 3, 4, 5, 6 ó 7 miembros sustituido o no sustituido, o donde R_3 es un heterocicloalquilo de 3, 4, 5, 6 ó 7 miembros sustituido o no sustituido. En otra variación de lo anterior, R_3 es un arilo sustituido o no sustituido, o donde R_3 es un heteroarilo sustituido o no sustituido.

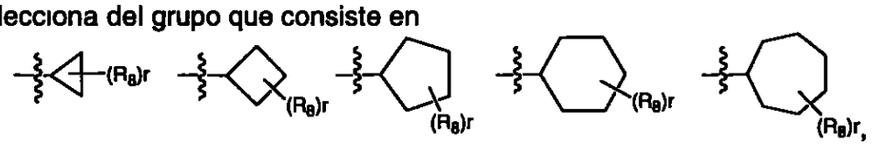
En una variación particular de las realizaciones y variaciones anteriores, R_3 se selecciona del grupo que consiste en



donde p es 0-12 y cada R_8 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, ciano, nitro, hidroxilo, alquilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

En otra variación particular de las realizaciones y variaciones anteriores, R_3

se selecciona del grupo que consiste en



donde r es 0-13 y cada R_8 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, ciano, nitro, hidroxilo, alquilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

De acuerdo con cada una de las realizaciones y variaciones anteriores, los inhibidores de DPP-IV de la presente invención pueden comprender compuestos donde R_3 es un heteroarilo sustituido o no sustituido seleccionado del grupo que consiste en furano, tiofeno, pirrol, pirazol, triazol, isoxazol, oxazol, tiazol, isotiazol, oxadiazol, piridina, piridazina, pirimidina, pirazina, triazina, benzofurano, isobenzofurano, benzotiofeno, isobenzotiofeno, imidazol, benzimidazol, indol, isoindol, quinolina, isoquinolina, cinolina, quinazolina, naftiridina, piridopiridina, quinoxalina, ftalazina y benzotiazol, cada uno sustituido o no sustituido.

Además, de acuerdo con las realizaciones y variaciones anteriores, R_3 puede seleccionarse del grupo que consiste en (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido. En otra variación, R_3 es un anillo de (C3-7)cicloalquilo sustituido o no sustituido, que comprende opcionalmente O, N(O), N, S, SO, SO_2 o un grupo carbonilo en el anillo.

De acuerdo con cada una de las realizaciones y variaciones anteriores, R_3 también puede estar sustituido, de modo que R_3 comprende un sustituyente

seleccionado del grupo que consiste en una amina primaria, secundaria terciaria, un heterocicloalquilo que comprende un átomo de nitrógeno en el anillo, y un heteroarilo que comprende un átomo de nitrógeno en el anillo.

En variaciones particulares de la presente invención, R_3 comprende un átomo de nitrógeno básico que es capaz de interactuar con la cadena lateral de ácido carboxílico de un residuo del sitio activo de una proteína. En una variación, el nitrógeno básico de R_3 está separado del átomo del anillo al que está unido R_3 por 1-5 átomos. En otra variación, el átomo de nitrógeno básico forma parte de una amina primaria, secundaria o terciaria. En aún otra variación, el átomo de nitrógeno básico es un átomo de nitrógeno de un anillo de heterocicloalquilo o heteroarilo.

En una variación de cada una de las realizaciones de la presente invención, R_3 incluye un nitrógeno básico capaz de interactuar con la cadena lateral de ácido carboxílico de un residuo DP-4 en el sitio activo, y, por consiguiente, contribuye a la afinidad de unión del compuesto con DP-4. Sobre la base de las estructuras cristalinas obtenidas por los solicitantes, la interacción observada entre el sustituyente de nitrógeno básico y el ácido carboxílico parece realizarse a través de una unión hidrógeno o a través de la formación de un puente de sal.

El nitrógeno básico de R_3 en esta variación que provee la interacción con la cadena lateral de ácido carboxílico deseada típicamente no está unido directamente al átomo del anillo al que está unido R_3. En este caso, el nitrógeno básico puede ser parte de un sustituyente de la porción R_3 total. Por ejemplo, en el caso en que R_3 es 3-amino-piperidinil-1-ilo, el nitrógeno básico es el grupo 3-amino, y no el nitrógeno del anillo de piperidina. Por consiguiente, R_3 puede contemplarse como un anillo de piperidina sustituido, que comprende además una

amina como sustituyente de nitrógeno básico. En una variación particular, el nitrógeno básico de R_3 está opcionalmente separado del átomo del anillo al que está unido R_3 por 1-5 átomos.

La porción del átomo de nitrógeno básico de R_3 puede seleccionarse opcionalmente del grupo que consiste en una amina primaria, secundaria o terciaria, un heterocicloalquilo que comprende un átomo de nitrógeno en el anillo, un heteroarilo que comprende un átomo de nitrógeno en el anillo, así como otras porciones que contienen nitrógeno, donde el nitrógeno puede actuar como una base de Lewis. Además de las porciones que contienen nitrógeno básico, se contempla que otras bases de Lewis, tales como oxígeno con pares solitarios básicos, puedan ser capaces de interactuar con la cadena lateral de ácido carboxílico de un residuo DP-4 en el sitio activo.

En determinadas realizaciones, se dice que R_3 está sustituido adicionalmente con uno o más sustituyentes R_8. Se destaca que al menos uno de los sustituyentes R_8 puede comprender el átomo de nitrógeno básico capaz de proporcionar la interacción con la cadena lateral de ácido carboxílico. En este caso, R_8 puede comprender opcionalmente una porción seleccionada del grupo que consiste en una amina primaria, secundaria o terciaria, un heterocicloalquilo que comprende un átomo de nitrógeno en el anillo, un heteroarilo que comprende un átomo de nitrógeno en el anillo, así como otras porciones que contienen nitrógeno, donde el nitrógeno puede actuar como base de Lewis.

Los ejemplos particulares de porciones con nitrógenos básicos de acuerdo con esta variación incluyen, sin limitaciones, $-NH_2$, $-NH(C_{1-5}\text{alquil})$, $-N(C_{1-5}\text{alquil})_2$, piperazina, imidazol, y piridina. Otros grupos R_3 particulares que comprenden un nitrógeno básico incluyen, sin limitaciones, 3-amino-piperidinil-1-ilo, 3-aminometil-

pirrolidin-1-ilo, 3-aminoazetidin-1-ilo, 3-amino-3-metilpiperidin-1-ilo, 3-aminociclopent-1-ilo, 3-aminometilciclopent-1-ilo, 3-aminometilciclohex-1-ilo, 3-aminohexahidroazepin-1-ilo, 3-amino-ciclohex-1-ilo, piperazin-1-ilo, homopiperazin-1-ilo, 3-amino-pirrolidin-1-ilo, R-3-aminopiperidin-1-ilo, R-3-amino-3-metilpiperidin-1-ilo, 3-amino-ciclohex-1-ilo, 3-amino-ciclopent-1-ilo, y 3-amino-pirrolidin-1-ilo, cada uno opcionalmente sustituido adicionalmente.

Respecto de una variación particular, al menos un R_8 comprende un átomo de nitrógeno básico capaz de interactuar con una cadena lateral de ácido carboxílico de un sitio activo de una proteína. En otra variación particular, el átomo de nitrógeno básico forma parte de una amina primaria, secundaria o terciaria. En otra variación de los compuestos anteriores, el átomo de nitrógeno básico es un átomo de nitrógeno de un anillo de heterocicloalquilo, que comprende un átomo de nitrógeno en el anillo, o un heteroarilo que comprende un átomo de nitrógeno en el anillo.

En una variación de cada una de las realizaciones de la presente invención, al menos un R_8 es una amina primaria, secundaria o terciaria. En otra variación, al menos un R_8 es un heterocicloalquilo sustituido o no sustituido que comprende un átomo de nitrógeno en el anillo, o un heteroarilo sustituido o no sustituido que comprende un átomo de nitrógeno en el anillo. En aún otra variación particular, al menos un R_8 se selecciona del grupo que consiste en $-NH_2$, $-NH(C_{1-5}$ alquilo), $-N(C_{1-5}$ alquil$)_2$, piperazina, imidazol, y piridina.

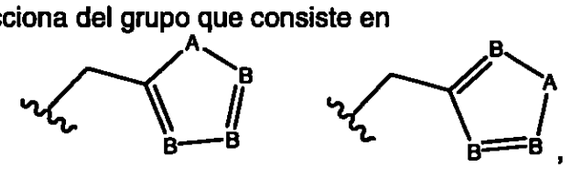
De acuerdo con cada una de las realizaciones y variaciones anteriores, R_3 se selecciona del grupo que consiste en 3-amino-piperidinil-1-ilo, 3-aminometil-pirrolidin-1-ilo, 3-aminoazetidin-1-ilo, 3-amino-3-metilpiperidin-1-ilo, 3-aminociclopent-1-ilo, 3-aminometilciclopent-1-ilo, 3-aminometilciclohex-1-ilo, 3-

aminohexahidroazepin-1-ilo, 3-amino-ciclohex-1-ilo, piperazin-1-ilo, homopiperazin-1-ilo, 3-amino-pirrolidin-1-ilo, R-3-aminopiperidin-1-ilo, R-3-amino-3-metilpiperidin-1-ilo, 3-amino-ciclohex-1-ilo, 3-amino-ciclopent-1-ilo, y 3-amino-pirrolidin-1-ilo, cada uno sustituido o no sustituido

En una variación particular, al menos uno de Q^1 y Q^2 es CO. En otra variación de los compuestos anteriores, Q^1 y Q^2 son CO.

Sustituyente M:

En otra variación particular, la presente invención provee compuestos donde M es nitrógeno. En aún otra variación particular, M es CR_4 y donde R_4 se selecciona del grupo que consiste en



donde

A es S, O o NR_{24};

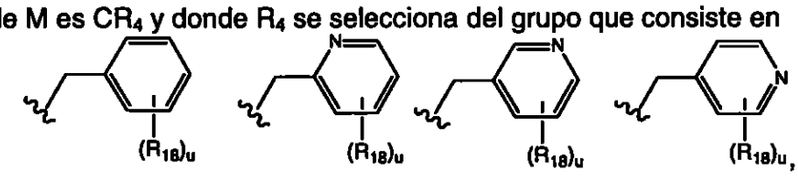
B es CR_{23} o N;

R_{23} se selecciona independientemente del grupo que consiste en hidrógeno, halo, perhalo(C_{1-10})alquilo, amino, tiol, ciano, CF_3, nitro, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido; y

R_{24} se selecciona independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo,

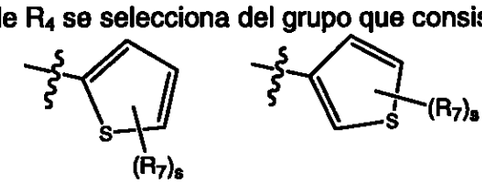
hetero(C_{8-12})bicicloanilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido

En otra variación particular, la presente invención provee compuestos donde M es CR_4 y donde R_4 se selecciona del grupo que consiste en



donde u es 0, 1, 2, 3, 4 ó 5; y cada R_{18} se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, arloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imina, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

En aún otra variación, se proporcionan compuestos donde M es CR_4 y donde R_4 se selecciona del grupo que consiste en



donde s es 0, 1, 2 ó 3; y cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo

sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

Sustituyentes R_5 y R_6:

En variaciones particulares de la presente invención, se proporcionan compuestos donde R_5 y R_6 son hidrógeno. En aún otra variación, R_5 y R_6 se toman juntos para formar un anillo. En aún otra variación, al menos uno de R_5 y R_6 es un haluro, tal como flúor.

En otra variación de la invención, se proporcionan compuestos donde al menos uno de R_5 y R_6 es un -(C_{1-8})alquilenoR_{13} sustituido o no sustituido, donde R_{13} se selecciona del grupo que consiste en (C_{3-12})cicloalquilo, hetero(C_{4-12})cicloalquilo, (C_{6-12})arilo, hetero(C_{5-12})arilo, (C_{9-12})bicicloalquilo, hetero(C_{9-12})bicicloalquilo, (C_{9-12})bicicloaril y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido.

En otra variación particular de los compuestos anteriores, R_5 y R_6 son hidrógeno, M es 1 ó 2, y cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, ciano, nitro, hidroxilo, alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

Respecto de una variación particular de la invención, se proporcionan compuestos donde dos R_7 se toman juntos para formar un anillo fusionado o con puentes sustituido o no sustituido.

En aún otra variación particular, se proporcionan compuestos donde n es 1, 2 ó 3; y R_5 y R_6 son hidrógeno. En otra variación, n es 1 ó 2; R_3 se selecciona del grupo que consiste en amino, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo,

un grupo imino, un grupo sulfonilo y un grupo sulfinilo, y un anillo sustituido o no sustituido de 4, 5, 6 ó 7 miembros; y R_5 y R_6 son hidrógeno.

En una variación particular de los compuestos anteriores, R_5 y R_6 son hidrógeno y R_7 es 2-ciano. En otra variación del compuesto anterior, n es 1. En aún otra variación particular de los compuestos anteriores, n es 1, 2 ó 3; R_5 y R_6 son hidrógeno; y R_3 se selecciona del grupo que consiste en (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})biciclоarilo, cada uno sustituido o no sustituido.

De acuerdo con una variación particular de los compuestos anteriores, n es 1, 2 ó 3; R_5 y R_6 son hidrógeno; y cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, alquenilo, alquinilo, CF_3, ciano, nitro, hidroxilo, heteroarilo, ariloxilo, heteroariloxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

Sustituyente R_7:

En variaciones particulares de lo anterior, se proporcionan compuestos donde dos R_7 se toman juntos para formar un anillo fusionado sustituido o no sustituido. En otra variación particular, dos R_7 se toman juntos para formar un anillo con puentes sustituido o no sustituido.

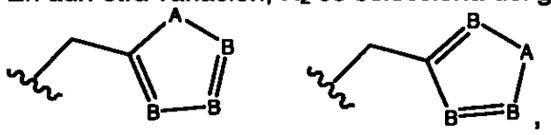
De acuerdo con una variación particular de los compuestos anteriores, dos de T, U, V, W e Y se toman juntos y se sustituyen con las valencias disponibles para formar un anillo fusionado o con puentes sustituido o no sustituido, con el anillo anterior formado por T, U, V, W e Y.

Sustituyente R_2:

De acuerdo con cada una de las realizaciones y variaciones anteriores, la

presente invención provee compuestos donde R_2 es un (C_{1-10})alquilo sustituido o no sustituido. En otra variación, R_2 es un (C_{1-4})alquilo sustituido o no sustituido. En aún otra variación, R_2 es -Y-Z, donde Y es un conector que proporciona una separación de 1, 2 ó 3 átomos entre Z y el anillo al que está unido Y, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y Z es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоanilo, hetero(C_{4-12})biciclоarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

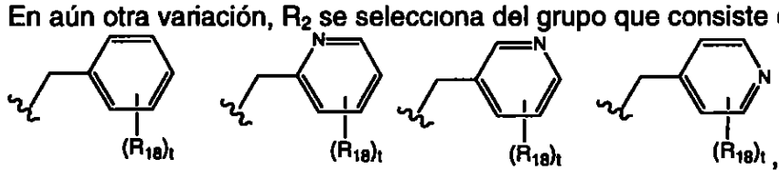
En aún otra variación, R_2 se selecciona del grupo que consiste en



donde A es S, O o NR_{24}; B es CR_{23} o N; R_{23} se selecciona independientemente del grupo que consiste en hidrógeno, halo, perhalo(C_{1-10})alquilo, amino, tiol, ciano, CF_3, nitro, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido; y R_{24} se selecciona independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, $(C_{3-}$

$_{12}$)cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido.

En aún otra variación, R_2 se selecciona del grupo que consiste en



donde t es 0, 1, 2, 3, 4 ó 5; y cada R_{18} se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imina, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

Los ejemplos particulares de inhibidores de DPP-IV de acuerdo con la presente invención incluyen, sin limitaciones:

2-(6-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-benzonitrilo;

2-(6-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-5-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3-amino-piperidin-1-il]-1-(2-bromo-bencil)-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-iodo-bencil)-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-bromo-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-cloro-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-cloro-4-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-bromo-bencil)-3-metil-1H-pirimidin-2,4-diona;

2-{6-[azepan-3(±)-ilamino]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (14);

2-{6-[3(±)-amino-azepan-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-[6-(2-amino-etilamino)-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(3-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(4-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-[6-(3-amino-piperidin-1-il)-3-(1H-benzoimidazol-2-ilmetil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3-(4-pirazol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3-(3-pirrol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil]-tiofeno-3-carbonitrilo;

metil éster de ácido 3-{4-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

ácido 3-{4-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

6-[3-amino-piperidin-1-il]-1,3-bis-(2-bromo-5-fluoro-bencil)-1H-pirimidin-2,4-diona;

2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-1-(2,5-*di*-cloro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-3,6-*di*-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

(R)-2-((6-(3-amino-3-metilpiperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidropirimidin-1(2H)-il)metil)-4-fluorobenzonitrilo; y

2-[6-(3-amino-piperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-4-fluoro-benzonitrilo.

Los ejemplos particulares de inhibidores de DPP-IV de acuerdo con la presente invención incluyen además:

2-{6-[3(R)-amino-piperidin-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-

benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-iodo-bencil)-1H-pirimidin-2,4-diona,

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona,

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-4-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-3-metil-1H-pirimidin-2,4-diona;

2-{6-[3(R)-amino-piperidin-1-il]-3-(3-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-(4-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-[6-(3-amino-piperidin-1-il)-3-(1H-benzoimidazol-2-ilmetil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(4-pirazol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(3-pirrol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-

1-ilmetil]-tiofeno-3-carbonitrilo;

metil éster de ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

6-[3(R)-amino-piperidin-1-il]-1,3-bis-(2-bromo-5-fluoro-bencil)-1H-pirimidin-2,4-diona; y

2-[6-(3(R)-amino-piperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-4-fluoro-benzonitrilo.

En otra realización, la presente invención provee los compuestos bajo la forma de una sal aceptable para el uso farmacéutico.

En aún otra realización, la presente invención provee los compuestos presentes en una mezcla de estereoisómeros. En aún otra realización, la presente invención provee los compuestos como estereoisómeros individuales.

En aún otra realización, la presente invención provee composiciones farmacéuticas que comprenden el compuesto como ingrediente activo. En aún otra variación, la presente invención provee composiciones farmacéuticas, donde la composición es una formulación sólida adaptada para administración oral. En aún otra variación particular, la presente invención provee una composición farmacéutica, donde la composición es una tableta. En otra variación particular, la presente invención provee la composición farmacéutica, donde la composición es una formulación líquida adaptada para una administración oral. En aún otra variación particular, la presente invención provee una composición farmacéutica, donde la composición es una formulación líquida adaptada para una administración parenteral.

En aún otra variación particular, la presente invención provee la composición farmacéutica que comprende el compuesto de la invención, 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 otra realización, la presente invención provee un conjunto de elementos que comprende un compuesto de la presente invención, e instrucciones que comprenden una o más formas de información, seleccionadas del grupo que consiste en la indicación del estado de enfermedad para el cual puede administrarse el compuesto, información de almacenamiento del compuesto, información de dosificación e instrucciones respecto de cómo administrar compuesto. En otra realización, la presente invención provee el conjunto de elementos, que comprende el compuesto en una forma de dosificaciones múltiples.

En otra realización, la presente invención provee un artículo de fabricación que comprende un compuesto de la presente invención y materiales de envasado. En otra variación, el material de envasado comprende un recipiente para alojar el compuesto. En aún otra variación, la invención provee el artículo de fabricación, donde el recipiente comprende una etiqueta que indica uno o más miembros del grupo que consiste en el estado de enfermedad para el cual se administra el compuesto, información de almacenamiento, información de dosificación y/o instrucciones sobre cómo administrar la composición.

En otra variación, la presente invención provee el artículo de fabricación, donde el artículo de fabricación comprende el compuesto en una forma de dosis múltiples.

En otra realización, la presente invención provee un método para inhibir DPP-IV, que comprende poner en contacto DPP-IV con un compuesto de acuerdo con la presente invención.

En otra realización, la presente invención provee un método para inhibir DPP-IV, que comprende introducir un compuesto de acuerdo con la presente invención en un sujeto, con el fin de inhibir DPP-IV *in vivo*.

En otra realización, la presente invención provee un método para inhibir DPP-IV, que comprende administrar un primer compuesto a un sujeto, que se convierte *in vivo* en un segundo compuesto, donde el segundo compuesto inhibe DPP-IV *in vivo*, donde el segundo compuesto es un compuesto de la presente invención.

En otra realización, la presente invención provee un método terapéutico que comprende: administrar un compuesto de acuerdo con la presente invención a un sujeto.

En otra realización, la presente invención provee un método para tratar un estado de enfermedad, a cuya patología y/o sintomatología contribuye la actividad que presenta DPP-IV, donde el método comprende introducir un compuesto de la presente invención en un sujeto, en una cantidad efectiva para el uso terapéutico para el estado de enfermedad.

En otra realización, la presente invención provee un método para tratar el cáncer en un paciente que lo necesita, que comprende administrar a dicho paciente una cantidad efectiva para el uso terapéutico de un compuesto de

acuerdo con la presente invención.

En otra realización, la presente invención provee un método para tratar una enfermedad, donde la enfermedad es diabetes tipo I o tipo II.

En otra realización, la presente invención provee un método para tratar trastornos autoinmunes, tales como, sin limitaciones, artritis reumatoide, psoriasis y esclerosis múltiple, en un paciente que lo necesita, que comprende administrar a dicho paciente una cantidad efectiva para el uso terapéutico de un compuesto de acuerdo con la presente invención.

En aún otra realización, la presente invención provee un método para tratar el cáncer, donde el cáncer a tratar es cáncer colorrectal, de próstata, de mama, de tiroides, de piel, de pulmón o de cabeza y cuello.

En otra realización, la presente invención provee un método para tratar una condición caracterizada por la activación o la concentración inadecuada de linfocitos o células hematopoyéticas en un paciente que lo necesita, que comprende administrar a dicho paciente una cantidad efectiva para el uso terapéutico de un compuesto de acuerdo con la presente invención.

En otra realización, la presente invención provee un método para tratar la infección de HIV en un paciente que lo necesita, que comprende administrar a dicho paciente una cantidad efectiva para el uso terapéutico de un compuesto de acuerdo con la presente invención.

En aún otra realización, la presente invención provee un método para tratar a condición caracterizada por la activación o la concentración inadecuada de linfocitos o células hematopoyéticas en un paciente que lo necesita, donde la condición es un efecto colateral de la quimioterapia o la terapia con radiación.

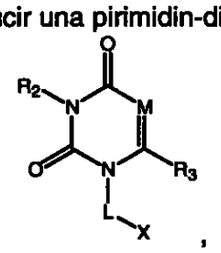
En aún otra realización, la presente invención provee un método para tratar

una condición caracterizada por la activación o la concentración inadecuada de linfocitos o células hematopoyéticas en un paciente que lo necesita, donde la condición es el resultado de una falla renal.

En aún otra realización, la presente invención provee un método para tratar una condición caracterizada por la activación o la concentración inadecuada de linfocitos o células hematopoyéticas en un paciente que lo necesita, donde la condición es el resultado de un trastorno en la médula ósea.

En otra realización, la presente invención provee un método para tratar una condición caracterizada por síntomas de inmunodeficiencia en un paciente que lo necesita, que comprende administrar a dicho paciente una cantidad efectiva para el uso terapéutico de un compuesto de acuerdo con la presente invención.

En aún otra realización, la presente invención provee un proceso para producir una pirimidin-diona de fórmula:



donde

M es N o CR_4;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo

carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

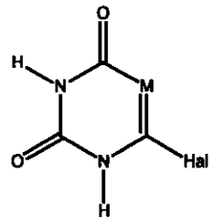
L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no

sustituido;

donde el proceso comprende los siguientes pasos:

(i) poner en contacto un compuesto de fórmula **A**



A

,

donde Hal es halógeno;

con un compuesto de fórmula **B**

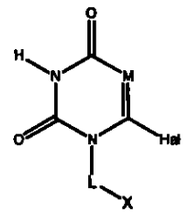
X—L—LG **B**,

donde LG es un grupo saliente;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

bajo condiciones suficientes para producir un compuesto de fórmula **C**



C

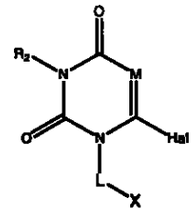
,

(ii) poner en contacto el compuesto de fórmula C con un compuesto de fórmula D

R_2—LG' D,

donde LG' es un grupo saliente;

bajo condiciones suficientes para producir un compuesto de fórmula E;



E

,

donde R_2 se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, anil(C_{1-10})alquilo, heteroanil(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido; y

(iii) poner en contacto el compuesto de fórmula E con un compuesto de fórmula R_3-H bajo condiciones suficientes para producir la pirimidin-diona.

En una variación, el producto de pirimidin-diona se convierte adicionalmente en una sal de adición ácida. En variaciones particulares, la sal de adición ácida se selecciona del grupo que consiste en acetato, citrato, clorhidrato, L-lactato, succinato, sulfato, p-toluensulfonato, bencensulfonato, benzoato,

metansulfonato, naftilen-2-sulfonato, propionato, bromhidrato, iodhidrato, R-mandelato y L-tartrato.

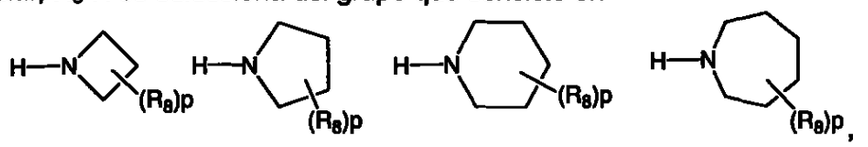
En otra variación de cada una de las realizaciones y variaciones anteriores, Hal se selecciona del grupo que consiste en Br, Cl y F en el compuesto de fórmula A.

En aún otra variación de cada una de las realizaciones y variaciones anteriores, el grupo saliente LG se selecciona del grupo que consiste en Br, Cl e I.

En aún otra variación de cada una de las realizaciones y variaciones anteriores, el paso (ii) comprende además la adición de una base. En variaciones particulares, la base es carbonato de potasio.

En aún otra variación de cada una de las realizaciones y variaciones anteriores, el producto E se purifica adicionalmente antes de someterlo al paso (iii). En una variación particular, la purificación del producto E se realiza empleando lavados con solventes y/o cromatografía.

En otra variación de cada una de las realizaciones y variaciones anteriores, R_3-H es una amina secundaria o un clorhidrato de amina. En una variación particular, R_3-H se selecciona del grupo que consiste en



donde p es 0-12 y cada R_8 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, ciano, nitro, hidroxilo, alquilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, o la sal de mono- o di-clorhidrato.

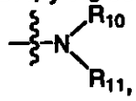
En aún otra variación de cada una de las realizaciones y variaciones anteriores, el paso (iii) comprende adicionalmente la purificación del producto, mediante el lavado del producto con uno o más solventes orgánicos, o mezclas de solventes, y/o por cromatografía en columna.

En otra variación de cada una de las realizaciones y variaciones anteriores, L se selecciona del grupo que consiste en –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -C(O)-, -CH_2C(O)-, -C(O)CH_2-, -CH_2-C(O)CH_2-, -C(O)CH_2CH_2-, -CH_2CH_2C(O)-, -O-, -OCH_2-, -CH_2O-, -CH_2OCH_2-, -OCH_2CH_2-, -CH_2CH_2O-, -N(CH_3)-, -$NHCH_2$-, -CH_2NH-, -CH_2NHCH_2-, -$NHCH_2CH_2$-, -CH_2CH_2NH-, -NH-C(O)-, -NCH_3-C(O)-, -C(O)NH-, -C(O)NCH_3-, -$NHC(O)CH_2$-, -C(O)$NHCH_2$-, -C(O)CH_2NH-, -$CH_2NHC(O)$-, -CH_2C(O)NH-, -$NHCH_2$C(O)-, -S-, -SCH_2-, -CH_2S-, -SCH_2CH_2-, -CH_2SCH_2-, -CH_2CH_2S-, -C(O)S-, -C(O)SCH_2-, -CH_2C(O)S-, -C(O)CH_2S-, y -$CH_2SC(O)$-, cada uno sustituido o no sustituido. En una variación particular, L se selecciona del grupo que consiste en -CH_2-, -C(O)-, -CH_2C(O)-, -C(O)CH_2-, -CH_2-C(O)CH_2-, -C(O)CH_2CH_2-, y -CH_2CH_2C(O)-, cada uno sustituido o no sustituido.

En aún otra variación de cada una de las realizaciones y variaciones anteriores, -L-X, tomados juntos, se seleccionan del grupo que consiste en -(CH_2)-(2-ciano)fenilo; -(CH_2)-(3-ciano)fenilo; -(CH_2)-(2-hidroxi)fenilo; -(CH_2)-(3-hidroxi)fenilo; -(CH_2)-(2-alquenil)fenilo; -(CH_2)-(3-alquenil)fenilo; -(CH_2)-(2-alquinil)fenilo; -(CH_2)-(3-alquinil)fenilo; -(CH_2)-(2-metoxi)fenilo; -(CH_2)-(3-metoxi)fenilo; -(CH_2)-(2-nitro)fenilo; -(CH_2)-(3-nitro)fenilo; -(CH_2)-(2-carboxi)fenilo; -(CH_2)-(3-carboxi)fenilo; -(CH_2)-(2-carboxamido)fenilo; -(CH_2)-(3-carboxamido)fenilo; -(CH_2)-(2-sulfonamido)fenilo; -(CH_2)-(3-sulfonamido)fenilo; -(CH_2)-(2-tetrazolil)fenilo; -(CH_2)-(3-tetrazolil)fenilo; -(CH_2)-(2-aminometil)fenilo; -(CH_2)-(3-aminometil)fenilo; -(CH_2)-(2-hidroximetil)fenilo; -(CH_2)-(3-

hidroximetil)fenilo; -(CH_2)-(2-fenil)fenilo; -(CH_2)-(3-fenil)fenilo; -(CH_2)-(2-halo)fenilo; -(CH_2)-(3-halo)fenilo; -(CH_2)-(2-$CONH_2$)fenilo; -(CH_2)-(3-$CONH_2$)fenilo; -(CH_2)-(2-$CONH(C_{1-7})$alquil)fenilo; -(CH_2)-(3-$CONH(C_{1-7})$alquil)fenilo; -(CH_2)-(2-$CO_2(C_{1-7})$alquil)fenilo; -(CH_2)-(3-$CO_2(C_{1-7})$alquil)fenilo; -(CH_2)-(2-NH_2)fenilo; -(CH_2)-(3-NH_2)fenilo; -(CH_2)-(2-(C_{3-7})alquil)fenilo; -(CH_2)-(3-(C_{3-7})alquil)fenilo; -(CH_2)-(2-(C_{3-7})cicloalquil)fenilo; -(CH_2)-(3-(C_{3-7})cicloalquil)fenilo; -(CH_2)-(2-aril)fenilo; -(CH_2)-(3-aril)fenilo; -(CH_2)-(2-heteroaril)fenilo; -(CH_2)-(3-heteroaril)fenilo; -(CH_2)-2-bromo-5-fluoro fenilo; -(CH_2)-2-cloro-5-fluoro fenilo; -(CH_2)-2-ciano-5-fluoro fenilo; -(CH_2)-2,5-dicloro fenilo; -(CH_2)-2,5-difluoro fenilo; -(CH_2)-2,5-dibromo fenilo; -(CH_2)-2-bromo-3,5-difluoro fenilo; -(CH_2)-2-cloro-3,5-difluoro fenilo; -(CH_2)-2,3,5-trifluoro fenilo; -(CH_2)-2,3,5,6-tetrafluorofenilo; -(CH_2)-2-bromo-3,5,6-trifluoro fenilo; -(CH_2)-2-cloro-3,5,6-trifluoro fenilo; -(CH_2)-2-ciano-3,5-difluoro fenilo; -(CH_2)-2-ciano-3,5,6-trifluoro fenilo; -(CH_2)-(2-heterocicloalquil)fenilo; y -(CH_2)-(3-heterocicloalquil)fenilo, cada uno sustituido o no sustituido.

En otra variación de cada una de las realizaciones y variaciones anteriores, M es CH, y R_3 comprende la fórmula

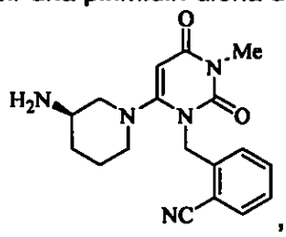


donde R_{10} y R_{11} se seleccionan cada uno independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo sulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido, o R_{10} y R_{11} se toman juntos para formar un anillo de 4, 5, 6 ó 7 miembros, cada uno sustituido o no sustituido.

En aún otra variación, M es CH y R_3 se selecciona del grupo que consiste en 3-amino-piperidinil-1-ilo, 3-aminometil-pirrolidin-1-ilo, 2-aminoazetidin-1-ilo, 3-amino-3-metilpiperidin-1-ilo, 3-aminociclopent-1-ilo, 3-aminometilciclopent-1-ilo, 3-aminometilciclohex-1-ilo, 3-aminohexahidroazepin-1-ilo, 3-amino-ciclohex-1-ilo, piperazin-1-ilo, homopiperazin-1-ilo, 3-amino-pirrolidin-1-ilo, R-3-aminopiperidin-1-ilo, R-3-amino-3-metilpiperidin-1-ilo, 3-amino-ciclohex-1-ilo, 3-amino-ciclopent-1-ilo, y 3-amino-pirrolidin-1-ilo, cada uno sustituido o no sustituido.

En aún otra variación, M es CH y R_2 es un (C_{1-10})alquilo sustituido o no sustituido.

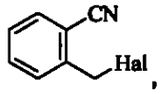
En otras realizaciones, la presente invención provee un proceso para producir una pirimidin-diona de fórmula



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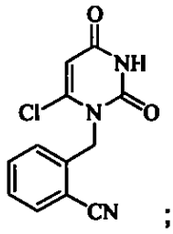
que comprende:

(i) mezclar 6-cloro-1H-pirimidin-2,4-diona con un haluro de arilo de fórmula



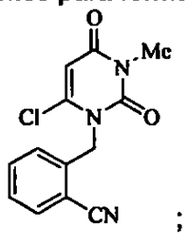
,

donde Hal es Br, Cl o I, bajo condiciones suficientes para producir un compuesto de fórmula



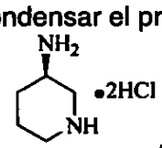
;

(ii) alquilar el producto anterior con un haluro de metilo bajo condiciones suficientes para formar un compuesto de fórmula



; y

(iii) condensar el producto anterior con un compuesto de fórmula



En una variación de la realización anterior, el proceso para producir una pirimidin-diona comprende además la formación de una sal de adición ácida. En una variación particular, la sal de adición ácida es una sal de benzoato.

En otra variación de cada una de las realizaciones y variaciones anteriores, la pirimidin-diona se selecciona del grupo que consiste en:

2-(6-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-benzonitrilo;

2-(6-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-5-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3-amino-piperidin-1-il]-1-(2-bromo-bencil)-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-iodo-bencil)-1H-pirimidin-2,4-diona,

6-[3-amino-piperidin-1-il]-1-(2-bromo-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-cloro-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-cloro-4-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-bromo-bencil)-3-metil-1H-pirimidin-2,4-diona;

2-{6-[azepan-3(±)-ilamino]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (14);

2-{6-[3(±)-amino-azepan-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-[6-(2-amino-etilamino)-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(3-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(4-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-[6-(3-amino-piperidin-1-il)-3-(1H-benzoimidazol-2-ilmetil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3-(4-pirazol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3-(3-pirrol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-

ilmetil]-tiofeno-3-carbonitrilo;

metil éster de ácido 3-{4-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

ácido 3-{4-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-1-(2,5-*di*-cloro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-3,6-*di*-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

(R)-2-((6-(3-amino-3-metilpiperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidropirimidin-1(2H)-il)metil)-4-fluorobenzonitrilo; y

6-[3-amino-piperidin-1-il]-1,3-bis-(2-bromo-5-fluoro-bencil)-1H-pirimidin-2,4-diona.

El proceso de la reivindicación 133, donde la pirimidin-diona se selecciona del grupo que consiste en:

2-{6-[3(R)-amino-piperidin-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-iodo-bencil)-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-4-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-3-metil-1H-pirimidin-2,4-diona;

2-{6-[3(R)-amino-piperidin-1-il]-3-(3-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-(4-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(4-pirazol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(3-pirrol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil]-tiofeno-3-carbonitrilo;

metil éster de ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico; y

6-[3(R)-amino-piperidin-1-il]-1,3-bis-(2-bromo-5-fluoro-bencil)-1H-pirimidin-2,4-diona.

En aún otra variación de cada una de las realizaciones y variaciones anteriores, la pirimidin-diona está presente como una mezcla de estereoisómeros. En aún otra variación, la pirimidin-diona comprende un único estereoisómero.

Se señala con respecto a todas las realizaciones, y cualquier realización, variante o compuesto particular adicional descrito o reivindicado en la presente que todas estas realizaciones, variaciones, y/o compuestos particulares incluyen todas las formas de sal aceptables para uso farmacéutico tanto en forma de un único éstereoisómero como una mezcla de éstereoisómeros, salvo que se establezca específicamente lo contrario De manera similar, cuando se encuentra presente uno o más centros potencialmente quirales en cualquiera de las realizaciones, variaciones, y/o compuestos particulares especificados o reivindicados en la presente, se abarcan ambos posibles centros quiral salvo que se establezca específicamente lo contrario.

A. Sales, hidratos y prodrogas de inhibidores de DPP-IV

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

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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, fémicas, 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°Currencia natural, aminas cíclicas y resinas de intercambio iónico básicas, por ejemplo, arginina, betaína, cafeína, cloroprocaína, colina, N,N'-dibenciletilendiamina (benzatina), diciclohexilamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilendiamina, N-etilmorfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, isopropilamina, 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.

3. Indicaciones para usar los inhibidores de DPP-IV

Se cree que DPP-IV contribuye a la patología y/o la sintomatología de diversas enfermedades, de modo que puede usarse la reducción de la actividad de DPP-IV en un sujeto, a través de su inhibición, para tratar en forma terapéutica estos estados de enfermedad. Se describen ejemplos de varias enfermedades que pueden tratarse usando los inhibidores de DPP-IV de la presente invención en la presente documentación. Debe destacarse que pueden identificarse posteriormente otras enfermedades, además de aquellas descriptas en la presente documentación, una vez que se comprenda mejor la función de DPP-IV en varias vías.

Un conjunto de indicaciones cuyo tratamiento puede efectuarse con los inhibidores DPP-IV de la presente invención incluye aquellas que comprenden la prevención y el tratamiento de la diabetes y la obesidad, en particular la diabetes mellitus tipo 2, la dislipidemia diabética, las condiciones de tolerancia alterada a la glucosa (IGT), las condiciones de glucosa en plasma en ayuno alterada (IFG), la acidosis metabólica, la cetosis, la regulación del apetito y la obesidad.

También pueden usarse los inhibidores de DPP-IV de la presente invención como inmunosupresores (o las drogas supresoras de la liberación de citoquina),

para tratar, entre otras indicaciones, el rechazo a transplantaes de órganos, enfermedades autoinmunes, tales como la enfermedad intestinal inflamatoria, la esclerosis múltiple y la artritis reumatoide, y el tratamiento del SIDA.

Los inhibidores de DPP-IV de la presente invención también pueden usarse para tratar varios cánceres, incluyendo cáncer de mama, cáncer de pulmón y cáncer de próstata.

Los inhibidores de DPP-IV de la presente invención también pueden usarse para tratar enfermedades dermatológicas, tales como psoriasis, artritis reumatoide (RA) y liquen plano.

Los inhibidores de DPP-IV de la presente invención también pueden usarse para tratar la infertilidad y la amenorrea.

Los inhibidores de DPP-IV de la presente invención también pueden usarse para modular el corte de varias citoquinas (a través de la estimulación de las células hematopoyéticas), factores de crecimiento y neuropéptidos. Por ejemplo, dichas condiciones°Curren frecuentemente en pacientes inmunosuprimidos, por ejemplo, como consecuencia de la quimioterapia y/o la terapia con radiación para tratar el cáncer.

Los inhibidores de DPP-IV de la presente invención también pueden usarse para prevenir o reducir el corte del fragmento Tyr-Ala N-terminal del factor liberador de hormona de crecimiento. Por consiguiente, pueden usarse estos inhibidores en el tratamiento de la estatura baja debida a deficiencias de hormonas de crecimiento (enanismo), y en la promoción del crecimiento o la regeneración tisular dependiente de GH.

Los inhibidores de DPP-IV de la presente invención también pueden usarse para tratar estados de enfermedad asociados con el corte de neuropéptidos, y,

por consiguiente, pueden ser útiles para regular o normalizar trastornos neurológicos.

Para indicaciones oncológicas, pueden usarse los inhibidores de DPP-IV de la presente invención, en combinación con otros agentes, para tratar la proliferación celular indeseable y descontrolada. Los ejemplos de otros agentes anti-proliferación celular que pueden usarse en combinación con los inhibidores de DPP-IV de la presente invención incluyen, sin limitaciones, ácido retinoide y derivados del mismo, 2-metoxiestradiol, proteína ANGIOSTATIN™, proteína ENDOSTATIN™, suramina, esqcalamina, inhibidor tisular de la metaloproteinasa-1, inhibidor tisular de la metaloproteinasa-2, inhibidor del activador del plasminógeno-1, inhibidor del activador del plasminógeno-2, inhibidor derivado de cartílagos, paclitaxel, factor plaquetario 4, sulfato de protamina (clupeína), derivados sulfatados de quitina (preparados a partir de caparazones de cangrejo reina), complejos sulfatados de polisacáridos y peptidoglicanos (sp-pg), estaurosporina, moduladores del metabolismo de la matriz, incluyendo, por ejemplo, análogos de prolina ((ácido 1-azetidin-2-carboxílico (LACA)), cishidroxiprolina, d,1-3,4-dehidroprolina, tiaprolina, fumarato de beta-aminopropionitrilo, 4-propil-5-(4-piridinil)-2(3H)-oxazolona, metotrexato, mitoxantrona, heparina, interferones, suero de 2 macroglobulina, chimp-3, quimostatina, tetradecasulfato de beta-ciclodextrina, eponemicina; fumagillna, tiomalato de oro de sodio, d-penicilamina (CDPT), suero de beta-1-anticolagenasa, alfa-2-antiplasmina, bisantreno, lobenzarit disodio, disodio de ácido n-2-carboxifenil-4-cloroantronílico o "CCA", talidomida; ésteroides angostáticos, carboxiaminoimidazol; inhibidores de metaloproteinasas, tales como BB94. Otros agentes anti-angiogénesis que pueden usarse incluyen anticuerpos, preferiblemente anticuerpos monoclonales contra estos factores de crecimiento angiogénicos: bFGF, aFGF, FGF-5, isoformas de VEGF, VEGF-C, HGF/SF y Ang-

1/Ang-2. Ferrara N. y Alitalo, K. "Clinical application of angiogenic growth factors and their inhibitors" (1999) Nature Medicine 5:1359-1364.

4. Composiciones que comprenden inhibidores de DPP-IV

Puede usarse una amplia variedad de composiciones y métodos de administración en combinación con los inhibidores de DPP-IV de la presente invención. Dichas composiciones pueden incluir, además de los inhibidores de DPP-IV de la presente invención, excipientes farmacéuticos convencionales y otros agentes convencionales sin actividad farmacéutica. Adicionalmente, las composiciones pueden incluir agentes activos, además de los inhibidores de DPP-IV 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 inhibidores de DPP-IV 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 DPP-IV, 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 DPP-IV, 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 inhibidores de DPP-IV 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 inhibidores de DPP-IV 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 inhibidores de DPP-IV 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 DPP-IV de la presente invención, para reducir la actividad de DPP-IV *in vivo*, para tratar el estado de enfermedad en el sujeto.

Las formas de dosificación o las composiciones pueden comprender opcionalmente uno o más inhibidores de DPP-IV 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 DPP-IV, opcionalmente 0,1-95%, y opcionalmente 1-95%.

Pueden prepararse sales, preferiblemente sales de sodio, de los inhibidores de DPP-IV, 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.

A. 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 inhibidores de DPP-IV 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 inhibidores de DPP-IV 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 inhibidores de DPP-IV 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 agregados 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 N° 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 N° Re 28819 y 4358603.

B. Inyectables, soluciones y emulsiones

La presente invención también hace referencia a composiciones diseñadas para administrar los inhibidores de DPP-IV de la presente invención por administración parenteral, generalmente caracterizada por inyección, ya sea 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 N° 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, mercuriales, 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 de DPP-IV en la formulación parenteral, de modo que una inyección pueda administrar una cantidad efectiva para el uso farmacéutico, suficiente para producir el efecto farmacológico deseado. La concentración de extracto de un inhibidor de DPP-IV, 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 DPP-IV, que se administrará a los tejidos a tratar. El inhibidor de DPP-IV 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 DPP-IV 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.

C. Polvos liofilizados

Los inhibidores de DPP-IV 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 DPP-IV 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.

D. Administración tópica

Los inhibidores de DPP-IV 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 DPP-IV 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 de DPP-IV 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 intracistémicas 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 DPP-IV, solo o en

combinación con otros excipientes aceptables para el uso farmacéutico.

E. 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 espermaceti 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.

F. 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

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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	hasta 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%.

5.Equipos que comprenden inhibidores de DPP-IV

La invención también se relaciona con equipos y otros artículos de manufactura para tratar enfermedades asociadas con la DPP-IV. Debe destacarse que estas enfermedades abarcan todas las condiciones donde DPP-IV posee 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 DPP-IV 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 DPP-IV 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 de manufactura 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.

EJEMPLOS

1. <u>Preparación de inhibidores de DPP-IV</u>

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 (enantiómeros, 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) como para poder separarlos 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 Resoluciones, 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, tetrahidrofuranoo 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:

g (gramos);	mg (miligramos);
l (litros);	ml (mililitros);
µl (microlitros);	psi (libras por pulgada cuadrada);
M (molar);	mM (milimolar);
i.v. (intravenoso);	Hz (Hertz);
M Hz (megahertz);	mol (moles);
mmol (milimoles);	RT (temperatura ambiente);
min (minutos);	h (horas);
mp (punto de fusión);	TLC (cromatografía en capa delgada);
Tr (tiempo de retención);	RP (fase inversa);
MeOH (metanol);	i-PrOH (isopropanol);
TEA (trietilamina);	TFA (ácido trifluoroacético);
TFAA (anhídrido trifluoroacético);	THF (tetrahidrofuranoo);
DMSO (dimetilsulfóxido);	EtOAc (acetato de etilo);
DME (1,2-dimetoxietano);	DCM (diclorometano);
DCE (dicloroetano);	DMF (N,N-dimetilformamida);
DMPU (N,N'-dimetilpropilenurea);	CDI (1,1-carbonildiimidazol);

IBCF (cloroformato de isobutilo); HOAc (ácido acético);

HOSu (N-hidroxisuccinimino); HOBT (1-hidroxibenzotriazol);

Et_2O (dietil éter); EDCI (clorhidrato de etilcarbodiimino);

BOC (ter-butiloxicarbonilo); FMOC (9-fluorenilmetoxicarbonilo);

DCC (diciclohexilcarbodiimino); CBZ (benciloxicarbonilo);

Ac (acetilo); atm (atmósfera);

TMSE (2-(trimetilsilil)etilo); TMS (trimetilsililo);

TIPS (triisopropilsililo); TBS (t-butildimetilsililo),

DMAP (4-dimetilaminopiridina); Me (metilo);

OMe (metoxilo); Et (etilo);

Et (etilo); tBu (ter-butilo);

HPLC (cromatografía líquida de alta presión);

BOP (cloruro bis(2-oxo-3-oxazolidinil)fosfínico);

TBAF (fluoruro de tetra-n-butilamonio);

mCPBA (ácido meta-cloroperbenzoico).

Todas las referencias a éter o Et_2O representan dietil éter; 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).

2. Esquemas de Síntesis Para Inhibidores de DPP-IV de la Presente Invención

Los inhibidores de DPP-IV de acuerdo con la presente invención pueden sintetizarse de acuerdo con diversos esquemas de reacción. Se proveen en los ejemplos de la presente algunos esquemas ilustrativos. Los especialistas en la materia pueden deducir fácilmente otros esquemas de reacción.

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.

Al cambiar los grupos Q^1 y Q^2, R_1, R_2 y R_3, puede sintetizarse una amplia variedad de inhibidores de DPP-IV diferentes de acuerdo con la presente invención.

En cada uno de los esquemas de reacción anteriores, pueden

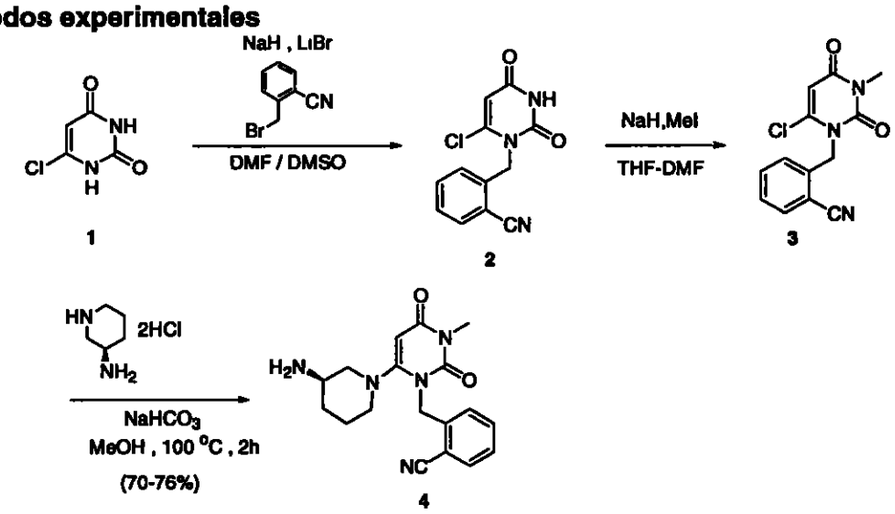
seleccionarse los distintos sustituyentes entre los diversos sustituyentes indicados en la presente documentación.

En la presente documentación se presentan descripciones de la síntesis de compuestos particulares de acuerdo con la presente invención, basadas en los esquemas de reacción anteriores.

3. Ejemplos de inhibidores de DPP-IV

La presente invención se ilustra adicionalmente, pero sin limitaciones, a través de los siguientes ejemplos, que describen la síntesis de compuestos particulares de acuerdo con la invención.

Métodos experimentales



2-(6-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-benzonitrilo (2). A una solución de 6-clorouracilo (20 g, 122 mmol) en una mezcla de DMF-DMSO (6:1, 600 ml) bajo nitrógeno a 0°C, se agregó hidruro de sodio (60%, 5,5 g, 137 mmol) en porciones. Después de 0,5 h, se agregó bromuro de litio (8 g, 96 mmol) en la mezcla y se agitó por 15 min a 0°C. Se agregó una solución de α-bromo-*o*-tolunitrilo (25,1 g, 128 mmol) en DMF (30 ml) por goteo, se agitó a esta

temperatura por 1 h y luego a RT durante la noche. Se comprenderá que la alquilación de la amina puede efectuarse bajo condiciones convencionales conocidas en la técnica, incluyendo el uso de una base, tal como NaH, LiH o semejantes, en un solvente orgánico o una mezcla de solventes. El solvente puede incluir DMSO, THF, DMF y semejantes, o mezclas de éstos. Además, pueden usarse aditivos, incluyendo LiBr, LiI, NaI y semejantes. La mezcla se evaporó y se co-evaporó con agua al vacío para eliminar la mayor parte del DMF, y luego se vertió en agua helada (1 l) Se recolectó el precipitado por filtración. El producto crudo se suspendió en AcOEt-$CHCl_3$ caliente y se sonicó por 5 min, se dejó reposar a 0 °C por 1 h, y luego se filtró para obtener un sólido blanco que comprendía el compuesto del título (19 g) con 54% de rendimiento. Aquellos entrenados en la técnica también comprenderán que puede lograrse la purificación usando varios métodos conocidos en la técnica, incluyendo el lavado con un solvente acuoso/orgánico o una mezcla de solventes, la recristalización y/o la cromatografía en columna. Los ejemplos no limitantes de solventes orgánicos y mezclas de solventes pueden incluir acetato de etilo, acetato de isopropilo, acetona, THF y semejantes. ^{1}H-NMR (400 M Hz, DMSO): δ 11,82 (s, 1H), 7,87 (d, 1H, J = 7,6 Hz), 7,71 (t, 1H, J = 7,6 Hz), 7,51 (t, 1H, J = 7,6 Hz), 7,37 (d, 1H, J = 8 Hz), 6,06 (s, 1H), 5,31 (s, 2H). MS (ES) [m+H] calculado para $C_{12}H_9ClN_3O_2$, 262,0; hallado 262,0.

2-(6-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-benzonitrilo (3). A una solución fría (0°C) de 6-clorouracilo bencilado **2** (10 g, 38 mmol) en DMF-THF (1:1, 300 ml) bajo nitrógeno, se agregó NaH (60%, 1,6 g, 39,9 mmol) en porciones, a lo que siguió la adición de LiBr (2g). La mezcla se agitó a temperatura ambiente por 20 min. Después de agregar iodometano (5,4 ml, 76

mmol), se selló el frasco y se agitó a esta temperatura por 10 min, a temperatura ambiente por 2 h, y a 35°C durante la noche, y luego se concentró al vacío. Se comprenderá que la alquilación de la amina puede efectuarse bajo condiciones convencionales conocidas en la técnica, incluyendo el uso de una base, tal como NaH, LiH o semejantes, en un solvente orgánico o una mezcla de solventes. El solvente puede incluir DMSO, THF, DMF y semejantes, o mezclas de éstos. Además, pueden usarse aditivos, incluyendo LiBr, LiI, NaI y semejantes. Por ejemplo, puede realizarse la alquilación usando ioduro de metilo y K_sCO_2 en acetona. La reacción puede realizarse a aproximadamente 15-45°C, preferiblemente a aproximadamente 20-43°C, y más preferiblemente a aproximadamente 35-41°C hasta completar la reacción. Se disolvió el residuo en $CHCl_3$ y se lavó con agua y solución salina, se secó (Na_2SO_4) y se filtró, luego se concentró al vacío. El producto crudo se cristalizó a partir de THF-hexanos para obtener 7,6 g (72%) del compuesto del título **3**. Aquellos entrenados en la técnica también comprenderán que puede lograrse la purificación del benzonitrilo en una variedad de solventes orgánicos o mezclas de solventes. Por ejemplo, puede purificarse el benzonitrilo agregando una mezcla de diclorometano y heptano. Opcionalmente, puede purificarse el benzonitrilo en un solvente orgánico o una mezcla de solventes, tal como diclorometano, cloroformo, acetonitrilo, THF, acetato de etilo, acetato de isopropilo y semejantes. Preferiblemente, el producto se purifica y se lava con acetato de etilo. ^{1}H NMR (400 M Hz, DMSO): δ 7,87 (d, 1H, J = 7,6 Hz), 7,70 (t, 1H, J = 7,6 Hz), 7,51 (t, 1H, J = 7,6 Hz), 7,40 (d, 1H, J = 8 Hz), 6,21 (s, 1H), 5,38 (s, 2H), 3,28 (s, 3H). MS (ES) [m+H] calculado para $C_{13}H_{11}ClN_3O_2$, 276,1; hallado 276,1.

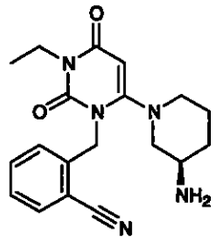
2-[6-[3(R)-amino-piperidin-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-

ilmetil}-benzonitrilo (4). Se agitó 2-(6-cloro-3-metil-2,4-dioxo-3,4-dihidro-2-H-pirimidin-1-ilmetil)-benzonitrilo (330 mg, 1,08 mmol), clorhidrato de (*R*)-3-amino-piperidina (246 mg, 1,4 mmol) y bicarbonato de sodio (500mg, 5,4 mmol) con 200 mg de tamices moleculares activados (4A) en MeOH seco (5 ml) a 100°C por 2 h. La reacción se filtró a través de Celite, se concentró al vacío y luego se diluyó con $CHCl_3$, y se lavó con agua. La fase acuosa se extrajo con $CHCl_3$ y se lavaron las fases orgánicas combinadas con agua, se secó (Na_2SO_4) y se filtró Se agregó TFA (1 ml) a la solución, que luego se concentró al vacío. Se disolvió el residuo en una pequeña cantidad de MeOH, y se agregó Et_2O para forzar la precipitación. La mezcla se dejó reposar a temperatura ambiente durante la noche. Aquellos entrenados en la técnica comprenderán que la condensación con al amina o el clorhidrato de amina puede realizarse en un solvente o una mezcla de solventes, con una base, tal como carbonato de potasio, bicarbonato de sodio y semejantes, o mezclas de éstos. El solvente puede comprender solventes próticos y apróticos, o mezclas de éstos. Por ejemplo, el solvente puede comprender una mezcla de alcohol isopropílico y agua. Además, puede calentarse la reacción a aproximadamente 30-100°C, preferiblemente a aproximadamente 35-55°C, y más preferiblemente a aproximadamente 45-50°C hasta su compleción. Se decantaron los solventes y se lavó el sólido con Et_2O dos veces para obtener 270 mg de producto como un polvo blanquecino. También se comprenderá que puede purificarse adicionalmente el producto lavándolo con un solvente orgánico o una mezcla de solventes. Los ejemplos no limitantes de solventes o mezclas de solventes incluyen acetato de isopropilo, acetato de etilo, diclorometano, heptano y semejantes. Además, puede purificarse opcionalmente el producto por cromatografía en columna.

Puede aislarse el producto de benzonitrilo como la base libre, si se lo desea, pero preferiblemente puede convertirse adicionalmente el producto en la sal de adición ácida correspondiente, tal como la sal de ácido benzoico. Preferiblemente, el producto de benzonitrilo se trata con ácido benzoico para formar benzoato de 2-[6-(3-amino-piperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo (**4**). La preparación y el aislamiento de la sal de benzoato puede realizarse empleando métodos convencionales para la formación de sales de adición ácida. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1): δ 7,82 (d, 1H, J = 7,6 Hz), 7,65 (t, 1H, J = 7,6 Hz), 7,46 (t, 1H, J = 7,6 Hz), 7,23 (d, 1H, J = 8,0 Hz), 5,42 (s, 1H), 5,50-5,00 (ABq, 2H, J = 41,6, 15,2 Hz), 3,30 (m, 2H), 3,16 (s, 3H), 2,91 (m, 1H), 2,76 (m, 2H), 1,93 (m, 1H), 1,79 (m, 1H), 1,51 (m, 2H). MS (ES) [m+H] calculado para $C_{18}H_{22}N_5O_2$, 340,2; hallado, 340,2.

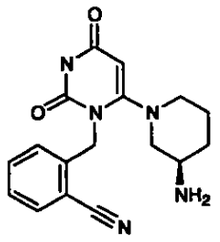
En cada uno de los pasos anteriores, pueden evitarse los pasos de aislamiento y/o purificación de los compuestos intermedios si se obtienen los intermediarios de la mezcla de reacción como compuestos relativamente puros, y si los subproductos o las impurezas de la mezcla de reacción no interfieren con los pasos de reacción subsiguientes. Cuando sea posible, podrá eliminarse uno o más pasos de aislamiento paras obtener tiempos de procesamiento más cortos, y la eliminación del procesamiento adicional también puede resultar en un mayor rendimiento total de la reacción.

Compuesto 5



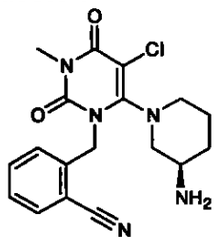
2-{6-[3(R)-amino-piperidin-1-il]-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo TFA salt (5). El compuesto del título, 5, se preparó a partir de la muestra 2, usando los procedimientos descriptos para la preparación de las muestras 3 y 4, excepto que se usó bromuro de etilo en lugar de iodometano. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1): δ 7,66 (d, *J* = 7,8 Hz, 1H), 7,59 (td, *J* = 7,8, 1,4 Hz, 1H), 7,40 (t, *J* = 7,6 Hz, 1H), 7,26 (d, *J* = 7,6 Hz, 1H), 5,41 (s, 1H), 5,13-5,23 (ABq, 2H, J = 41,6, 15,2 Hz), 3,91 (q, *J* = 7,1 Hz, 2H), 3,37 (m, 2H), 2,87-2,98 (m, 2H), 2,70 (m, 1H), 2,12 (m, 1H), 1,88 (m, 1H), 1,67 (m, 2H), 1,15 (t, *J* = 6,9 Hz, 3H). MS (ES) [m+H] calculado para $C_{19}H_{24}N_5O_2$, 354,2; hallado, 354,2.

Compuesto 6



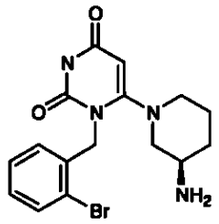
2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (6). El compuesto del título 6 se preparó a partir del compuesto 2, empleando el procedimiento usado en la preparación del compuesto 4. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1): δ 7,65 (d, *J* = 7,5 Hz, 1H), 7,58 (t, *J* = 7,8 Hz, 1H), 7,39 (t, *J* = 7,5 Hz, 1 H), 7,27 (d, *J* = 7,8 Hz, 1H), 5,32 (s, 1H), 5,13-5,13 (ABq, 2H, J = 30,0, 15,0 Hz), 3,39 (m, 2H), 2,95 (m, 2H), 2,69 (m, 1H), 2,12 (m, 1H), 1,85 (m, 1H), 1,64 (m, 2H). MS (ES) [m+H] calculado para $C_{17}H_{20}N_5O_2$, 326,2; hallado, 326,2.

Compuesto 7



2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (7). El compuesto 4 (40 mg, 0,1 mmol), en $CHCl_3$ (2 ml), se trató $SOCl_2$ (200 µl) a 100°C por 30 min, se concentró, y luego se purificó por LC-MS para obtener el compuesto del título **7**. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1): δ 7,73 (d, *J* = 7,6 Hz, 1H), 7,64 (t, *J* = 7,6 Hz, 1H), 7,45 (t, *J* = 7,6 Hz, 1H), 7,14 (d, *J* = 8,1 Hz, 1H), 5,32-5,42 (m, 2H), 3,43 (s, 3H), 3,33-3,40 (m, 2H), 3,17 (m, 2H), 2,87 (s, 1H), 2,08 (m, 1H), 1,70 (m, 1H), 1,32-1,43 (m, 2H). MS (ES) [m+H] calculado para $C_{18}H_{21}ClN_5O_2$, 374,1; hallado, 374,1.

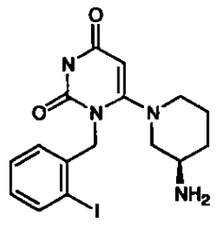
Compuesto 8



6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-1H-pirimidin-2,4-diona (8). El compuesto del título se preparó en dos pasos. El primer paso se completó usando el procedimiento empleado para la preparación del compuesto 2, excepto que se usó bromuro de 2-bromobencilo en lugar de α-bromo-*o*-tolunitrilo. Luego se convirtió el producto en el compuesto del título, empleando el método usado en la preparación del compuesto 4. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1): δ 7,52 (d, *J* = 8,1 Hz, 1H), 7,24 (t, *J* = 7,8 Hz, 1H), 7,10 (t, *J* = 7,8 Hz, 1H), 6,89 (d, *J* = 7,579

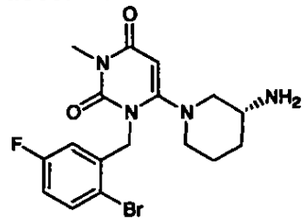
Hz, 1H), 5,27 (s, 1H), 4,92-5,04 (ABq, J = 34,1, 15,0 Hz, 2H), 3,27 (bd, J = 10,4 Hz, 1H), 3,09-3,18 (m, 1H), 2,89 (m, 1H), 2,70 (t, J = 10,9 Hz, 1H), 2,48 (t, J = 12,0 Hz, 1H), 2,03 (m, 1H), 1,60-1,71 (m, 1H), 1,42-1,53 (m, 2H). MS (ES) [m+H] calculado para $C_{16}H_{20}BrN_4O_2$, 379,1; hallado, 379,1.

Compuesto 9



6-[3 (R)-amino-piperidin-1-il]-1-(2-iodo-bencil)-1H-pirimidin-2,4-diona (9). El compuesto del título se preparó empleando el procedimiento descripto para la preparación del compuesto 8, excepto que se usó cloruro de 2-iodobencilo como reactivo bencilante. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1): δ 7,76 (d, J = 7,6 Hz, 1H), 7,21 (t, J = 7,3 Hz, 1H), 6,89 (t, J = 7,2 Hz, 1H), 6,79 (d, J = 7,3 Hz, 1H), 5,26 (s, 1H), 4,79 – 4,92 (ABq, J = 34,1, 6,7,0 Hz, 2H), 3,27 (m, 1H), 3,13 (s, 1H), 2,85 (d, J = 11,6 Hz, 1H), 2,70 (m, 1H), 2,41 (m, 1H), 2,02 (m, 1H), 1,60 (m, 1H), 1,45 (m, 2H). MS (ES) [m+H] calculado para $C_{16}H_{20}IN_4O_2$, 427,1; hallado, 427,1.

Compuesto 10

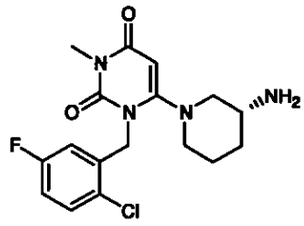


6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona (10). A una solución de 6-clorouracilo (220 mg, 1,5 mmol) en una mezcla de DMF-DMSO seco (6:1, 5 ml) bajo nitrógeno a 0°C, se agregó hidruro de

sodio (60%, 61 mg, 1,8 mmol) en porciones. Después de 0,5 h, se agregó bromuro de litio (83 mg, 1 mmol) y se agitó la mezcla por 15 min a 0°C. Se agregó una solución de bromuro de 2-bromo-5-fluoro-bencilo (497 mg, 1,8 mmol) en DMF (30 ml) por goteo, y se agitó a esta temperatura por 1 h, y luego a temperatura ambiente durante la noche. La mezcla se evaporó y se co-evaporó con agua al vacío para eliminar la mayor parte del DMF, y luego se vertió en agua helada. El precipitado se recolectó por filtración, y luego se suspendió en MeOH frío y se filtró. La solución se concentró para obtener el producto monobencilado crudo.

El producto crudo se trató con NaH y MeI, usando el procedimiento descripto para la preparación del compuesto 3, seguido por el procedimiento usado en la preparación del compuesto 4m para obtener el compuesto del título. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,46 (dd, *J* = 8,7, 5,2 Hz, 1H), 6,82 (td, *J* = 8,3, 2,9 Hz, 1H), 6,59 (dd, *J* = 9,1, 3,0 Hz, 1H), 5,28 (s, 1H), 4,99-5,06 (ABq, *J* = 41,7, 16,7 Hz, 2H), 3,28 (m, 1H), 3,23 (s, 3H), 3,13-3,21 (m, 1H), 2,86 (bd, *J* = 12,6 Hz, 1H), 2,71 (t, *J* = 10,5 Hz, 1H), 2,47 (t, *J* = 11,0 Hz, 1H), 2,00-2,08 (m, 1H), 1,65-1,74 (m, 1H), 1,42-1,53 (m, 2H). MS (ES) [m+H] calculado para $C_{17}H_{21}BrFN_4O_2$, 411,1; hallado, 411,1.

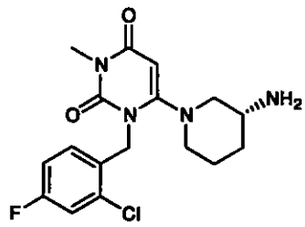
Compuesto 11



6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona (11). El compuesto del título se preparó a partir del compuesto 1, usando el mismo procedimiento que para la preparación del compuesto 10,

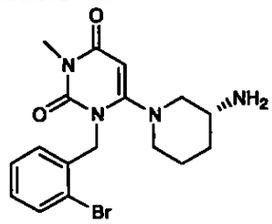
excepto que se usó bromuro de 2-cloro-5-fluoro-bencilo en lugar de bromuro de 2-bromo-5-fluoro-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1): δ 7,34-7,40 (dd, *J* = 8,5, 5,1 Hz, 1H), 6,97 (td, *J* = 8,3, 2,9 Hz, 1H), 6,72 (dd, *J* = 9,0, 2,9 Hz, 1H), 5,41 (s, 1H), 5,11-5,19 (ABq, *J* = 41,7, 16,7 Hz, 2H), 3,37 (s, 1H), 3,32 (s, 3H), 3,23-3,30 (m, 1H), 2,96 (d, *J* = 12,1 Hz, 1H), 2,81 (t, *J* = 10,2 Hz, 1H), 2,59 (t, *J* = 11,1 Hz, 1H), 2,13 (d, *J* = 10,4 Hz, 1H), 1,76-1,86 (m, 1H), 1,52-1,63 (m, 2H). MS (ES) [m+H] calculado para $C_{17}H_{21}ClFN_4O_2$, 367,1; hallado 367,1.

Compuesto 12



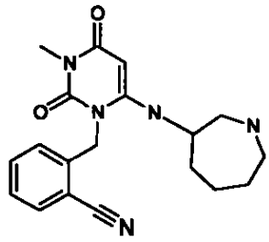
6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-4-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona (12). El compuesto del título se preparó a partir del compuesto 1, usando el mismo procedimiento descripto para la preparación del compuesto 10, excepto que se usó bromuro de 2-cloro-4-fluoro-bencilo en lugar de bromuro 2-bromo-5-fluoro-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,15 (dd, *J* = 8,211, 2,400 Hz, 1H), 6,95-7,06 (m, 2H), 5,40 (s, 1H), 5,09-5,18 (ABq, *J* = 37,7, 15,9 Hz, 2H), 3,33-3,39 (m, 1H), 3,30 (s, 3H), 3,23-3,29 (m, 1H), 2,98 (bd, *J* = 12,9 Hz, 1H), 2,79 (t, *J* = 10,4 Hz, 1H), 2,55-2,66 (t, *J* = 11,2 Hz, 1H), 2,13 (m, 1H), 1,78-1,88 (m, 1H), 1,55-1,65 (m, 2H). MS (ES) [m+H] calculado para $C_{17}H_{21}ClFN_4O_2$, 367,1; hallado 367,1.

Compuesto 13

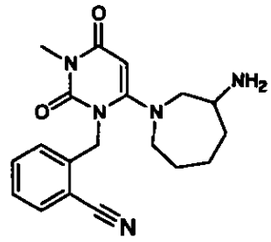


6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-3-metil-1H-pirimidin-2,4-diona (13) El compuesto del título se preparó a partir del compuesto 1, usando los procedimientos descriptos para la síntesis del compuesto **10**, excepto que se usó bromuro de 2-bromo bencilo en lugar de bromuro de 2-bromo-5-fluoro-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1): δ 7,45 (d, *J* = 7,8 Hz, 1H), 7,16 (t, *J* = 7,5 Hz, 1H), 7,03 (t, *J* = 7,2 Hz, 1H), 6,80 (d, *J* = 7,3 Hz, 1H), 5,28 (s, 1H), 4,93-5,05 (ABq, 2H, J = 36,4, 16,4 Hz), 3,22 (m, 1H), 3,19 (m, 3H), 3,09 (m, 1H), 2,84 (d, *J* = 12,6 Hz, 1H), 2,63 (t, *J* = 10,5 Hz, 1H), 2,42 (t, *J* = 10,9 Hz, 1H), 1,97 (d, *J* = 11,1 Hz, 1H), 1,58-1,69 (m, 1H), 1,38-1,48 (m, 2H). MS (ES) [m+H] calculado para $C_{17}H_{22}BrN_4O_2$, 393,1; hallado, 393,1.

Compuesto 14



Compuesto 15



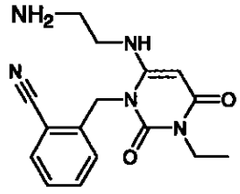
2-{6-[azepan-3(±)-ilamino]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (14) y 2-{6-[3(±)-amino-azepan-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (15). Los compuestos de los títulos 14 y 15 se prepararon a partir del compuesto 3 (70 mg, 0,27 mmol) y azepan-3-

ılamina (70 mg, 0,61 mg), usando el mismo procedimiento que para la preparación del compuesto 4. ambos compuestos se purificaron por LC-MS.

14: ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,77 (d, *J* = 7,8 Hz, 1H), 7,66 (t, *J* = 7,6 Hz, 1H), 7,47 (t, *J* = 8,0 Hz, 1H), 7,36 (d, *J* = 8,1 Hz, 1H), 5,54 (s, 1H), 5,49 (s, 1H), 5,27-5,36 (ABq, *J* = 26,0, 16,4 Hz, 2H), 3,50 (m, 2H), 3,37 (s, 2H), 3,26 (s, 3H), 3,12 (m, 1H), 3,04 (m, 1H), 2,07 (m, 1H), 1,86 (m, 1H), 1,60-1,71 (m, 3H). MS (ES) [m+H] calculado para $C_{19}H_{24}N_5O_2$, 354,2; hallado, 354,2.

15: ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,77 (d, *J* = 8,1 Hz, 1H), 7,63 (t, *J* = 7,6 Hz, 1H), 7,46 (t, *J* = 8,0 Hz, 1H), 7,19 (d, *J* = 7,6 Hz, 1H), 5,48 (s, 1H), 5,44-5,52 (ABq, *J* = 61,9, 18,4 Hz, 2H), 3,80 (s, 1H), 3,58-3,50 (m, 1H), 3,39-3,39 (m, 1H), 3,26 (s, 3H), 3,13 (m, 1H), 2,89 (t, *J* =12,4 Hz, 1H), 2,04 (m, 1H), 1,93 (m, 1H), 1,86 (m, 2H), 1,59-1,70 (m, 2H). MS (ES) [m+H] calculado para $C_{19}H_{24}N_5O_2$, 354,2; hallado, 354,2.

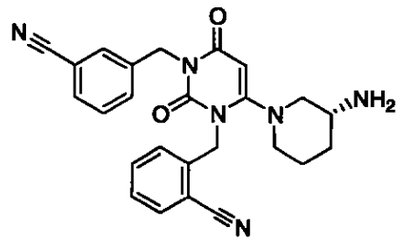
Compuesto 16



2-[6-(2-amino-etilamino)-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo (16). Se trató el compuesto 2 (150 mg, 0,57 mmol) en THF–DMSO (6:1, 4ml) con 60% de NaH (26 mg, 0,65 mmol), seguido por la adición de bromuro de etilo (300 µl). En un tubo sellado, se trató aproximadamente 20% de producto crudo en MeOH seco (3 ml) con $NaHCO_3$ y etano-1,2-diamina (200 µl) a 120 °C por 2 h, y se purificó por LC-MS para obtener el compuesto del título 16. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,70 (d, *J* = 7,8 Hz, 1H), 7,58 (t, *J* = 7,7 Hz, 1H), 7,40 (t, *J* = 7,4 Hz, 1H), 7,12 (d, *J* = 8,1 Hz, 1H), 5,37 (s, 2H), 3,95 (q, *J* =

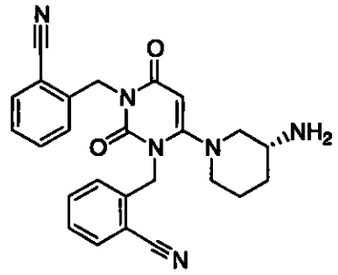
6,8 Hz, 2H), 3,45 (t, J = 5,9 Hz, 2H), 3,11 (t, J = 6,1 Hz, 2H), 1,19 (t, J = 6,8 Hz, 3H). MS (ES) [m+H] calculado para $C_{16}H_{20}N_5O_2$, 314,2; hallado 314,2.

Compuesto 17



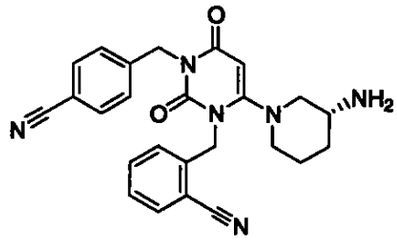
2-{6-[3(R)-amino-piperidin-1-il]-3-(3-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (17). Se trató el compuesto 2 (65 mg, 0,25 mmol) en DME-DMF (2:1, 2,5 ml) con 60% de NaH (15 mg, 0,38 mmol) a 0 °C por 20 min, y luego se agregó LiBr (25 mg). 10 min más tarde, se agregó bromuro de *m*-ciano-bencilo (55 mg, 0,28 mg), se agitó la mezcla a temperatura ambiente por 5 h, y se concentró. Se disolvió el residuo crudo en MeOH (3 ml). Se agregó diclorhidrato de (*R*)-3-amino-piperidina (52 mg, 0,3 mmol) y bicarbonato de sodio (100 mg). La mezcla se calentó en un tubo sellado a 120°C por 2 h, y luego se filtró y se concentró. La purificación por LC-MS permitió obtener el compuesto del título 17 con 84% de rendimiento. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,67 (d, J = 7,8 Hz, 1H), 7,52-7,62 (m, 4H), 7,35-7,46 (m, 2H), 7,27 (d, J = 7,8 Hz, 1H), 5,43 (s, 1H), 5,15-5,31 (ABq, J = 40,9, 13,7 Hz, 2H), 5,04 (s, 2H), 3,40 (s, 1H), 3,40 (m 1H), 3,03 (m,1H), 2,91 (m, 1H), 2,76 (s, 1H), 2,13 (s, 1H), 1,92 (m, 1H), 1,63-1,74 (m, 2H). MS (ES) [m+H] calculado para $C_{25}H_{25}N_6O_2$, 441,2; hallado 441,2.

Compuesto 18



2-{6-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (18). El compuesto del título 18 se preparó empleando los métodos usados en la preparación del compuesto 17, excepto que se usó *α*-bromo-*o*-tolunitrilo en lugar de bromuro de *m*-ciano-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,64 (d, *J* = 6,8 Hz, 1H), 7,60 (d, *J* = 7,8 Hz, 1H), 7,55 (t, *J* = 7,8 Hz, 2H), 7,44 (t, *J* = 7,6 Hz, 1H), 7,38 (t, *J* = 7,5 Hz, 1H), 7,31 (t, *J* = 7,6 Hz, 1H), 7,27 (d, *J* = 7,8 Hz, 1H), 7,12 (d, *J* = 7,8 Hz, 1H), 5,45 (s, 1H), 5,15-5,32 (m, 4H), 3,36-3,47 (m, 2H), 2,98 (m, 2H), 2,10 (m, 1H), 1,91 (m, 1H), 1,68 (m, 2H). MS (ES) [m+H] calculado para $C_{25}H_{25}N_6O_2$, 441,2; hallado 441,2.

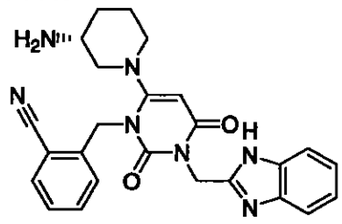
Compuesto 19



2-{6-[3(R)-amino-piperidin-1-il]-3-(4-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (19). El compuesto del título 19 se preparó empleando los métodos usados en la preparación del compuesto 17, excepto que se usó bromuro de *p*-ciano-bencilo en lugar de bromuro de m-ciano-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,70 (d, *J* = 7,8 Hz, 1H), 7,56-7,63 (m,

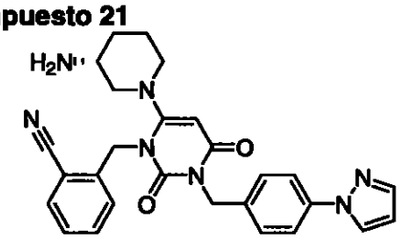
3H), 7,46 (m, 3H), 7,29 (d, J = 7,8 Hz, 1H), 5,47 (s, 1H), 5,16-5,36 (ABq, J = 51,1, 14,7 Hz, 2H), 5,11 (s, 2H), 3,36-3,47 (m, 2H), 2,90-3,07 (m, 2H), 2,79 (s, 1H), 2,15 (s, 1H), 1,95 (s, 1H), 1,73 (s, 2H). MS (ES) [m+H] calculado para $C_{25}H_{25}N_6O_2$, 441,2; hallado 441,2.

Compuesto 20



2-[6-(3-amino-piperidin-1-il)-3-(1H-benzoimidazol-2-ilmetil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo (20). El compuesto del título 20 se preparó empleando los métodos usados en la preparación del compuesto 17, excepto que se usó 2-clorometil benzimidazol en lugar de bromuro de m-ciano-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,67(d, J = 3,0 Hz, 1H), 7,65-7,56(m, 2H), 7,47 (d, J = 3,3 Hz, 2H), 7,46 (d, J = 3,3 Hz, 1H), 7,37-7,40 (m, 2H), 5,52 (s, 3H), 5,23 (s, 2H), 3,51 (d, J = 9,6 Hz, 1H), 3,36 (m, 1H), 2,87-2,92 (m, 2H), 2,64-2,72 (m, 1H), 2,09 (m, 1H), 1,76 (m, 1H), 1,52-1,64 (m, 2H). MS (ES) [m+H] calculado para $C_{25}H_{26}N_7O_2$, 456,2; hallado 456,2.

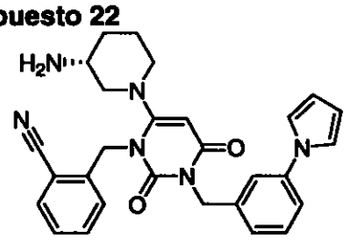
Compuesto 21



2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(4-pirazol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (21). El compuesto del título 21 se preparó

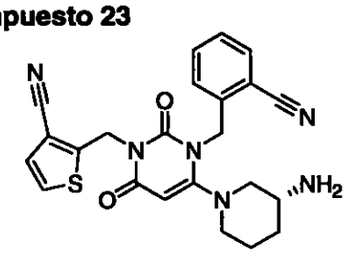
empleando los métodos usados en la preparación del compuesto 17, excepto que se usó 1-(4-bromometil-fenil)-1H-pirazol en lugar de bromuro de m-ciano-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,90 (d, *J* = 2,5 Hz, 1H), 7,71 (d, *J* = 1,8 Hz, 1H), 7,65 (d, *J* = 7,6 Hz, 1H), 7,51-7,58 (m, 3H), 7,43-7,37(m, 3H), 7,22 (d, *J* = 7,8 Hz, 1H), 6,47 (t, *J* = 2,1 Hz, 1H), 5,43 (s, 1H), 5,14-5,30 (ABq, *J* = 41,2, 16,4 Hz, 2H), 5,05 (s, 2H), 3,32-3,40 (m, 2H), 2,96 (m,1H), 2,89 (m, 1H), 2,70 (m, 1H), 2,10 (m, 1H), 1,88 (m, 1H), 1,66 (s, 2H). MS (ES) [m+H] calculado para $C_{27}H_{28}N_7O_2$, 482,2; hallado 482,2.

Compuesto 22



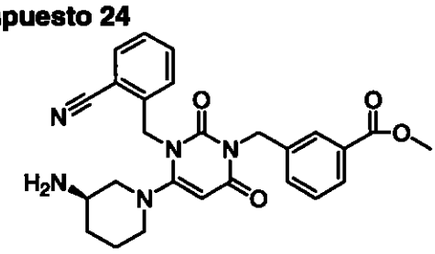
2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(3-pirrol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (22). El compuesto del título 22 se preparó empleando los métodos usados en la preparación del compuesto 17, excepto que se usó 1-(3-bromometil-fenil)-1H-pirrol en lugar de bromuro de m-ciano-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,59 (d, *J* = 7,3 Hz, 1H), 7,48 (t, *J* = 7,7 Hz, 1H), 7,24-7,36 (m, 4H), 7,21 (t, *J* = 7,6 Hz, 2H), 7,02 (t, *J* = 2,1 Hz, 2H), 6,32 (t, *J* = 2,0 Hz, 2H), 5,42 (s, 1H), 5,11-5,20 (ABq, *J* = 44,7, 15,9 Hz, 2H), 5,06 (s, 2H), 3,36 (m, 2H), 2,98 (m, 1H), 2,89 (m, 1H), 2,70 (m, 1H), 2,10 (m, 1H), 1,88 (m, 1H), 1,73-1,58 (m, 2H). MS (ES) [m+H] calculado para $C_{28}H_{29}N_6O_2$, 481,2; hallado 481,2.

Compuesto 23



6-[3 (R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil]-tiofeno-3-carbonitrilo (23). El compuesto del título 23 se preparó empleando los métodos usados en la preparación del compuesto 17, excepto que se usó 2-bromometil-tiofeno-3-carbonitrilo en lugar de bromuro de m-ciano-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,65 (d, J = 7,6 Hz, 1H), 7,57 (t, J = 7,8 Hz, 1H), 7,40 (t, J = 7,7 Hz, 1H), 7,29 (d, J = 7,8 Hz, 1H), 7,25 (dd, J = 5,3, 1,3 Hz, 1H), 7,11 (dd, J = 5,3, 1,0 Hz, 1H), 5,45 (s, 1H), 5,35 (s, 2H), 5,15-5,33 (ABq, J = 45,0, 15,5 Hz, 2H), 3,38 (bd, J = 10,1 Hz, 2H), 2,98 (m, 2H), 2,72 (s, 1H), 2,12 (d, J = 7,3 Hz, 1H), 1,83-1,93 (m, 1H), 1,61-1,72 (m, 2H). MS (ES) [m+H] calculado para $C_{23}H_{23}N_6O_4$, 447,1; hallado 447,1.

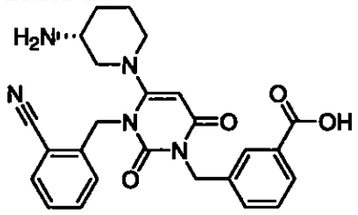
Compuesto 24



Metil éster de ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico (24). El compuesto del título 24 se preparó empleando los métodos usados en la preparación del compuesto 17, excepto que se usó metil éster de ácido 3-bromometil-benzoico en lugar de bromuro de m-ciano-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,99 (s,

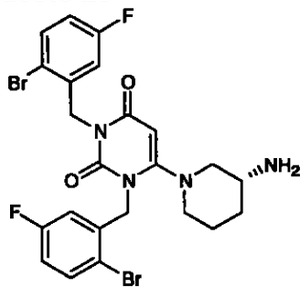
1H), 7,91 (d, J = 7,8 Hz, 1H), 7,65 (d, J = 7,6 Hz, 1H), 7,56 (d, J = 7,9 Hz, 1H), 7,52 (d, J = 7,6 Hz, 1H), 7,39 (t, J = 7,6 Hz, 1H), 7,34 (t, J = 7,6 Hz, 1H), 7,23 (d, J = 8,1 Hz, 1H), 5,44 (s, 1H), 5,12-5,31 (ABq, J = 43,7, 15,9 Hz, 2H), 5,08 (s, 2H), 3,90 (s, 3H), 3,31-3,39 (m, 2H), 2,98 (d, J = 11,9 Hz, 1H), 2,87 (m, 1H), 2,71 (m, 1H), 2,11 (m, 1H), 1,89 (m, 1H), 1,73-1,59 (m, 2H). MS (ES) [m+H] calculado para $C_{26}H_{28}N_5O_4$, 474,2; hallado 474,2.

Compuesto 25



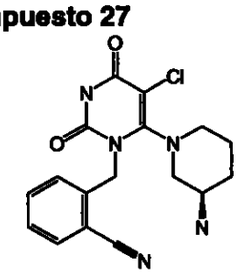
Ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico (25). Se trató una mezcla cruda de compuesto 24 (aproximadamente 50 mg) con LiOH en THF-agua (10:1) para obtener el compuesto del título 25. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,90 (s, 1H), 7,86 (d, J = 7,6 Hz, 1H), 7,60 (d, J = 7,6 Hz, 1H), 7,50 (t, J = 8,2 Hz, 1H), 7,45 (d, J = 7,3 Hz, 1H), 7,26-7,36 (m, 2H), 7,17 (d, J = 8,1 Hz, 1H), 5,39 (s, 1H), 5,10-5,25 (ABq, J = 36,9, 15,5 Hz, 2H), 5,03 (s, 2H), 3,31 (m,2H), 2,95 (m, 1H), 2,81 (m, 1H), 2,64 (m, 1H), 2,07 (m, 1H), 1,82 (m, 1H), 1,51-1,68 (m, 2H). MS (ES) [m+H] calculado para $C_{25}H_{26}N_5O_4$, 460,2; hallado 460,2.

Compuesto 26



6-[3 (R)-amino-piperidin-1-il]-1,3-bis-(2-bromo-5-fluoro-bencil)-1H-pirimidin-2,4-diona (26). El compuesto del título se preparó a partir de **1** por di-bencilación, usando el procedimiento descripto para la preparación de **2**, excepto que se usó bromuro de 2-bromo-5-fluoro-bencilo en lugar de α-bromo-*o*-tolunitrilo, a lo que siguió un tratamiento con 3-(R)-amino-piperidina bajo las condiciones descriptas para la preparación del compuesto 4. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ 7,42 (dd, J=8,6, 5,3 Hz, 2H), 7,11-7,08 (dd, J=9,1, 2,2 Hz, 1H), 7,06 (dd, J=9,3, 2,8 Hz, 1H), 6,78-6,84 (m, 2H), 5,71 (s, 1H), 5,29 (s, 4H), 4,22 (d, J = 11,1 Hz, 1H), 3,82 (d, J=13,4 Hz, 1H), 3,07-3,24 (m, 3H), 2,06 (m, 1H), 1,75-1,83 (m, 1H), 1,63-1,72 (m, 1H), 1,50-1,59 (m, 1H). MS (ES) [m+H] calculado para $C_{23}H_{23}Br_2F_2N_3O_2$, 583,01; hallado 583,01.

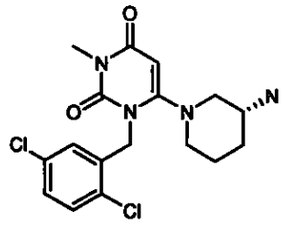
Compuesto 27



2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (27). Se trató el compuesto 4 (100 mg) en THF (2 ml) HCl 4 M en dioxano (1ml) a temperatura ambiente por 1 h, se concentró y luego se

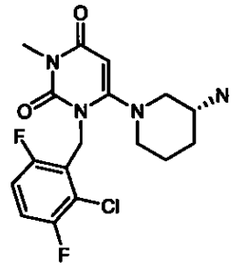
purificó por LC-MS para obtener el compuesto del título. ^{1}H-NMR (400 M Hz, DMSO-D6): δ ppm 12,0 (s, 1H), 7,88 (d, *J* = 7,6 Hz, 1H), 7,68 (t, *J* = 7,7 Hz, 1H), 7,49 (t, *J* = 7,7 Hz, 1H), 7,36 (d, *J* = 7,8 Hz, 1H), 5,09-5,21 (m, 2H), 3,17 (m, 2H), 2,96 (t, *J* = 11,1 Hz, 1H), 2,86 (d, *J* = 10,6 Hz, 1H), 2,65 (m, 1H), 1,90 (d, *J* = 11,6 Hz, 1H), 1,57 (d, *J* = 13,1 Hz, 1H), 1,19-1,31 (m, 1H), 1,03-1,15 (m, 1H). MS (ES) [m+H] calculado para $C_{17}H_{19}ClN_5O_2$, 360,1; hallado, 360,1.

Compuesto 28



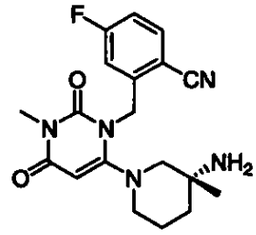
6-[3 (R)-amino-piperidin-1-il]-1-(2,5-*di*-cloro-bencil)-3-metil-1H-pirimidin-2,4-diona (28). El compuesto del título se preparó a partir del compuesto 1, usando el mismo procedimiento que para la preparación del compuesto 10, excepto que se usó bromuro de 2,5-di-cloro-bencilo en lugar de bromuro de 2-bromo-5-fluoro-bencilo. ^{1}H-NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1): δ ppm 7,50 (d, *J* = 8,6 Hz, 1H), 7,39 (dd, *J* = 8,3, 2,526 Hz, 1H), 7,22 (d, *J* = 2,5 Hz, 1H), 5,41 (s, 1H), 5,01 – 4,93 (ABq, *J* = 41,9, 16,2 Hz, 2H), 3,25 (m, 2H), 3,10 (s, 3H), 2,85 (m, 1H), 2,76 (m, 1H), 2,67 (m, 1H), 1,91 (m, 1H), 1,75 (m, 1H), 1,45 (m, 2H). MS (ES) [m+H] calculado para $C_{17}H_{21}Cl_2N_4O_2$, 383,1; hallado 383,1.

Compuesto 29



6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-3,6-*di*-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona (29). El compuesto del título se preparó a partir del compuesto 1, usando el mismo procedimiento que para la preparación del compuesto 10, excepto que se usó bromuro de 2-cloro-3,6-*di*-fluoro-bencilo en lugar de bromuro de 2-bromo-5-fluoro-bencilo. 1H NMR (400 M Hz, $CDCl_3$-CD_3OD 10:1) δ ppm 6,98-7,06 (m, 2H), 6,90 (m, 2H), 5,31 (s, 1H), 5,01 – 5,20 (ABq, *J* = 24,2, 14,4 Hz, 2H), 3,28-3,37 (m, 2H) 3,13 (s,3H), 3,01-2,94 (m, 1H), 2,6-2,9 (m, 2H), 2,10 (m, 1H), 1,92 (m, 2H), 1,73 (s, 1H), 1,6-1,75 (m, 2H). MS (ES) [m+H] calculado para $C_{17}H_{20}ClF_2N_4O_2$, 385,1; hallado 385,1.

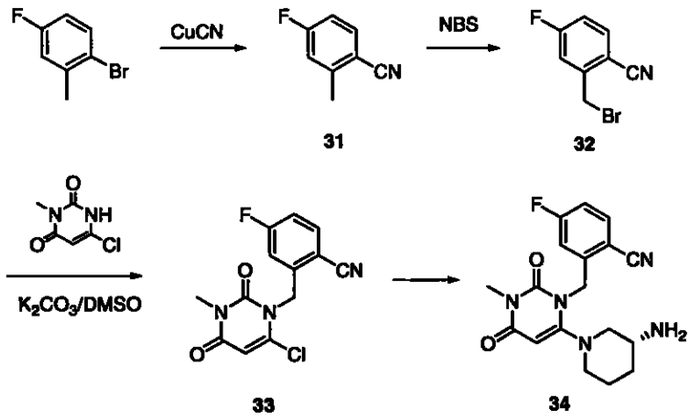
Compuesto 30



(R)-2-((6-(3-amino-3-metilpiperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidropirimidin-1(2H)-il)metil)-4-fluorobenzonitrilo (30). Se agitó 2-(6-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-4-fluoro-benzonitrilo (300 mg, 1,0 mmol), diclorhidrato de (R)-3-amino-3-metil-piperidina (266 mg, 1,4 mmol) y bicarbonato de sodio (500 mg, 5,4 mmol) en un tubo sellado en EtOH (3 ml), a 100°C por 2

horas. Se obtuvo el compuesto final como una sal de TFA, después de purificar por HPLC. 1H-NMR (400 M Hz, CD3OD): δ. 7,78-7,83 (m, 1H), 7,14-7,26 (m, 2H), 5,47 (s, 1H), 5,12-5,36 (ABq, 2H, J = 105,2, 15,6 Hz), 3,21 (s, 1H), 2,72-3,15 (m, 4H), 1,75-1,95 (m, 4H), 1,39 (s, 3H) MS (ES) [m+H] calculado para C19H22FN5O2, 372,41; hallado, 372,41.

Compuesto 34



4-Fluoro-2-metilbenzonitrilo (31). Una mezcla de 2-bromo-5fluorotolueno (3,5 g, 18,5 mmol) y CuCN (2 g, 22 mmol) en DMF (100 ml) se calentó a reflujo por 24 horas. La reacción se diluyó con agua y se extrajo con hexano. La fase orgánica se secó sobre $MgSO_4$ y se eliminó el solvente para obtener el producto **31** (con un rendimiento de 60%). ^{1}H-NMR (400 M Hz, $CDCl_3$): δ 7,60 (dd, J = 5,6, 8,8 Hz, 1H), 6,93-7,06 (m, 2H), 2,55 (s, 3H).

2-bromometil-4-fluorobenzonitrilo (32). Una mezcla de 4-fluoro-2-metilbenzonitrilo (2 g, 14,8 mmol), NBS (2,64 g, 15 mmol) y AIBN (100 mg) en CCl_4 se calentó a reflujo bajo nitrógeno por 2 horas. La reacción se enfrió a temperatura ambiente. Se eliminó el sólido por filtración. La solución orgánica se concentró para obtener el producto crudo como un aceite, que se usó en el siguiente paso sin purificaciones adicionales. ^{1}H-NMR (400 M Hz, $CDCl_3$): δ 7,68

(dd, J = 5,2, 8,4 Hz, 1H), 7,28 (dd, J = 2,4, 8,8 Hz, 1H), 7,12 (m, 1H), 4,6 (s, 2H).

2-(6-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-4-fluoro-benzonitrilo (33). Se agitó una mezcla de 3-metil-6-clorouracilo crudo (0,6 g, 3,8 mmol), 2-bromometil-4-fluorobenzonitrilo (0,86 g, 4 mmol) y K_2CO_3 (0,5 g, 4 mmol) en DMSO (10 ml), a 60°C por 2 horas. La reacción se diluyó con agua y se extrajo con EtOAc. La fase orgánica se secó sobre $MgSO_4$ y se eliminó el solvente. El residuo se purificó por cromatografía en columna. Se obtuvieron 0,66 g de producto (rendimiento: 60%). ^{1}H-NMR (400 M Hz, $CDCl_3$): δ 7,73 (dd, J = 7,2, 8,4 Hz, 1H), 7,26 (d, J-4,0 Hz, 1H), 7,11-7,17 (m, 1H), 6,94 (dd, J = 2,0, 9,0 Hz, 1H), 6,034 (s, 2H), 3,39 (s, 3H). MS (ES) [m+H] calculado para $C_{13}H_9ClFN_3O_2$, 293,68; hallado 293,68.

2-[6-(3-amino-piperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-4-fluoro-benzonitrilo (34). Se agitó 2-(6-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-4-fluoro-benzonitrilo (300 mg, 1,0 mmol), diclorhidrato de (*R*)-3-amino-piperidina (266 mg, 1,5 mmol) y bicarbonato de sodio (500 mg, 5,4 mmol) en un tubo sellado en EtOH (3 ml), a 100°C por 2 horas. Se obtuvo el compuesto final como una sal de TFA, después de purificar por HPLC. ^{1}H-NMR (400 M Hz, CD_3OD): δ. 7,77-7,84 (m, 1H), 7,16-7,27 (m, 2H), 5,46 (s, 1H), 5,17-5,34 (ABq, 2H, J = 35,2, 15,6 Hz), 3,33-3,47 (m, 2H), 3,22 (s, 3H), 2,98-3,08 (m, 1H), 2,67-2,92 (m, 2H), 2,07-2,17 (m, 1H), 1,82-1,92 (m, 1H), 1,51-1,79 (m, 2H). MS (ES) [m+H] calculado para $C_{18}H_{20}FN_5O_2$, 357,38; hallado, 357,38.

4. Ejemplos ensayos *in vitro*

Pueden determinarse fácilmente la actividad de inhibición de proteasas de los inhibidores de DPP-IV empleando métodos conocidos por aquellos entrenados en la técnica, ya que se conocen ensayos *in vitro* apropiados para medir la

actividad de las proteasas y su inhibición por compuestos de prueba. Se detallan a continuación ejemplos de ensayos que pueden usarse para medir la actividad de inhibición de proteasas, y la selectividad de éstas.

Ensayo de DPP-IV

Se prepararon soluciones de los compuestos de prueba con concentraciones variadas (≤10 mM de concentración final) en dimetil sulfóxido (DMSO), y luego se diluyó en un amortiguador de ensayo que comprendía Tris 20 mM, pH 7,4; KCl 20 mM; y 0,1 mg/ml de BSA. Se agregó DPP-IV humano (0,1 nM de concentración final) a las diluciones y se pre-incubó por 10 minutos a temperatura ambiente, antes de iniciar la reacción con A-P-7-amido-4-trifluorometilcumarina (AP-AFC; 10 µM de concentración final). El volumen total de la mezcla de reacción fue de 10-100 µl, dependiendo de los formatos de ensayo usados (placas de 384 ó 96 cavidades). Se siguió la reacción en forma cinética (excitación a λ=400 nm; emisión a λ=505 nm) por 5-10 minutos, o se midió un punto terminal después de 10 minutos. Se calcularon las constantes de inhibición (IC_{50}) a partir de curvas de progreso de la enzima, usando modelos matemáticos convencionales.

Ensayo de FAPα

Se prepararon soluciones de los compuestos de prueba con concentraciones variadas (≤10 mM de concentración final) en dimetil sulfóxido (DMSO), y luego se diluyó en un amortiguador de ensayo que comprendía Tris 20 mM, pH 7,4; KCl 20 mM; y 0,1 mg/ml de BSA. Se agregó FAPα humano (2 nM de concentración final) a las diluciones y se pre-incubó por 10 minutos a temperatura ambiente, antes de iniciar la reacción con A-P-7-amido-4-trifluorometilcumarina

(AP-AFC; 40 µM de concentración final). El volumen total de la mezcla de reacción fue de 10-100 µl, dependiendo de los formatos de ensayo usados (placas de 384 ó 96 cavidades). Se siguió la reacción en forma cinética (excitación a λ=400 nm; emisión a λ=505 nm) por 5-10 minutos, o se midió un punto terminal después de 10 minutos. Se calcularon las constantes de inhibición (IC_{50}) a partir de curvas de progreso de la enzima, usando modelos matemáticos convencionales.

Ensayo de PREP

Se prepararon soluciones de los compuestos de prueba con concentraciones variadas (≤10 mM de concentración final) en dimetil sulfóxido (DMSO), y luego se diluyó en un amortiguador de ensayo que comprendía fosfato de sodio 20 mM, pH 7,4; EDTA 0,5 mM; DTT 0,5 mM; y 0,1 mg/ml de BSA. Se agregó PREP (EC3.4.21.26, de *Flavobacterium meningosepticum*; 0,2 nM de concentración final) a las diluciones. Se pre-incubó el PREP y el compuesto por 10 minutos a temperatura ambiente, antes de iniciar la reacción con Z-G-P-amC (10 µM de concentración final). El volumen total de la mezcla de reacción fue de 10-100 µl, dependiendo de los formatos de ensayo usados (placas de 384 ó 96 cavidades). Se siguió la reacción en forma cinética (excitación a λ=375 nm; emisión a λ=460 nm) por 10 minutos, o se midió un punto terminal después de 10 minutos. Se calcularon las constantes de inhibición (IC_{50}) a partir de curvas de progreso de la enzima, usando modelos matemáticos convencionales.

Ensayo de triptasa

Se prepararon soluciones de los compuestos de prueba con concentraciones variadas (≤10 mM de concentración final) en dimetil sulfóxido (DMSO), y luego se diluyó en un amortiguador de ensayo que comprendía Hepes

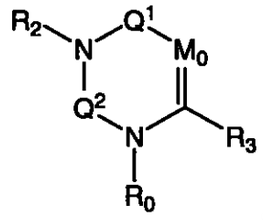
100 mM, pH 7,4; 0,01% de Brij35; y 10% de glicerol. Se agregó triptasa (rhLung beta; 0,1 nM de concentración final) a las diluciones y se pre-incubó con el compuesto por 10 minutos a temperatura ambiente. Se inició la reacción enzimática con Z-lys-SBzl 25 µM y DTNB 400 µM. El volumen total de la mezcla de reacción fue de 100 µl en placas Costar A/2 de 96 cavidades. La reacción se siguió en forma colorimétrica (λ=405 nm) por 10 minutos. Se calcularon las constantes de inhibición (IC_{50}) a partir de curvas de progreso de la enzima, usando modelos matemáticos convencionales.

Se evaluaron los compuestos de la invención de acuerdo con los ensayos descriptos previamente para la inhibición de proteasas, y se observó que presentaban una actividad de inhibición selectiva de DPP-IV. Por ejemplo, se descubrió que los compuestos de la invención inhibían la actividad de DPP-IV a concentraciones al menos 50 veces menores que aquellas concentraciones requeridas para producir una inhibición equiactiva de la actividad de proteasa para FAPα. Las constantes de inhibición aparente (K_i) para los compuestos de la invención contra DPP-IV estuvieron en el rango de entre aproximadamente 10^{-9}M y aproximadamente 10^{-5}M.

Será evidente para aquellos entrenados en la técnica que pueden efectuarse distintas modificaciones y variaciones a los compuestos, las composiciones, los conjuntos de elementos y los métodos de la presente invención, sin apartarse del espíritu o el alcance de la invención. Por consiguiente, la presente invención abarca las modificaciones y las variaciones de esta invención, siempre que estén dentro del alcance de las reivindicaciones adjuntas y sus equivalentes.

REIVINDICACIONES:

1. Un compuesto que comprende:



donde

M_0 es –C–LX, N o CR_4;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_0 es R_1 o –LX, con la condición de que solamente uno de R_0 y M_0 es -LX;

R_1 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil (C_{1-3})alquilo, tiocarbonil (C_{1-3})alquilo, sulfonil (C_{1-3})alquilo, sulfinil (C_{1-3})alquilo, imino (C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno

sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

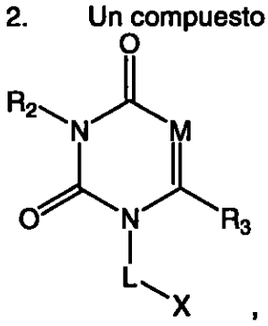
R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo,

alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

2. Un compuesto de acuerdo con la reivindicación 1, que comprende:



donde

M es N o CR_4;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un

grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

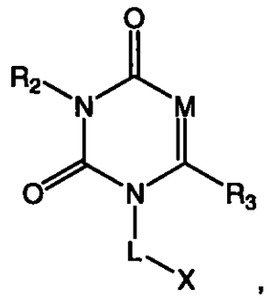
R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_1-$_{10}$)alquilo, amino, ciano, tiol, (C_1-$_{10}$)alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_1-$_{10}$)alquilo, (C_{3-12})cicloalquilo, hetero(C_3-$_{12}$)cicloalquilo, aril(C_1-$_{10}$)alquilo, heteroaril(C_1-$_5$)alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

3. Un compuesto de acuerdo con la reivindicación 2, que comprende:



donde

M es N o CR_4,

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

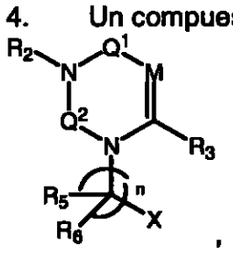
R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil$(C_{1-}$

$_3$)alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, arioxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

4. Un compuesto de acuerdo con la reivindicación 2, que comprende:



,

donde

n es 1, 2 ó 3;

M es N o CR_4;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-}

$_{12}$)cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})biciclоarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})biciclоaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

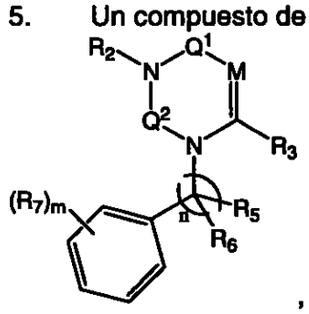
cada R_5 y R_6 es independientemente hidrógeno, o se selecciona del grupo que consiste en a sustituido o no sustituido (C_{1-10})alquilo, a sustituido o no sustituido (C_{1-10})alcoxilo, ciano, y halo, o donde R_5 y R_6 se toman juntos para formar un anillo;

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo,

heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

5. Un compuesto de acuerdo con la reivindicación 4, que comprende:



,

donde

M es 0, 1, 2, 3, 4 ó 5;

n es 1, 2 ó 3;

M es N o CR_4;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C{=}NR_9$;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo,

tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

cada R_5 y R_6 es independientemente hidrógeno, o se selecciona del grupo que consiste en a sustituido o no sustituido (C_{1-10})alquilo, a sustituido o no sustituido (C_{1-10})alcoxilo, ciano, y halo, o donde R_5 y R_6 se toman juntos para formar un anillo;

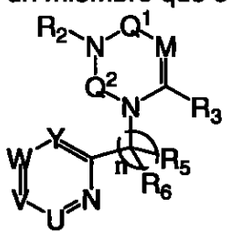
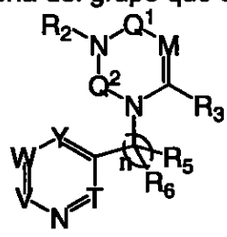
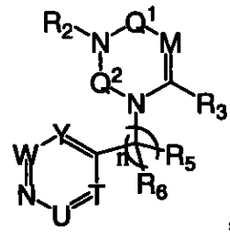
cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino,

tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido; y

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido.

6. Un compuesto de acuerdo con la reivindicación 4, que comprende:

un miembro que se selecciona del grupo que consiste en

donde

n es 1, 2 ó 3;

M es N o CR_4;

cada de T, U, V, W e Y es independientemente nitrógeno o CR_{18}, teniendo en cuenta que no más de dos de T, U, V, W e Y son nitrógeno;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno

sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

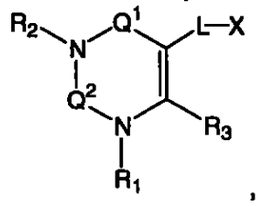
cada R_5 y R_6 es independientemente hidrógeno, o se selecciona del grupo que consiste en a sustituido o no sustituido (C_{1-10})alquilo, a sustituido o no sustituido (C_{1-10})alcoxilo, ciano, y halo, o donde R_5 y R_6 se toman juntos para formar un anillo;

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido; y

cada R_{16} se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino,

tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

7. Un compuesto de acuerdo con la reivindicación 1, que comprende:



donde

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_8$;

R_1 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo,

heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

8. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-3, donde los 1, 2 ó 3 átomos de L que proporcionan la separación consisten en átomos de carbono.

9. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-3 y 7, donde L separa X del anillo por un átomo.

10. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3,

donde L se selecciona del grupo que consiste en –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -C(O)-, -$CH_2C(O)$-, -$C(O)CH_2$-, -CH_2-$C(O)CH_2$-, -$C(O)CH_2CH_2$-, -$CH_2CH_2C(O)$-, -O-, -OCH_2-, -CH_2O-, -CH_2OCH_2-, -OCH_2CH_2-, -CH_2CH_2O-, -$N(CH_3)$-, -$NHCH_2$-, -CH_2NH-, -CH_2NHCH_2-, -$NHCH_2CH_2$-, -CH_2CH_2NH-, -NH-C(O)-, -NCH_3-C(O)-, -C(O)NH-, -$C(O)NCH_3$-, -$NHC(O)CH_2$-, -$C(O)NHCH_2$-, -$C(O)CH_2NH$-, -$CH_2NHC(O)$-, -$CH_2C(O)NH$-, -$NHCH_2C(O)$-, -S-, -SCH_2-, -CH_2S-, -SCH_2CH_2-, -CH_2SCH_2-, -CH_2CH_2S-, -C(O)S-, -$C(O)SCH_2$-, -$CH_2C(O)S$-, -$C(O)CH_2S$-, y -$CH_2SC(O)$-, cada uno sustituido o no sustituido.

11. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-3 y 7, donde L se selecciona del grupo que consiste en -CH_2-, -C(O)-, -$CH_2C(O)$-, -$C(O)CH_2$-, -CH_2-$C(O)CH_2$-, -$C(O)CH_2CH_2$-, y -$CH_2CH_2C(O)$-, cada uno sustituido o no sustituido.

12. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-3 y 7, donde -L-X, tomados juntos, se seleccionan del grupo que consiste en -(CH_2)-(2-ciano)fenilo; -(CH_2)-(3-ciano)fenilo; -(CH_2)-(2-hidroxi)fenilo; -(CH_2)-(3-hidroxi)fenilo; -(CH_2)-(2-alquenil)fenilo; -(CH_2)-(3-alquenil)fenilo; -(CH_2)-(2-alquinil)fenilo; -(CH_2)-(3-alquinil)fenilo; -(CH_2)-(2-metoxi)fenilo; -(CH_2)-(3-metoxi)fenilo; -(CH_2)-(2-nitro)fenilo; -(CH_2)-(3-nitro)fenilo; -(CH_2)-(2-carboxi)fenilo; -(CH_2)-(3-carboxi)fenilo; -(CH_2)-(2-carboxamido)fenilo; -(CH_2)-(3-carboxamido)fenilo; -(CH_2)-(2-sulfonamido)fenilo; -(CH_2)-(3-sulfonamido)fenilo; -(CH_2)-(2-tetrazolil)fenilo; -(CH_2)-(3-tetrazolil)fenilo; -(CH_2)-(2-aminometil)fenilo; -(CH_2)-(3-aminometil)fenilo; -(CH_2)-(2-hidroximetil)fenilo; -(CH_2)-(3-hidroximetil)fenilo; -(CH_2)-(2-fenil)fenilo; -(CH_2)-(3-fenil)fenilo; -(CH_2)-(2-halo)fenilo; -(CH_2)-(3-halo)fenilo; -(CH_2)-(2-$CONH_2$)fenilo; -(CH_2)-(3-$CONH_2$)fenilo; -(CH_2)-(2-$CONH(C_{1-7})$alquil)fenilo; -(CH_2)-(3-$CONH(C_{1-7})$alquil)fenilo; -(CH_2)-(2-$CO_2(C_{1-7})$alquil)fenilo; -(CH_2)-(3-$CO_2(C_{1-7})$alquil)fenilo; -

(CH_2)-(2-NH_2)fenilo; -(CH_2)-(3-NH_2)fenilo, -(CH_2)-(2-(C_{3-7})alquil)fenilo; -(CH_2)-(3-(C_{3-7})alquil)fenilo; -(CH_2)-(2-(C_{3-7})cicloalquil)fenilo; -(CH_2)-(3-(C_{3-7})cicloalquil)fenilo; -(CH_2)-(2-aril)fenilo; -(CH_2)-(3-aril)fenilo; -(CH_2)-(2-heteroaril)fenilo; -(CH_2)-(3-heteroaril)fenilo; -(CH_2)-2-bromo-5-fluoro fenilo; -(CH_2)-2-cloro-5-fluoro fenilo; -(CH_2)-2-ciano-5-fluoro fenilo; -(CH_2)-2,5-dicloro fenilo; -(CH_2)-2,5-difluoro fenilo; -(CH_2)-2,5-dibromo fenilo; -(CH_2)-2-bromo-3,5-difluoro fenilo; -(CH_2)-2-cloro-3,5-difluoro fenilo; -(CH_2)-2,3,5-trifluoro fenilo; -(CH_2)-2,3,5,6-tetrafluorofenilo; -(CH_2)-2-bromo-3,5,6-trifluoro fenilo; -(CH_2)-2-cloro-3,5,6-trifluoro fenilo; -(CH_2)-2-ciano-3,5-difluoro fenilo; -(CH_2)-2-ciano-3,5,6-trifluoro fenilo; -(CH_2)-(2-heterocicloalquil)fenilo; y -(CH_2)-(3-heterocicloalquil)fenilo, cada uno sustituido o no sustituido.

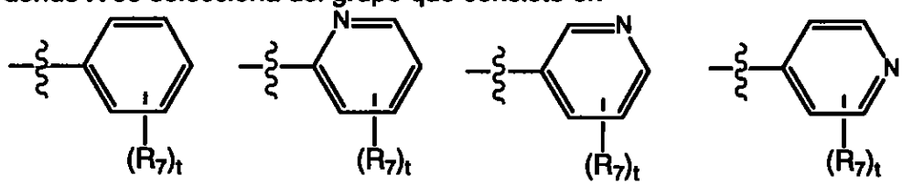
13. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 7-11, donde X es (C_{3-7})cicloalquilo, (C_{3-7})heterocicloalquilo, arilo, fenilo, heteroarilo, halofenilo, dihalofenilo, haloarilo, haloheteroarilo, dihaloarilo, dihaloheteroarilo sustituido o no sustituido, o un grupo que contiene anillos o cíclico que tiene un sustituyente distinto de hidrógeno en la posición 2 ó 3 del anillo, cada uno sustituido o no sustituido.

14. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 7-11, donde X es un grupo que contiene anillos o un grupo cíclico, que tiene un sustituyente distinto de hidrógeno en la posición 2 ó 3 del anillo, seleccionado del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil (C_{1-3})alquilo, tiocarbonil (C_{1-3})alquilo, sulfonil (C_{1-3})alquilo, sulfinil (C_{1-3})alquilo, imino (C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, ciano, nitro, halo, un grupo imino, un grupo

sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

15. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 7-11, donde X se selecciona del grupo que consiste en (2-ciano)fenilo; (3-ciano)fenilo; (2-hidroxi)fenilo; (3-hidroxi)fenilo; (2-alquenil)fenilo; (3-alquenil)fenilo; (2-alquinil)fenilo; (3-alquinil)fenilo; (2-metoxi)fenilo; (3-metoxi)fenilo; (2-nitro)fenilo; (3-nitro)fenilo; (2-carboxi)fenilo; (3-carboxi)fenilo; -(CH_2)-(2-carboxamido)fenilo; (3-carboxamido)fenilo; (2-sulfonamido)fenilo; (3-sulfonamido)fenilo; (2-tetrazolil)fenilo; (3-tetrazolil)fenilo; (2-aminometil)fenilo; (3-aminometil)fenilo; (2-hidroximetil)fenilo; (3-hidroximetil)fenilo; (2-fenil)fenilo; (3-fenil)fenilo; (2-halo)fenilo; (3-halo)fenilo; (2-$CONH_2$)fenilo; (3-$CONH_2$)fenilo; (2-CONH(C_{1-7})alquil)fenilo, (3-CONH(C_{1-7})alquil)fenilo; (2-CO_2(C_{1-7})alquil)fenilo; (3-CO_2(C_{1-7})alquil)fenilo; (2-NH_2)fenilo; (3-NH_2)fenilo; (2-(C_{3-7})alquil)fenilo; (3-(C_{3-7})alquil)fenilo; (2-(C_{3-7})cicloalquil)fenilo; (3-(C_{3-7})cicloalquil)fenilo; (2-aril)fenilo; (3-aril)fenilo; (2-heteroaril)fenilo; (3-heteroaril)fenilo; 2-bromo-5-fluoro fenilo; 2-cloro-5-fluoro fenilo; 2-ciano-5-fluoro fenilo; 2,5-dicloro fenilo; 2,5-difluoro fenilo; 2,5-dibromo fenilo; 2-bromo-3,5-difluoro fenilo; 2-cloro-3,5-difluoro fenilo; 2,3,5-trifluoro fenilo; 2,3,5,6-tetrafluorofenilo; 2-bromo-3,5,6-trifluoro fenilo; 2-cloro-3,5,6-trifluoro fenilo; 2-ciano-3,5-difluoro fenilo; 2-ciano-3,5,6-trifluoro fenilo; (2-heterocicloalquil)fenilo; y (3-heterocicloalquil)fenilo, cada uno sustituido o no sustituido.

16. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 7-11, donde X se selecciona del grupo que consiste en



donde

t es 0, 1, 2, 3, 4 o 5, y

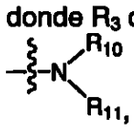
cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

17. El compuesto de acuerdo con la reivindicación 16, donde R_7 se selecciona independientemente del grupo que consiste en -ciano, -metoxilo, -nitro, -carboxilo, -sulfonamido, -tetrazolilo, -aminometilo, -hidroximetilo, -fenilo, -halo, $-CONH_2$, -CONH(C_{1-7})alquilo, $-CO_2$(C_{1-7})alquilo, $-NH_2$, -OH, -(C_{1-5})alquilo, -alquenilo, -alquinilo, (C_{1-5})cicloalquilo, arilo, heteroarilo, y heterocicloalquilo, cada uno sustituido o no sustituido.

18. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 7-11, donde X es halofenilo o dihalofenilo sustituido o no sustituido.

19. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 se selecciona del grupo que consiste en amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, y heteroarilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros.

20. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 comprende la fórmula



donde R_{10} y R_{11} se seleccionan cada uno independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, (C_{3-}

$_{12}$)cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo sulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido, o R_{10} y R_{11} se toman juntos para formar un anillo de 4, 5, 6 ó 7 miembros, cada uno sustituido o no sustituido.

21. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 es un anillo de 3, 4, 5, 6 ó 7 miembros sustituido o no sustituido.

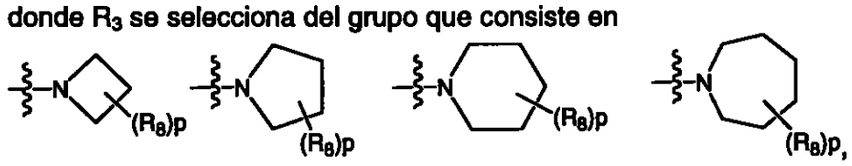
22. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 es un cicloalquilo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros.

23. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 es un heterocicloalquilo de 3, 4, 5, 6 ó 7 miembros sustituido o no sustituido.

24. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 es un arilo sustituido o no sustituido.

25. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 es un heteroarilo sustituido o no sustituido.

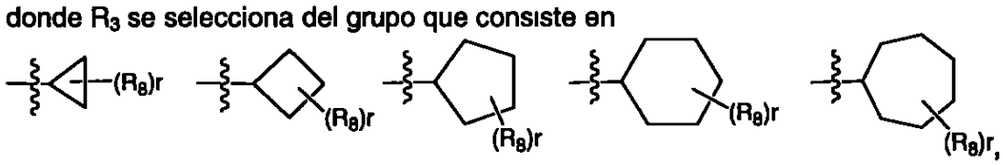
26. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 se selecciona del grupo que consiste en



donde p es 0-12 y cada R_8 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, ciano, nitro, hidroxilo, alquilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino,

tiol, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

27. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 se selecciona del grupo que consiste en



donde r es 0-13 y cada R_8 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, ciano, nitro, hidroxilo, alquilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

28. El compuesto de acuerdo con cualquiera de las reivindicaciones 26 y 27, donde al menos un R_8 comprende un átomo de nitrógeno básico que es capaz de interactuar con una cadena lateral de ácido carboxílico de un residuo en un sitio activo de una proteína.

29. El compuesto de la reivindicación 28, donde el átomo de nitrógeno básico forma parte de una amina primaria, secundaria o terciaria.

30. El compuesto de acuerdo con cualquiera de las reivindicaciones 26 y 27, donde al menos un R_8 es una amina primaria, secundaria o terciaria.

31. El compuesto de acuerdo con cualquiera de las reivindicaciones 26 y 27, donde al menos un R_8 es un heterocicloalquilo sustituido o no sustituido que comprende un átomo de nitrógeno en el anillo o un heteroarilo sustituido o no sustituido que comprende un átomo de nitrógeno en el anillo.

32. El compuesto de acuerdo con cualquiera de las reivindicaciones 26 y 27,

donde al menos un R_8 se selecciona del grupo que consiste en $-NH_2$, $-NH(C_{1-5}$ alquil), $-N(C_{1-5}$ alquil)$_2$, piperazina, imidazol, y piridina.

33. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 es un heteroarilo sustituido o no sustituido seleccionado del grupo que consiste en furano, tiofeno, pirrole, pirazol, triazol, isoxazol, oxazol, tiazol, isotiazol, oxadiazol, piridina, piridazina, pirimidina, pirazina, triazina, benzofurano, isobenzofurano, benzotiofeno, isobenzotiofeno, imidazol, benzimidazol, indol, isoindol, quinolina, isoquinolina, cinolina, quinazolina, naftiridine, piridopiridina, quinoxalina, ftalazina, y benzotiazol, cada uno sustituido o no sustituido.

34. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 se selecciona del grupo que consiste en (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril (C_{1-5})alquilo, (C_{8-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido.

35. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 es un anillo de (C_{3-7})cicloalquilo sustituido o no sustituido, que comprende opcionalmente O, N(O), N, S, SO, SO_2 o un grupo carbonilo en el anillo.

36. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 comprende un átomo de nitrógeno básico que es capaz de interactuar con una cadena lateral de ácido carboxílico de un residuo en un sitio activo de una proteína.

37. El compuesto de la reivindicación 36, donde el nitrógeno básico de R_3 está separado del átomo del anillo al que está unido R_3 por entre 1-5 átomos.

38. El compuesto de la reivindicación 36, donde el átomo de nitrógeno básico forma parte de una amina primaria, secundaria o terciaria.

39. El compuesto de la reivindicación 36, donde el átomo de nitrógeno básico es un átomo de nitrógeno en el anillo de heterocicloalquilo o heteroarilo.

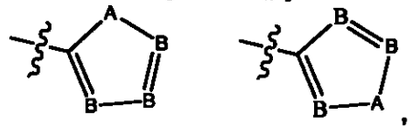
40. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-18, donde R_3 se selecciona del grupo que consiste en 3-amino-piperidinil-1-ilo, 3-aminometil-pirrolidin-1-ilo, 3-aminoazetidin-1-ilo, 3-amino-3-metilpiperidin-1-ilo, 3-aminociclopent-1-ilo, 3-aminometilciclopent-1-ilo, 3-aminometilciclohex-1-ilo, 3-aminohexahidroazepin-1-ilo, 3-amino-ciclohex-1-ilo, piperazin-1-ilo, homopiperazin-1-ilo, 3-amino-pirrolidin-1-ilo, R-3-aminopiperidin-1-ilo, R-3-amino-3-metilpiperidin-1-ilo, 3-amino-ciclohex-1-ilo, 3-amino-ciclopent-1-ilo, y 3-amino-pirrolidin-1-ilo, cada uno sustituido o no sustituido.

41. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-40, donde R_3 está sustituido de modo tal que R_3 comprende un sustituyente seleccionado del grupo que consiste en una amina primaria, secundaria o terciaria, un heterocicloalquilo que comprende un átomo de nitrógeno en el anillo, y un heteroarilo que comprende un átomo de nitrógeno en el anillo.

42. El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 4-41, donde al menos uno de Q^1 y Q^2 es CO.

43. El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 4-41, donde Q^1 y Q^2 son CO.

44. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-6 y 8-43, donde M o M_0 es CR_4, y donde R_4 se selecciona del grupo que consiste en



donde

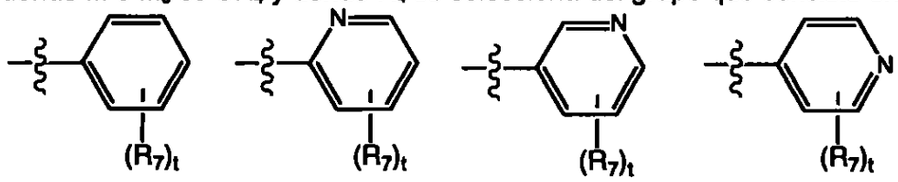
A es S, O o NR_{24};

B es CR_{23} o N;

R_{23} se selecciona independientemente del grupo que consiste en hidrógeno, halo, perhalo(C_{1-10})alquilo, amino, tiol, ciano, CF_3, nitro, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido; y

R_{24} se selecciona independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido.

45. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-6 y 8-43, donde M o M_0 es CR_4 y donde R_4 se selecciona del grupo que consiste en



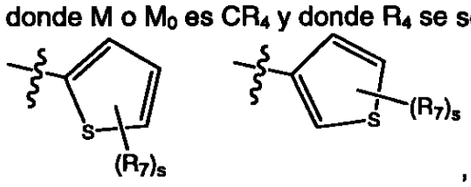
donde

u es 0, 1, 2, 3, 4 ó 5; y

cada R_{18} se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo,

heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

46. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-6 y 8-43, donde M o M_0 es CR_4 y donde R_4 se selecciona del grupo que consiste en



donde

s es 0, 1, 2 ó 3; y

cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

47. El compuesto de acuerdo con cualquiera de las reivindicaciones 4-6 y 8-46, donde R_5 y R_6 son hidrógeno.

48. El compuesto de acuerdo con cualquiera de las reivindicaciones 4-6 y 8-47, donde:

n es 1, 2 ó 3; y

R_5 y R_6 son hidrógeno.

49. El compuesto de acuerdo con cualquiera de las reivindicaciones 4-6 y 8-48, donde:

n es 1 ó 2;

R_3 se selecciona del grupo que consiste en amino, alcoxilo, ariloxilo,

heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, y un anillo de 4, 5, 6 ó 7 miembros sustituido o no sustituido; y

R_5 y R_6 son hidrógeno.

50. El compuesto de acuerdo con cualquiera de las reivindicaciones 5 y 8-49, donde: R_5 y R_6 son hidrógeno y R_7 es 2-ciano.

51. El compuesto de acuerdo con cualquiera de las reivindicaciones 4-6 y 8-48, donde:

n es 1, 2 ó 3;

R_5 y R_6 son hidrógeno; y

R_3 se selecciona del grupo que consiste en (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril (C_{1-5})alquilo, (C_{9-12})bicicloarilo, y hetero(C_{4-12})bicicloarilo, cada uno sustituido o no sustituido.

52. El compuesto de acuerdo con cualquiera de las reivindicaciones 5 y 8-48, donde:

n es 1, 2 ó 3;

R_5 y R_6 son hidrógeno; y

Cada R_7 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, alquenilo, alquinilo, CF_3, ciano, nitro, hidroxilo, heteroarilo, ariloxilo, heteroariloxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

53. El compuesto de acuerdo con cualquiera de las reivindicaciones 4-6 y 8-52, donde n es 1.

54. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-53, donde R_2 es un (C_{1-10})alquilo sustituido o no sustituido.

55. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-53,

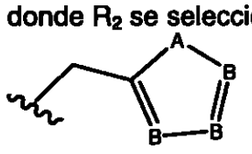
donde R_2 es un (C_{1-4})alquilo sustituido o no sustituido.

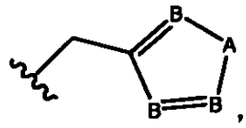
56 El compuesto de acuerdo con cualquiera de las reivindicaciones 1-53, donde R_2 es -Y-Z, donde

Y es un conector que proporciona una separación de 1, 2 ó 3 átomos entre Z y el anillo al que está unido Y, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

Z es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

57. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-53, donde R_2 se selecciona del grupo que consiste en





donde

A es S, O o NR_{24};

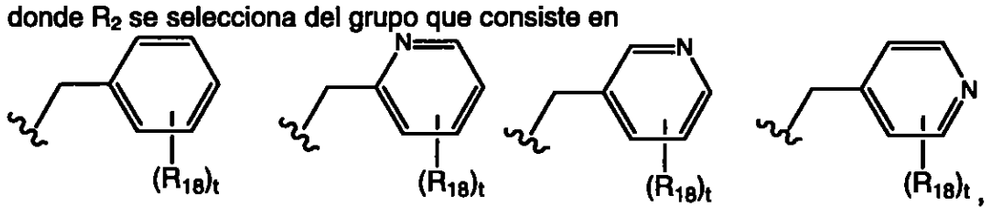
B es CR_{23} o N;

R_{23} se selecciona independientemente del grupo que consiste en hidrógeno, halo, perhalo(C_{1-10})alquilo, amino, tiol, ciano, CF_3, nitro, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo,

heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido; y

R_{24} se selecciona independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{8-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo imino, un grupo carbonilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido.

58. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-53, donde R_2 se selecciona del grupo que consiste en



donde

t es 0, 1, 2, 3, 4 ó 5; y

cada R_{18} se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, (C_{1-10})alquilo, alquenilo, alquinilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, ciano, nitro, hidroxilo, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido.

59. Un compuesto que se selecciona del grupo que consiste en:

2-(6-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-benzonitrilo;

2-(6-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirımıdin-1-ilmetil)-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-metil-2,4-dıoxo-3,4-dıhidro-2H-pirimidin-1-ilmetil}-benzonitrılo;

2-{6-[3-amino-piperidin-1-ıl]-3-etıl-2,4-dioxo-3,4-dıhidro-2H-pirimidin-1-ılmetıl}-benzonitrilo;

2-{6-[3-amıno-piperıdin-1-il]-2,4-dioxo-3,4-dihıdro-2H-pırımıdın-1-ilmetil}-benzonıtrılo;

2-{6-[3-amino-piperidın-1-ıl]-5-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pırımıdin-1-ılmetıl}-benzonıtrılo;

6-[3-amıno-piperidin-1-il]-1-(2-bromo-bencıl)-1H-pırimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-iodo-bencıl)-1H-pirımidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-bromo-5-fluoro-bencıl)-3-metıl-1H-pirimidin-2,4-diona;

6-[3-amino-pıperidın-1-il]-1-(2-cloro-5-fluoro-bencil)-3-metil-1H-pırımıdin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-cloro-4-fluoro-bencil)-3-metıl-1H-pırimidin-2,4-dıona;

6-[3-amino-piperidin-1-il]-1-(2-bromo-bencil)-3-metil-1H-pirimidın-2,4-diona;

2-{6-[azepan-3(±)-ilamino]-3-metil-2,4-dıoxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (14);

2-{6-[3(±)-amino-azepan-1-ıl]-3-metıl-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ılmetıl}-benzonitrilo;

2-[6-(2-amino-etilamino)-3-etıl-2,4-dıoxo-3,4-dıhidro-2H-pirimidin-1-ilmetil]-benzonitrilo;

2-{6-[3-amıno-piperıdın-1-il]-3-(3-ciano-bencil)-2,4-dioxo-3,4-dıhıdro-2H-pırımıdin-1-ilmetil}-benzonitrilo;

2-{6-[3-amıno-piperıdın-1-il]-3-(2-ciano-bencil)-2,4-dioxo-3,4-dıhidro-2H-pirimidin-1-

ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(4-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-[6-(3-amino-piperidin-1-il)-3-(1H-benzoimidazol-2-ilmetil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3-(4-pirazol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3-(3-pirrol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil]-tiofeno-3-carbonitrilo;

metil éster de ácido 3-{4-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

ácido 3-{4-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

6-[3-amino-piperidin-1-il]-1,3-bis-(2-bromo-5-fluoro-bencil)-1H-pirimidin-2,4-diona;

2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-1-(2,5-*di*-cloro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-3,6-*di*-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

(R)-2-((6-(3-amino-3-metilpiperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidropirimidin-1(2H)-il)metil)-4-fluorobenzonitrilo; y

2-[6-(3-amino-piperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-4-fluoro-benzonitrilo.

60. Un compuesto que se selecciona del grupo que consiste en:

2-{6-[3(R)-amino-piperidin-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-iodo-bencil)-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-4-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-3-metil-1H-pirimidin-2,4-diona;

2-{6-[3(R)-amino-piperidin-1-il]-3-(3-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-(4-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-[6-(3-amino-piperidin-1-il)-3-(1H-benzoimidazol-2-ilmetil)-2,4-dioxo-3,4-dihidro-

2H-pirimidin-1-ilmetil]-benzonitrilo

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(4-pirazol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(3-pirrol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil]-tiofeno-3-carbonitrilo;

metil éster de ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

6-[3(R)-amino-piperidin-1-il]-1,3-bis-(2-bromo-5-fluoro-bencil)-1H-pirimidin-2,4-diona; y

2-[6-(3(R)-amino-piperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-4-fluoro-benzonitrilo.

61. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-60, donde el compuesto tiene la forma de una sal aceptable para el uso farmacéutico.

62. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-61, donde el compuesto tiene al menos un estereocentro y está presente como una mezcla de estereoisómeros.

63. El compuesto de acuerdo con cualquiera de las reivindicaciones 1-61, donde el compuesto tiene al menos un estereocentro y está presente como un único estereoisómero.

64. Una composición farmacéutica que comprende, como ingrediente activo, un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63.

65. Un conjunto de elementos que comprende:

un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 o una composición de acuerdo con la reivindicación 64; e

instrucciones que comprenden una o más formas de informaciones seleccionadas del grupo que consiste en indicaciones sobre el estado de enfermedad para el cual debe administrarse el compuesto, información para almacenar el compuesto, información de dosificación e instrucciones respecto de cómo administrar el compuesto.

66. Un artículo fabricado que comprende:

un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63; y

materiales de envasado.

67. Un método para inhibir DPP-IV que comprende:

poner en contacto DPP-IV con un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63.

68. Un método para inhibir DPP-IV que comprende:

introducir un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en un sujeto para inhibir DPP-IV *in vivo*.

69. Un método para inhibir DPP-IV que comprende:

administrar un primer compuesto a un sujeto, que se convierte *in vivo* en un segundo compuesto, donde el segundo compuesto inhibe DPP-IV *in vivo*, donde el segundo compuesto es un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63.

70. Un método terapéutico que comprende:

administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 a un sujeto.

71. Un método para tratar un estado de enfermedad en cuya patología y/o sintomatología contribuye la actividad que presenta DPP-IV, que comprende introducir un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en un sujeto, en una cantidad efectiva para el uso terapéutico para el estado de enfermedad.

72. El método de acuerdo con la reivindicación 71, donde la enfermedad es diabetes tipo I o tipo II.

73. Un método para tratar el cáncer en un paciente que lo necesita, que comprende administrarle a dicho paciente una cantidad efectiva para el uso terapéutico de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63.

74. El método de la reivindicación 73, donde el cáncer tratado es cáncer colorrectal, de próstata, de mama, tiroides, piel, pulmón, o de cabeza y cuello.

75. Un método para tratar trastornos autoinmunes en un paciente que lo necesita, que comprende administrarle a dicho paciente una cantidad efectiva para el uso terapéutico de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63.

76. Un método para tratar una infección de VIH en un paciente que lo necesita, que comprende administrarle a dicho paciente una cantidad efectiva para el uso terapéutico de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63.

77. Un método para tratar una condición caracterizada por la activación o la concentración inadecuada de linfocitos o células hematopoyéticas en un paciente que lo necesita, que comprende administrar a dicho paciente una cantidad

efectiva para el uso terapéutico de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63.

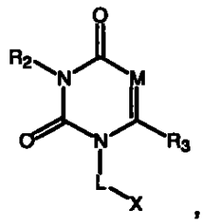
78. El método de la reivindicación 77, donde dicha condición es un efecto colateral de la quimioterapia o la terapia con radiación.

79. El método de la reivindicación 77, donde dicha condición es el resultado de una falla renal.

80. El método de la reivindicación 77, donde dicha condición es el resultado de un trastorno de médula ósea.

81. Un método para tratar una condición caracterizada por síntomas de inmunodeficiencia en un paciente que lo necesita, que comprende administrar a dicho paciente una cantidad efectiva para el uso terapéutico de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63.

82. Un proceso para producir una pirimidin-diona de fórmula:



donde

M es N o CR_4;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo,

amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

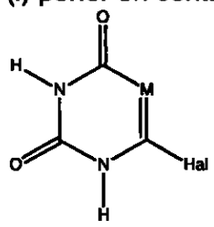
L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un

grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

que comprende los pasos de:

(i) poner en contacto un compuesto de fórmula **A**



A

donde Hal es halógeno;

con un compuesto de fórmula **B**

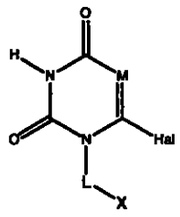
X—L—LG **B**,

donde LG es un grupo saliente;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, alquenilo, alquinilo, un grupo carbonilo, ciano, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

bajo condiciones suficientes para producir un compuesto de fórmula **C**



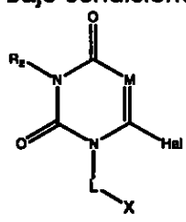
C

(ii) poner en contacto el compuesto de fórmula C con un compuesto de fórmula D

R_2—LG' D,

donde LG' es un grupo saliente;

bajo condiciones suficientes para producir un compuesto de fórmula E;



E

donde R_2 se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido; y

(iii) poner en contacto el compuesto de fórmula E con un compuesto de fórmula R_3-H bajo condiciones suficientes para producir la pirimidin-diona.

83. El proceso de la reivindicación 82, donde el producto de pirimidin-diona se convierte adicionalmente en una sal de adición ácida.

84. El proceso de la reivindicación 83, donde la sal de adición ácida se selecciona del grupo que consiste en acetato, citrato, clorhidrato, L-lactato,

succinato, sulfato, p-toluensulfonato, bencensulfonato, benzoato, metansulfonato, naftilen-2-sulfonato, propionato, p-toluensulfonato, bromhidrato, iodhidrato, R-mandelato y L-tartrato.

85. El proceso de la reivindicación 82, donde Hal se selecciona del grupo que consiste en Br, Cl y F en el compuesto de fórmula A.

86. El proceso de la reivindicación 82, donde el grupo saliente LG se selecciona del grupo que consiste en Br, Cl e I.

87. El proceso de la reivindicación 82, donde el paso (ii) comprende además la adición de una base.

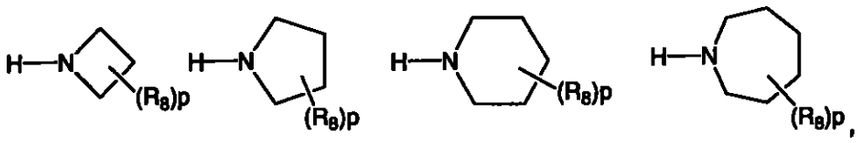
88. El proceso de la reivindicación 87, donde la base es carbonato de potasio.

89. El proceso de la reivindicación 82, donde el producto E se purifica adicionalmente sometiéndolo al paso (iii).

90. El proceso de la reivindicación 89, donde la purificación del producto E se realiza empleando lavados con solvente y/o por cromatografía.

91. El proceso de la reivindicación 82, donde R_3-H es una amina secundaria o un clorhidrato de amina.

92. El proceso de la reivindicación 82, donde R_3-H se selecciona del grupo que consiste en



donde p es 0-12 y cada R_8 se selecciona independientemente del grupo que consiste en halo, perhalo(C_{1-10})alquilo, CF_3, ciano, nitro, hidroxilo, alquilo, arilo, heteroarilo, aminosulfonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, ariloxilo, heteroariloxilo, arilalquilo, heteroarilalquilo, cicloalquilo, heterocicloalquilo, amino, tiol, alcoxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo

sulfinilo, cada uno sustituido o no sustituido, o la sal de mono o di-clorhidrato.

93. El proceso de la reivindicación 82, donde el paso (iii) comprende adicionalmente un paso de purificación que comprende lavar el producto con solventes orgánicos, o con una mezcla de solventes, y/o realizar una cromatografía en columna.

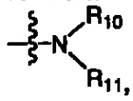
94. El proceso de la reivindicación 82, donde L se selecciona del grupo que consiste en $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, $-NH-C(O)-$, $-NCH_3-C(O)-$, $-C(O)NH-$, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, $-S-$, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, $-C(O)S-$, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, y $-CH_2SC(O)-$, cada uno sustituido o no sustituido.

95. El proceso de la reivindicación 94, donde L se selecciona del grupo que consiste en $-CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, y $-CH_2CH_2C(O)-$, cada uno sustituido o no sustituido.

96. El proceso de la reivindicación 82, donde -L-X, tomados juntos, se seleccionan del grupo que consiste en $-(CH_2)$-(2-ciano)fenilo; $-(CH_2)$-(3-ciano)fenilo; $-(CH_2)$-(2-hidroxi)fenilo; $-(CH_2)$-(3-hidroxi)fenilo; $-(CH_2)$-(2-alquenil)fenilo; $-(CH_2)$-(3-alquenil)fenilo; $-(CH_2)$-(2-alquinil)fenilo; $-(CH_2)$-(3-alquinil)fenilo; $-(CH_2)$-(2-metoxi)fenilo; $-(CH_2)$-(3-metoxi)fenilo; $-(CH_2)$-(2-nitro)fenilo; $-(CH_2)$-(3-nitro)fenilo; $-(CH_2)$-(2-carboxi)fenilo; $-(CH_2)$-(3-carboxi)fenilo; $-(CH_2)$-(2-carboxamido)fenilo; $-(CH_2)$-(3-carboxamido)fenilo; $-(CH_2)$-(2-sulfonamido)fenilo; $-(CH_2)$-(3-sulfonamido)fenilo; $-(CH_2)$-(2-tetrazolil)fenilo; $-(CH_2)$-(3-tetrazolil)fenilo; $-(CH_2)$-(2-aminometil)fenilo; $-(CH_2)$-(3-aminometil)fenilo; $-(CH_2)$-

(2-hidroximetil)fenilo; -(CH_2)-(3-hidroximetil)fenilo; -(CH_2)-(2-fenil)fenilo; -(CH_2)-(3-fenil)fenilo; -(CH_2)-(2-halo)fenilo; -(CH_2)-(3-halo)fenilo; -(CH_2)-(2-$CONH_2$)fenilo; -(CH_2)-(3-$CONH_2$)fenilo; -(CH_2)-(2-CONH(C_{1-7})alquil)fenilo; -(CH_2)-(3-CONH(C_{1-7})alquil)fenilo; -(CH_2)-(2-CO_2(C_{1-7})alquil)fenilo; -(CH_2)-(3-CO_2(C_{1-7})alquil)fenilo; -(CH_2)-(2-NH_2)fenilo; -(CH_2)-(3-NH_2)fenilo; -(CH_2)-(2-(C_{3-7})alquil)fenilo; -(CH_2)-(3-(C_{3-7})alquil)fenilo; -(CH_2)-(2-(C_{3-7})cicloalquil)fenilo; -(CH_2)-(3-(C_{3-7})cicloalquil)fenilo; -(CH_2)-(2-aril)fenilo; -(CH_2)-(3-aril)fenilo; -(CH_2)-(2-heteroaril)fenilo; -(CH_2)-(3-heteroaril)fenilo; -(CH_2)-2-bromo-5-fluoro fenilo; -(CH_2)-2-cloro-5-fluoro fenilo; -(CH_2)-2-ciano-5-fluoro fenilo; -(CH_2)-2,5-dicloro fenilo; -(CH_2)-2,5-difluoro fenilo; -(CH_2)-2,5-dibromo fenilo; -(CH_2)-2-bromo-3,5-difluoro fenilo; -(CH_2)-2-cloro-3,5-difluoro fenilo; -(CH_2)-2,3,5-trifluoro fenilo; -(CH_2)-2,3,5,6-tetrafluorofenilo; -(CH_2)-2-bromo-3,5,6-trifluoro fenilo; -(CH_2)-2-cloro-3,5,6-trifluoro fenilo; -(CH_2)-2-ciano-3,5-difluoro fenilo; -(CH_2)-2-ciano-3,5,6-trifluoro fenilo; -(CH_2)-(2-heterocicloalquil)fenilo; y -(CH_2)-(3-heterocicloalquil)fenilo, cada uno sustituido o no sustituido.

97. El proceso de la reivindicación 82, donde M es CH, y R_3 comprende la fórmula



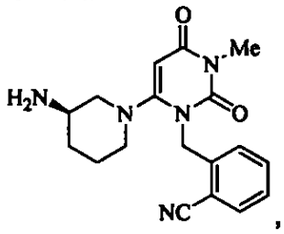
donde R_{10} y R_{11} se seleccionan cada uno independientemente del grupo que consiste en hidrógeno, perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{9-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo sulfonilo, y un grupo sulfinilo, cada uno sustituido o no sustituido, o R_{10} y R_{11} se toman juntos para formar un anillo de 4, 5, 6 ó 7

miembros, cada uno sustituido o no sustituido.

98. El proceso de la reivindicación 82, donde M es CH, y donde R_3 se selecciona del grupo que consiste en 3-amino-piperidinil-1-ilo, 3-aminometil-pirrolidin-1-ilo, 2-aminoazetidin-1-ilo, 3-amino-3-metilpiperidin-1-ilo, 3-aminociclopent-1-ilo, 3-aminometilciclopent-1-ilo, 3-aminometilciclohex-1-ilo, 3-aminohexahidroazepin-1-ilo, 3-amino-ciclohex-1-ilo, piperazin-1-ilo, homopiperazin-1-ilo, 3-amino-pirrolidin-1-ilo, R-3-aminopiperidin-1-ilo, R-3-amino-3-metilpiperidin-1-ilo, 3-amino-ciclohex-1-ilo, 3-amino-ciclopent-1-ilo, y 3-amino-pirrolidin-1-ilo, cada uno sustituido o no sustituido.

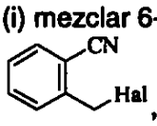
99. El proceso de la reivindicación 82, donde M es CH, y donde R_2 es un (C_{1-10})alquilo sustituido o no sustituido.

100. El proceso de la reivindicación 82 para producir una pirimidin-diona de fórmula

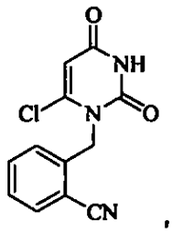


que comprende:

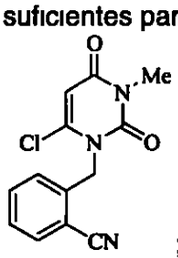
(i) mezclar 6-cloro-1H-pirimidin-2,4-diona con un haluro de arilo de fórmula



donde Hal es Br, Cl o I, bajo condiciones suficientes para producir un compuesto de fórmula

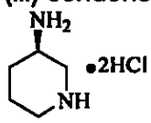


(ii) alquilar el producto anterior con un haluro de metilo bajo condiciones suficientes para formar un compuesto de fórmula



; y

(iii) condensar el producto anterior con un compuesto de fórmula



101. El proceso para producir una pirimidin-diona de la reivindicación 100, que comprende además la formación de la sal de adición ácida.

102. El proceso de la reivindicación 101, donde la sal de adición ácida es la sal de benzoato.

103. El proceso de la reivindicación 82, donde la pirimidin-diona se selecciona del grupo que consiste en:

2-(6-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-benzonitrilo;

2-(6-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil)-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-5-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3-amino-piperidin-1-il]-1-(2-bromo-bencil)-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-iodo-bencil)-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-bromo-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-cloro-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-cloro-4-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3-amino-piperidin-1-il]-1-(2-bromo-bencil)-3-metil-1H-pirimidin-2,4-diona;

2-{6-[azepan-3(±)-ilamino]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo (14);

2-{6-[3(±)-amino-azepan-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-[6-(2-amino-etilamino)-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(3-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-3-(4-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-[6-(3-amino-piperidin-1-il)-3-(1H-benzoimidazol-2-ilmetil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil]-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3-(4-pirazol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3-amino-piperidin-1-il]-2,4-dioxo-3-(3-pirrol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil]-tiofeno-3-carbonitrilo;

metil éster de ácido 3-{4-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

ácido 3-{4-[3-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-1-(2,5-*di*-cloro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-3,6-*di*-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

(R)-2-((6-(3-amino-3-metilpiperidin-1-il)-3-metil-2,4-dioxo-3,4-dihidropirimidin-1(2H)-il)metil)-4-fluorobenzonitrilo; y

6-[3-amino-piperidin-1-il]-1,3-bis-(2-bromo-5-fluoro-bencil)-1H-pirimidin-2,4-diona.

104. El proceso de la reivindicación 82, donde la pirimidin-diona se selecciona del grupo que consiste en:

2-{6-[3(R)-amino-piperidin-1-il]-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-etil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-

benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-5-cloro-3-metil-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-iodo-bencil)-1H-pirimidin-2,4-diona,

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-5-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-cloro-4-fluoro-bencil)-3-metil-1H-pirimidin-2,4-diona;

6-[3 (R)-amino-piperidin-1-il]-1-(2-bromo-bencil)-3-metil-1H-pirimidin-2,4-diona;

2-{6-[3(R)-amino-piperidin-1-il]-3-(3-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-3-(4-ciano-bencil)-2,4-dioxo-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(4-pirazol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

2-{6-[3(R)-amino-piperidin-1-il]-2,4-dioxo-3-(3-pirrol-1-il-bencil)-3,4-dihidro-2H-pirimidin-1-ilmetil}-benzonitrilo;

6-[3 (R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil]-tiofeno-3-carbonitrilo;

metil éster de ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-

3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico;

ácido 3-{4-[3(R)-amino-piperidin-1-il]-3-(2-ciano-bencil)-2,6-dioxo-3,6-dihidro-2H-pirimidin-1-ilmetil}-benzoico; y

6-[3(R)-amino-piperidin-1-il]-1,3-bis-(2-bromo-5-fluoro-bencil)-1H-pirimidin-2,4-diona.

105 El proceso de la reivindicación 82, donde la pirimidin-diona está presente en una mezcla de éstereoisómeros.

106. El proceso de la reivindicación 82, donde la pirimidin-diona comprende un único éstereoisómero.

107. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 para usar como un medicamento.

108. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en la fabricación de un medicamento para inhibir DPP-IV.

109. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en la fabricación de un medicamento para tratar un estado de enfermedad para el cual DPP-IV posee una actividad que contribuye a la patología y/o la sintomatología del estado de enfermedad.

110. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en la fabricación de un medicamento para tratar el cáncer.

111. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en la fabricación de un medicamento para tratar la diabetes tipo I o tipo II.

112. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en la fabricación de un medicamento para tratar trastornos autoinmunes.

113. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en la fabricación de un medicamento para tratar una condición caracterizada

por una activación o una concentración inapropiada de linfocitos o células hemapoyéticas.

114. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en la fabricación de un medicamento para tratar una infección de VIH.

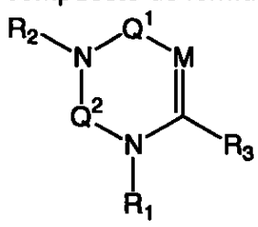
115. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-63 en la fabricación de un medicamento para tratar una condición caracterizada por síntomas de inmunodeficiencia.

418 95

INHIBIDORES DE DIPEPTIDIL PEPTIDASA

RESUMEN

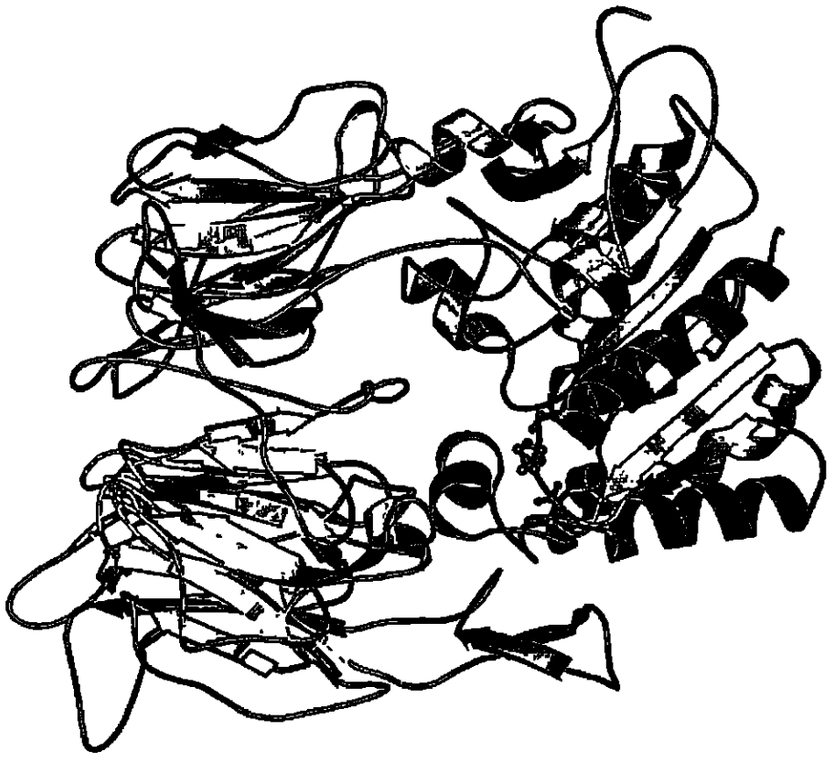
Compuestos, composiciones farmacéuticas, conjuntos de elementos y métodos para usar con DPP-IV y otras proteasas S9, que comprenden un compuesto de fórmula I:



I

donde M es N o CR_4; Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, SO, SO_2, y $C=NR_9$; y cada R_1, R_2, R_3, R_4 y R_9 tienen los valores definidos en la presente documentación.

FIGURE 1



From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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

(PCT Rule 44 1)

To
SYRRX, INC.
Attn. Weitz, David J.
10410 Science Center Drive
San Diego CA 92121
UNITED STATES OF AMERICA

	Date of mailing *(day/month/year)* 14/06/2005
Applicant's or agent's file reference DP4-5016-PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No PCT/US2004/042209	International filing date *(day/month/year)* 15/12/2004
Applicant SYRRX, INC.	

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

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

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Fascimile No. (41-22) 740.14 35

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

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

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

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

[ ] no decision has been made yet on the protest, the applicant will be notified as soon as a decision is made.

4 **Reminders**

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

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

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

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

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

Name and mailing address of the International Searching Authority European Patent Office, P B 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Josef Ullrich

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication Furthermore, it should be emphasized that provisional protection is available in some States only

What parts of the international application may be amended?

Under Article 19, only the claims may be amended

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

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

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46 1)

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46 2)

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

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

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

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

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

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter

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

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

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged,

(ii) the claim is cancelled,

(iii) the claim is new,

(iv) the claim replaces one or more claims as filed,

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1 [Where originally there were 48 claims and after amendment of some claims there are 51]
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged, new claims 49 to 51 added "

2 [Where originally there were 15 claims and after amendment of all claims there are 11]
"Claims 1 to 15 replaced by amended claims 1 to 11 "

3 [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]
"Claims 1 to 6 and 14 unchanged, claims 7 to 13 cancelled; new claims 15, 16 and 17 added " or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added, all other claims unchanged "

4 [Where various kinds of amendments are made]
"Claims 1-10 unchanged, claims 11 to 13, 18 and 19 cancelled, claims 14, 15 and 16 replaced by amended claim 14, claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added "

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1))

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be *brief*, not exceeding 500 words if in English or if translated into English

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence)

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below
DP4-5016-PCT		
International application No	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2004/042209	15/12/2004	15/03/2004
Applicant		
SYRRX, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18 A copy is being transmitted to the International Bureau

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report

1 **Basis of the report**

a With regard to the **language**, the International search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item

[ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23 1(b))

b [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No I

2 [ ] **Certain claims were found unsearchable** (See Box II)

3 [ ] **Unity of invention is lacking (see Box III).**

4 With regard to the **title,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established by this Authority to read as follows

5 With regard to the **abstract,**

[X] the text is approved as submitted by the applicant

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

6 With regard to the **drawings,**

a the figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] as selected by this Authority, because the applicant failed to suggest a figure.

[ ] as selected by this Authority, because this figure better characterizes the invention

b [X] none of the figures is to be published with the abstract.

A CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 C07D401/12 C07D401/14 A61K31/506 A61P3/10 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)
IPC 7 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, PAJ, WPI Data, 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
P,A	WEBER, A.E.: "DIPEPTIDYL PEPTIDASE IV INHIBITORS FOR THE TREATMENT OF DIABETES" JOURNAL OF MEDICINAL CHEMISTRY, vol. 47, 2004, pages 4135-4141, XP002329845 figure 2	1-161
A	WO 03/035057 A (FERRING B.V; EVANS, DAVID, MICHAEL; ASHWORTH, DOREEN, MARY) 1 May 2003 (2003-05-01) the whole document	1-161
X	PATENT ABSTRACTS OF JAPAN vol. 2003, no. 12, 5 December 2003 (2003-12-05) & JP 2003 300977 A (SUMITOMO PHARMACEUT CO LTD), 21 October 2003 (2003-10-21) abstract	1-161

-/--

[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in 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 May 2005	14/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Baston, E

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DE 21 50 686 A1 (BADISCHE ANILIN- & SODA-FABRIK AG) 19 April 1973 (1973-04-19) claim 1	1-161
X	EP 0 442 473 A (TAKEDA CHEMICAL INDUSTRIES, LTD) 21 August 1991 (1991-08-21) tables 1a-4a,5	1-161
X	BOTTA, M., SALADINO, R., LAMBA, D., NICOLETTI, R.: "Researches on Antiviral Agents. 31. Synthesis and Transformations of Racemic and Chiral 6-Oxiranyl Pyrimidinones" TETRAHEDRON, vol. 49, 1993, pages 6053-6070, XP002329846 examples 3,6	1
X	FRAISSE, L. ET AL.: "Long-Chain-Substituted Uric Acid and 5,6-Diaminouracil Derivatives as Novel Agents against Free Radical Processes: Synthesis and in Vitro Activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, 1993, pages 1465-1473, XP002329847 example 4k	1
X	KIM, H.O. ET AL.: "Structure-Activity Relationships of 1,3-Dialkylxanthine Derivatives at Rat A3 adenosine Receptors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, 1994, pages 3373-3382, XP002329848 example 38b	1

1

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03035057 A	01-05-2003	CA 2464254 A1	01-05-2003
		CN 1571667 A	26-01-2005
		EP 1446116 A1	18-08-2004
		WO 03035057 A1	01-05-2003
		HU 0401738 A2	28-12-2004
		JP 2005511541 T	28-04-2005
		MX PA04003829 A	16-07-2004
		NZ 532048 A	29-10-2004
		US 2005043299 A1	24-02-2005
JP 2003300977 A	21-10-2003	NONE	
DE 2150686 A1	19-04-1973	NONE	
EP 0442473 A	21-08-1991	AT 169915 T	15-09-1998
		CA 2036304 A1	16-08-1991
		DE 69129998 D1	24-09-1998
		DE 69129998 T2	24-12-1998
		EP 0442473 A1	21-08-1991
		JP 3032844 B2	17-04-2000
		JP 4330072 A	18-11-1992
		US 5162326 A	10-11-1992

From the
INTERNATIONAL SEARCHING AUTHORITY

To

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis* 1)

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/042209	15 12 2004	15 03 2004

International Patent Classification (IPC) or both national classification and IPC
C07D401/04, C07D401/12, C07D401/14, A61K31/506, A61P3/10, A61P35/00

Applicant
SYRRX, INC

1 This opinion contains indications relating to the following items.

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

2 **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66 1*bis*(b) that written opinions of this International Searching Authority will not be so considered

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

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

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

Name and mailing address of the ISA

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

Authorized Officer

Baston, E

Telephone No +49 89 2399-8229

Box No. I Basis of the opinion

1 With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item

☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23 1(b))

2 With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of

a type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form

☐ furnished subsequently to this Authority for the purposes of search

3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished

4. Additional comments.

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

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

☐ the entire international application,

☒ claims Nos 1-161(part), 113-127 "with respect to industrial applicability"

because

☒ the said international application, or the said claims Nos 113-127 relate to the following subject matter which does not require an international preliminary examination *(specify)*

see separate sheet

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

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

☒ no international search report has been established for the whole application or for said claims Nos 1-161(part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

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

☐ See separate sheet for further details

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

1 Statement

Novelty (N)	Yes.	Claims	1-161(part)
	No	Claims	
Inventive step (IS)	Yes	Claims	1-161(part)
	No	Claims	
Industrial applicability (IA)	Yes	Claims	1-112,128-161
	No.	Claims	

2 Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1 Certain published documents (Rules 43*bis* 1 and 70 10)

and / or

2 Non-written disclosures (Rules 43*bis* 1 and 70 9)

see form 210

To section III

Claims 113-127 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to those structures according to formula of claim 1 having the following features:
Q_1,Q_2: C=O
M_0: C
R_0,R_1: CH_2-Ph (possibly substituted)
R_2: as defined in claim 1
R_3: N (possibly substituted) or being part of a cycle

To section V

The following documents were cited in the search report and were considered for the examination of the present application.

D1: WEBER, A.E.: "DIPEPTIDYL PEPTIDASE IV INHIBITORS FOR THE TREATMENT OF DIABETES" JOURNAL OF MEDICINAL CHEMISTRY, vol. 47, 2004, pages 4135-4141,

D2: WO 03/035057 A (FERRING B.V; EVANS, DAVID, MICHAEL; ASHWORTH, DOREEN, MARY) 1 May 2003

D3: PATENT ABSTRACTS OF JAPAN vol. 2003, no. 12, 5 December 2003 (2003-12-05) & JP 2003 300977 A (SUMITOMO PHARMACEUT CO LTD), 21 October 2003

D4: DE 21 50 686 A1 (BADISCHE ANILIN- & SODA-FABRIK AG) 19 April 1973

D5: EP-A-0 442 473 (TAKEDA CHEMICAL INDUSTRIES, LTD) 21 August 1991

D6: BOTTA, M., SALADINO, R., LAMBA, D., NICOLETTI, R.: "Researches on Antiviral Agents 31. Synthesis and Transformations of Racemic and Chiral 6-Oxiranyl

Pyrimidinones" TETRAHEDRON, vol. 49, 1993, pages 6053-6070,

D7. FRAISSE, L. ET AL.: "Long-Chain-Substituted Uric Acid and 5,6-Diaminouracil Derivatives as Novel Agents against Free Radical Processes: Synthesis and in Vitro Activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, 1993, pages 1465-1473,

D8. KIM, H.O. ET AL.: "Structure-Activity Relationships of 1,3-Dialkylxanthine Derivatives at Rat A3 adenosine Receptors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, 1994, pages 3373-3382

The following considerations only relate to structures as defined under section III:
The present application is directed to 2,4-dioxo-pyrimidines which are considered to be useful for the treatment of diabetes or cancer due to an inhibition of the enzyme dipeptidy peptidase, specially isoform IV.
Those X-citations of the search report give some examples for compounds falling under the scope of original claim 1. However structures as defined under section III having a benzyl group are not anticipated by any document cited and thus the requirements of Art 33(2) PCT are met.
The description reveals that the compounds have good inhibitory properties with respect to dipeptidyl peptidase IV (page 112, section 368). Documents D2 and D3 are directed to inhibitors of the same enzyme as well, but do not suggest 2,4-dioxo-pyrimidines. The structures according to the above definition are thus considered to involve an inventive step (Art. 33(3) PCT).

Claims 113-115 and claim 117 are not acceptable in view of Art. 6 PCT due to the expression "inhibition of DPP-IV" which has to be replaced by a well defined pathological condition.

The numbering of the claims is not correct, since claim 13 is missing (Art. 6 PCT).

For the assessment of the present claims 113-127 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the

manufacture of a medicament for a new medical treatment.

To section VI

The priority document of the present application is not yet available. In case that the presently claimed subject matter is not fully supported by the priority document, D1 might be relevant for the assessment of novelty and / or inventive step in the national / European phase.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis 1 and Administrative Instructions, Section 422)

To:

WEITZ, David, J.
Takeda San Diego, INC.
10410 Science Center Drive
San Diego, California 92121
United States of America

Date of mailing (day/month/year)	
26 April 2006 (26.04.2006)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
DP4-5016-PCT	
International application No.	**International filing date (day/month/year)**
PCT/US2004/042209	15 December 2004 (15.12.2004)

1. The following indications appeared on record concerning

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
TAKEDA SAN DIEGO, INC. 10410 Science Center Drive San Diego, California 92121 United States of America	US	US
	Telephone No (858) 622-8528	
	Facsimile No. (858) 550-0992	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
TAKEDA PHARMACEUTICAL COMPANY LIMITED 1-1, Doshomachi 4-chome, Chuo-ku Osaka-shi, Osaka 541-0045 Japan	JP	JP
	Telephone No +81 6 6204-2880	
	Facsimile No. +81 6 6204-2111	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer David LANIEL (Fax 338-87-20)
Facsimile No (41-22) 338 89.86	Telephone No. (41-22) 338 8773

Form PCT/IB/306 (March 1994) 006938456

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WEITZ, David, J.
Takeda San Diego, INC.
10410 Science Center Drive
San Diego, California 92121
United States of America

Date of mailing (day/month/year)	
18 October 2005 (18.10.2005)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
DP4-5016-PCT	
International application No.	**International filing date (day/month/year)**
PCT/US2004/042209	15 December 2004 (15.12.2004)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
SYRRX, INC. 10410 Science Center Drive San Diego, California 92121 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
TAKEDA SAN DIEGO, INC. 10410 Science Center Drive San Diego, California 92121 United States of America	US	US
	Telephone No.	
	Facsimile No	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to.

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer T. Vernhes (Fax 338-8995)
Facsimile No. (41-22) 338.89 95	Telephone No. (41-22) 338 8938

Form PCT/IB/306 (March 1994) 006829293

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WEITZ, David, J.
Takeda San Diego, INC.
10410 Science Center Drive
San Diego, California 92121
United States of America

Date of mailing (day/month/year)	
18 October 2005 (18.10.2005)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
DP4-5016-PCT	
International application No.	**International filing date (day/month/year)**
PCT/US2004/042209	15 December 2004 (15 12.2004)

1. The following indications appeared on record concerning.

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No	
	Teleprinter No	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
ULYSSE, Luckner 601 Highwood Circle Albany, NY 12203 United States of America	US	US
	Telephone No.	
	Facsimile No	
	Teleprinter No.	

3. Further observations, if necessary:

The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer T. Vernhes (Fax 338-8995)
Facsimile No. (41-22) 338.89.95	Telephone No. (41-22) 338 8936

Form PCT/IB/306 (March 1994) 006829312

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To.

WEITZ, David, J.
Takeda San Diego, INC
10410 Science Center Drive
San Diego, California 92121
United States of America

Date of mailing (day/month/year)	
18 October 2005 (18.10.2005)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
DP4-5016-PCT	
International application No.	**International filing date** (day/month/year)
PCT/US2004/042209	15 December 2004 (15.12.2004)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SALSBURY, Jonathon 38 Woodlake Road, Apt. 3 Albany, NY 12203 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and Inventor for all designated States.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer T Vernhes (Fax 338-8995)
Facsimile No. (41-22) 338 89.95	Telephone No. (41-22) 338 8938

Form PCT/IB/308 (March 1994) 006829318

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To

WEITZ, David, J.
Takeda San Diego, INC.
10410 Science Center Drive
San Diego, California 92121
United States of America

Date of mailing (day/month/year)	
18 October 2005 (18.10.2005)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
DP4-5016-PCT	
International application No.	**International filing date (day/month/year)**
PCT/US2004/042209	15 December 2004 (15.12.2004)

1. The following indications appeared on record concerning

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
PALMER, Grant 4704 Foxwood Drive South Clifton Park, NY 12065 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer T. Vernhes (Fax 338-8995)
Facsimile No (41-22) 338 89.95	Telephone No (41-22) 338 8936

Form PCT/IB/306 (March 1994) 006829309

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WEITZ, David, J
Takeda San Diego, INC.
10410 Science Center Drive
San Diego, California 92121
United States of America

Date of mailing (day/month/year)	
18 October 2005 (18.10.2005)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
DP4-5016-PCT	
International application No.	**International filing date (day/month/year)**
PCT/US2004/042209	15 December 2004 (15 12.2004)

1. The following indications appeared on record concerning

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
ISBESTER, Paul 34 Green Avenue Castleton, NY 12033 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer T Vernhes (Fax 338-8995)
Facsimile No. (41-22) 338.89 95	Telephone No (41-22) 338 8838

Form PCT/IB/308 (March 1994) 006828307

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WEITZ, David, J.
Takeda San Diego, INC.
10410 Science Center Drive
San Diego, California 92121
United States of America

Date of mailing (day/month/year)	
18 October 2005 (18.10.2005)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
DP4-5016-PCT	
International application No.	**International filing date (day/month/year)**
PCT/US2004/042209	15 December 2004 (15.12.2004)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No	
	Facsimile No	
	Teleprinter No	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
ELDER, Bruce 21 White Tail Circle Wynantskill, NY 12198 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary

The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

[X] the receiving Office
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[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer T. Vernhes (Fax 338-8995)
Facsimile No. (41-22) 338 89 95	Telephone No. (41-22) 338 8936

Form PCT/IB/306 (March 1994) 006829306

SUPERINTENDENCIA

FORMATO DE DIGITALIZACIC
RELACION DE ANEXOS

Royal Technologies S.A.

411

Item	Expediente No	No de unidades	No de Folio √
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA X	1	1
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS		

Observaciones: Sobe con art Final .

442

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-094099- -00000-0000
Fec: 2006-09-19 16:07:35 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII
Eva: 379 FASENACIONALII
Act 411 PRESENTACION Folios: 441

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 [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

443

PETITORI

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-094099- -00000-0000
Fec: 2006-09-19 16:07:35 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEYII
Eve: 379 FASENACIONALII
Act 411 PRESENTACION
Folios: 441

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 15/10/06

1) SOLICITUD DE:

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☐ Capitulo I. ☒ Capitulo II.

2) SOLICITANTE (71)	**Nombre: TAKEDA PHARMACEUTICAL COMPANY LIMITED** **Dirección: 1-1, Doshomachi 4-chome Chuo-ku, Osaka-shi Osaka 541-0045 Japón** **Nacionalidad o domicilio: Osaka, Japón** **Lugar de constitución: Japón**	**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: VER LISTA ADJUNTA** **Dirección:** **Nacionalidad o Domicilio:**	

5) PCT (86)
Solicitud Internacional No. PCT/US2004/042209 Fecha: DICIEMBRE 15, 2004

Publicación Internacional No. WO2005/095381 A1 Fecha: OCTUBRE 13, 2005

6)Título (54) INHIBIDORES DE DIPEPTIDIL PEPTIDASA

7) Clasificación Internacional: C07D 401/04, 401/12, 401/14, A61K 31/506, A61P 3/10, 35/00

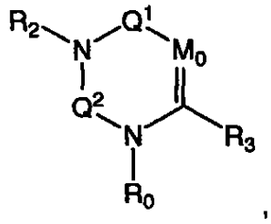
8) PRIORIDAD SI ☒ NO ☐	**33) País de Origen**	**(32) Fecha**	**(31) Número de Solicitud**
	Estados Unidos	**Marzo 15, 2004**	**60/553,571**
	Estados Unidos	**Nov. 18, 2004**	**60/629,524**

9) Comprobante de pago N° 06 61 912 **Fecha:** 15/09/06

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

REIVINDICACIONES:

1. Un compuesto que comprende:



donde

M_0 es –C–LX, N o CR_4;

Q^1 y Q^2 se seleccionan cada uno independientemente del grupo que consiste en CO, CS, SO, SO_2, y $C=NR_9$;

R_0 es R_1 o –LX, con la condición de que solamente uno de R_0 y M_0 es -LX;

R_1 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil (C_{1-3})alquilo, tiocarbonil (C_{1-3})alquilo, sulfonil (C_{1-3})alquilo, sulfinil (C_{1-3})alquilo, imino (C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_2 es hidrógeno o se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, (C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquil(C_{1-5})alquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloarilo, hetero(C_{4-12})bicicloarilo, hetero(C_{4-12})bicicloaril(C_{1-5})alquilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno

sustituido o no sustituido;

R_3 se selecciona del grupo que consiste en perhalo(C_{1-10})alquilo, amino, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido, y un anillo sustituido o no sustituido de 3, 4, 5, 6 ó 7 miembros;

R_4 es hidrógeno o se selecciona del grupo que consiste en halo, perhalo(C_{1-10})alquilo, amino, ciano, tiol, (C_{1-10})alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, arilo, heteroarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, hidroxilo, alcoxilo, ariloxilo, heteroariloxilo, un grupo carbonilo, un grupo imino, un grupo sulfonilo y un grupo sulfinilo, cada uno sustituido o no sustituido;

R_9 es hidrógeno o se selecciona del grupo que consiste en alquilo, cicloalquilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, bicicloarilo, y heterobicicloarilo, cada uno sustituido o no sustituido;

L es un conector que proporciona una separación de 1, 2 ó 3 átomos entre X y el anillo al que está unido L, donde los átomos del conector que proporcionan la separación se seleccionan del grupo que consiste en átomos de carbono, oxígeno, nitrógeno y azufre; y

X se selecciona del grupo que consiste en (C_{1-10})alquilo, (C_{3-12})cicloalquilo, hetero(C_{3-12})cicloalquilo, aril(C_{1-10})alquilo, heteroaril(C_{1-5})alquilo, (C_{8-12})bicicloanilo, hetero(C_{4-12})bicicloarilo, carbonil(C_{1-3})alquilo, tiocarbonil(C_{1-3})alquilo, sulfonil(C_{1-3})alquilo, sulfinil(C_{1-3})alquilo, imino(C_{1-3})alquilo, amino, arilo, heteroarilo, hidroxilo,

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RODRIGUEZ DILIA MARIA

REFERENCIA	Radicación No.	6 94099
	Solicitud internacional	PCT/US2004/042209
	Fecha inicio fase nacional	15/10/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	13576

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

3. Debe aclarar el número de reivindicaciones, por cuanto presenta inconsistencias la publicación internacional con la solicitud presentada en fase nacional.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha
aalvarado 24 NOV. 2006