PCT

Industria y Comercio
SUPERINTENDENCIA
República de Colombia
Ministerio de Comercio, Industria y Turismo

PROPIEDAD INDUSTRIAL

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO INVENTARIO

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SOLICITUD DE

PATENTE DE INVENCION
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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21. EXPEDIENTE No. __

54. TITULO: **ACTIVADORES DE GLUCOQUINASA**

52. CLASIFICACION INTERNACIONAL: **C07D 231/56, C07D 403/12, C07D 405/14, C07D 417/14, C07D 471/04, C07D 513/04, A61K 31/4155, A61P 3/10**

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22. BOGOTA, D.C., 07 DIC 2010

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Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISION A TRAMITE - NUEVAS CREACIONES

PATENTE DE INVENCION [ ] **MODELO DE UTILIDAD** [ ] **Art. 33 Decisión 486/00**

[ ]	Indicación que se solicita una patente
[ ]	Datos de identificación del solicitante o de la persona que presenta la solicitud
[ ]	Descripción de la invención
[ ]	Dibujos de ser estos pertinentes
[ ]	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [ ] Incompleta [ ]

PATENTE DE INVENCION PCT [X] **MODELO DE UTILIDAD PCT** [ ] **Art. 33 Decisión 486/00 Circular Única**

[X]	Indicación que se solicita una PCT
[X]	Datos de identificación del solicitante o de la persona que presenta la solicitud
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DISEÑO INDUSTRIAL [ ] **(Art. 119 Decisión 486/00)**

[ ]	Indicación que se solicita diseño industrial
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ESQUEMA DE TRAZADO [ ] **(Art. 92 Decisión 486/00)**

[ ]	Indicación que se solicita un esquema de trazado
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[ ]	Comprobante de pago de las tasas establecidas

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ificación

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SOLICITUD DE:

(1)

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

[X] Capítulo I [ ] Capítulo II

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

(10) Anexos

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: **Tarjeta Propietario, Extracto para la publicación**

(11) FIGURA CARACTERISTICA:

(12) Solicito la concesión de la patente,

NOMBRE: **MARGARITA CASTELLANOS ABONDANO**

FIRMA:

C.C. No. 39'779.654 Usaquén - TPA 70.819 C.S.J.

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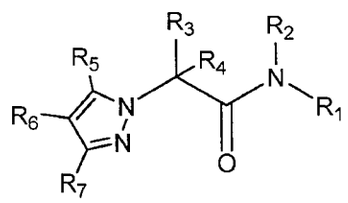
(74) Agents: **BRUSTEIN, Mitchell, R.** et al.; Takeda San Diego, Inc., 10410 Science Center Drive, San Diego, CA 92121 (US).

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(54) **Title**: GLUCOKINASE ACTIVATORS



(57) **Abstract**: Compounds are provided for use with glucokinase that comprise the formula: ##STR## wherein the variables are as defined herein. Also provided are pharmaceutical compositions, kits and articles of manufacture comprising such compounds; methods and intermediates useful for making the compounds; and methods of using said compounds.

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GLUCOKINASE ACTIVATORS

FIELD OF THE INVENTION

[0001] The present invention relates to compounds that may be used to activate hexokinases, as well as compositions of matter, kits and articles of manufacture comprising these compounds. The invention also relates to methods for activating hexokinases and treatment methods using compounds according to the present invention. In addition, the invention relates to methods of making the compounds of the present invention, as well as intermediates useful in such methods. In particular, the present invention relates to glucokinase activators, compositions of matter, kits and articles of manufacture comprising these compounds, methods for activating glucokinase, and methods of making the activators.

BACKGROUND OF THE INVENTION

[0002] Glucokinase (GK, Hexokinase IV) is one of four hexokinases that are found in mammals (Colowick, S. P., in The Enzymes, Vol. 9 (P. Boyer, ed.) Academic Press, New York, N.Y., pages 1-48, 1973). The hexokinases catalyze the first step in the metabolism of glucose, *i.e.*, the conversion of glucose to glucose-6-phosphate. Glucokinase is found principally in pancreatic β-cells and liver parenchymal cells, two cell types that are known to play critical roles in whole-body glucose homeostasis. Specifically, GK is a rate-controlling enzyme for glucose metabolism in these two cell types (Chipkin, S. R., Kelly, K. L., and Ruderman, N. B. in Joslin's Diabetes (C. R. Khan and G. C. Wier, eds.), Lea and Febiger, Philadelphia, Pa., pages 97-115, 1994).

[0003] The concentration of glucose at which GK demonstrates half-maximal activity is approximately 8 mM. The other three hexokinases are saturated with glucose at much lower concentrations (<1 mM). Therefore, the flux of glucose through the GK pathway rises as the concentration of glucose in the blood increases from fasting levels (5 mM) to postprandial levels following a carbohydrate-containing meal (about 10-15 mM) (Printz, R. G., Magnuson, M. A., and Granner, D. K. in Ann. Rev. Nutrition Vol. 13 (R. E. Olson, D. M. Bier, and D. B. McCormick, eds.), Annual Review, Inc., Palo Alto, Calif., pages 463-496, 1993). These findings suggest that GK functions as a glucose sensor in β-cells and hepatocytes (Meglasson, M. D. and Matschinsky, F. M. Amer. J Physiol. 246, E1-E13, 1984).

[0004] More recently, studies in transgenic animals confirmed that GK does indeed play a critical role in whole-body glucose homeostasis. Animals that do not express GK die within days of birth with severe diabetes, while animals overexpressing GK have improved glucose tolerance (Grupe, A., Hultgren, B., Ryan, A. *et al.*, Cell 83, 69-78, 1995; Ferrie, T., Riu, E., Bosch, F. et al., FASEB J., 10, 1213-1218, 1996). An increase in glucose exposure is coupled through GK in β-cells to increased insulin secretion and in hepatocytes to increased glycogen deposition and perhaps decreased glucose production.

[0005] The finding that type II maturity-onset diabetes of the young (MODY-2) is caused by loss of function mutations in the GK gene suggests that GK also functions as a glucose sensor in humans (Liang, Y., Kesavan, P., Wang, L. *et al.*, Biochem. J. 309, 167-173, 1995). Additional evidence supporting an important role for GK in the regulation of glucose metabolism in humans was provided by the identification of patients that express a mutant form of GK with increased enzymatic activity. These patients exhibit a fasting hypoglycemia associated with an inappropriately elevated level of plasma insulin (Glaser, B., Kesavan, P., Heyman, M. *et al.*, New England J. Med. 338, 226-230, 1998). Accordingly, compounds that activate GK and, thereby, increase the sensitivity of the GK sensor system are expected to be useful in the treatment of the hyperglycemia characteristic of all type II diabetes. Glucokinase activators should increase the flux of glucose metabolism in β-cells and hepatocytes, which will be coupled to increased insulin secretion.

[0006] There is a continued need to find new therapeutic agents to treat human diseases. The hexokinases, specifically but not limited to glucokinase, are especially attractive targets for the discovery of new therapeutics due to their important role in diabetes, hyperglycemia and other diseases.

SUMMARY OF THE INVENTION

[0007] The present invention relates to compounds that activate glucokinase. The present invention also provides compositions, articles of manufacture and kits comprising these compounds. In addition, the invention relates to methods of making the compounds of the present invention, as well as intermediates useful in such methods.

[0008] In one embodiment, a pharmaceutical composition is provided that comprises a glucokinase activator 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 activators of this invention. These pharmaceutical compositions may be administered or coadministered by a wide variety of routes, including for example, orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, or intrathecally. The compositions may also be administered or coadministered in slow release dosage forms.

[0009] The invention is also directed to kits and other articles of manufacture for treating disease states associated with glucokinase.

[0010] In one embodiment, a kit is provided that comprises a composition comprising at least one glucokinase activator 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.

[0011] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one glucokinase activator 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.

[0012] 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.

[0013] Also provided are methods for using compounds, compositions, kits and articles of manufacture according to the present invention.

[0014] In one embodiment, the compounds, compositions, kits and articles of manufacture are used to modulate glucokinase. In particular, the compounds, compositions, kits and articles of manufacture can be used to activate glucokinase.

[0015] In another embodiment, the compounds, compositions, kits and articles of manufacture are used to treat a disease state for which increasing glucokinase activity ameliorates the pathology and/or symptomology of the disease state.

[0016] In another embodiment, a compound is administered to a subject wherein glucokinase activity within the subject is altered and, in one embodiment, increased.

[0017] In another embodiment, a prodrug of a compound is administered to a subject that is converted to the compound *in vivo* where it activates glucokinase.

[0018] In another embodiment, a method of activating glucokinase is provided that comprises contacting glucokinase with a compound according to the present invention.

[0019] In another embodiment, a method of activating glucokinase is provided that comprises causing a compound according to the present invention to be present in a subject in order to activate glucokinase *in vivo*.

[0020] In another embodiment, a method of activating glucokinase is provided that comprises administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound activates glucokinase *in vivo*. It is noted that the compounds of the present invention may be the first or second compounds.

[0021] In another embodiment, a therapeutic method is provided that comprises administering a compound according to the present invention.

[0022] In another embodiment, a method of treating a condition in a patient that is known to be mediated by glucokinase, or which is known to be treated by glucokinase activators, is provided comprising administering to the patient a therapeutically effective amount of a compound according to the present invention.

[0023] In another embodiment, a method is provided for treating a disease state for which increasing glucokinase activity ameliorates 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.

[0024] In another embodiment, a method is provided for treating a disease state for which increasing glucokinase activity ameliorates 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.

[0025] In another embodiment, a method is provided for treating a disease state for which increasing glucokinase activity ameliorates 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.

[0026] In another embodiment, a method is provided for using a compound according to the present invention in order to manufacture a medicament for use in the treatment of a disease state that is known to be mediated by glucokinase, or that is known to be treated by glucokinase activators.

[0027] It is noted in regard to all of the above embodiments that the present invention is intended to encompass all pharmaceutically acceptable ionized forms (*e.g.*, salts) and solvates (*e.g.*, hydrates) of the compounds, regardless of whether such ionized forms and solvates are specified since it is well know in the art to administer pharmaceutical agents in an ionized or solvated form. It is also noted that unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all possible stereoisomers (*e.g.*, enantiomers or diastereomers depending on the number of chiral centers), independent of whether the compound is present as an individual isomer or a mixture of isomers. Further, unless otherwise specified, recitation of a compound is intended to encompass all possible resonance forms and tautomers. With regard to the claims, the language "compound comprising the formula" is intended to encompass the compound and all pharmaceutically acceptable ionized forms and solvates, all possible stereoisomers, and all possible resonance forms and tautomers unless otherwise specifically specified in the particular claim.

[0028] 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 activating glucokinase and thus may themselves be prodrugs for another compound. Such prodrugs of another compound may or may not themselves independently have glucokinase activity.

BRIEF DESCRIPTION OF THE FIGURES

[0029] Figure 1 illustrates SEQ. ID No. 1 referred to in this application.

DEFINITIONS

[0030] Unless otherwise stated, the following terms used in the specification and claims shall have the following meanings for the purposes of this Application.

[0031] It is noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Further, definitions of standard chemistry terms may be found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A (2000) and B (2001), Plenum Press, New York. Also, unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art are employed.

[0032] "Alicyclic" means a moiety comprising a non-aromatic ring structure. Alicyclic moieties may be saturated or partially unsaturated with one, two or more double or triple bonds. Alicyclic moieties may also optionally comprise heteroatoms such as nitrogen, oxygen and sulfur. The nitrogen atoms can be optionally quaternerized or oxidized and the sulfur atoms can be optionally oxidized. Examples of alicyclic moieties include, but are not limited to moieties with (C_{3-8}) rings such as cyclopropyl, cyclohexane, cyclopentane, cyclopentene, cyclopentadiene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, cycloheptene, cycloheptadiene, cyclooctane, cyclooctene, and cyclooctadiene.

[0033] "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.

[0034] "Alkenyl" means a straight or branched, carbon chain that contains at least one carbon-carbon double bond (-CR=CR'- or –CR=CR'R", wherein R, R' and R" are each independently hydrogen or further substituents). Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like. In particular embodiments, "alkenyl," either alone or represented along with another radical, can be a (C_{2-20})alkenyl, a (C_{2-15})alkenyl, a (C_{2-10})alkenyl, a (C_{2-5})alkenyl or

a (C_{2-3})alkenyl. Alternatively, "alkenyl," either alone or represented along with another radical, can be a (C_2)alkenyl, a (C_3)alkenyl or a (C_4)alkenyl.

[0035] "Alkenylene" means a straight or branched, divalent carbon chain having one or more carbon-carbon double bonds (-CR=CR'-, wherein R and R' are each independently hydrogen or further substituents). Examples of alkenylene include ethene-1,2-diyl, propene-1,3-diyl, methylene-1,1-diyl, and the like. In particular embodiments, "alkenylene," either alone or represented along with another radical, can be a (C_{2-20}) alkenylene, a (C_{2-15}) alkenylene, a (C_{2-10}) alkenylene, a (C_{2-5}) alkenylene or a (C_{2-3}) alkenylene. Alternatively, "alkenylene," either alone or represented along with another radical, can be a (C_2) alkenylene, a (C_3) alkenylene or a (C_4) alkenylene.

[0036] "Alkoxy" means an oxygen moiety having a further alkyl substituent. The alkoxy groups of the present invention can be optionally substituted.

[0037] "Alkyl" represented by itself means a straight or branched, saturated aliphatic radical having a chain of carbon atoms, optionally with one or more of the carbon atoms being replaced with oxygen (See "oxaalkyl"), a carbonyl group (See "oxoalkyl"), sulfur (See "thioalkyl"), and/or nitrogen (See "azaalkyl"). (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 and the like) 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). In particular embodiments, "alkyl," either alone or represented along with another radical, can be a (C_{1-20})alkyl, a (C_{1-15})alkyl, a (C_{1-10})alkyl, a (C_{1-5})alkyl or a (C_{1-3})alkyl. Alternatively, "alkyl," either alone or represented along with another radical, can be a (C_1)alkyl, a (C_2)alkyl or a (C_3)alkyl.

[0038] "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. In particular embodiments, "alkylene," either alone or represented along with another radical, can be a (C_{1-20})alkylene, a (C_{1-15})alkylene, a (C_{1-10})alkylene, a (C_{1-5})alkylene or a (C_{1-3})alkylene. Alternatively, "alkylene," either alone or represented along with another radical, can be a (C_1)alkylene, a (C_2)alkylene or a (C_3)alkylene.

[0039] "Alkylidene" means a straight or branched, saturated or unsaturated, aliphatic radical connected to the parent molecule by a double bond. (C_X)alkylidene and (C_{X-Y})alkylidene are typically used where X and Y indicate the number of carbon atoms in the chain. For example, (C_{1-6})alkylidene includes methylene (=CH_2), ethylidene (=$CHCH_3$), isopropylidene (=$C(CH_3)_2$), propylidene (=$CHCH_2CH_3$), allylidene (=CH-CH=CH_2), and the like. In particular embodiments, "alkylidene," either alone or represented along with another radical, can be a (C_{1-20})alkylidene, a (C_{1-15})alkylidene, a (C_{1-10})alkylidene, a (C_{1-5})alkylidene or a (C_{1-3})alkylidene. Alternatively, "alkylidene," either alone or represented along with another radical, can be a (C_1)alkylidene, a (C_2)alkylidene or a (C_3)alkylidene.

[0040] "Alkynyl" means a straight or branched, carbon chain that contains at least one carbon-carbon triple bond (-C≡C- or –C≡CR, wherein R is hydrogen or a further substituent). Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like. In particular embodiments, "alkynyl," either alone or represented along with another radical, can be a (C_{2-20})alkynyl, a (C_{2-15})alkynyl, a (C_{2-10})alkynyl, a (C_{2-5})alkynyl or a (C_{2-3})alkynyl. Alternatively, "alkynyl," either alone or represented along with another radical, can be a (C_2)alkynyl, a (C_3)alkynyl or a (C_4)alkynyl.

[0041] "Alkynylene" means a straight or branched, divalent carbon chain having one or more carbon-carbon triple bonds (-CR≡CR'-, wherein R and R' are each independently hydrogen or further substituents). Examples of alkynylene include ethyne-1,2-diyl, propyne-1,3-diyl, and the like. In particular embodiments, "alkynylene," either alone or represented along with another radical, can be a (C_{2-20}) alkynylene, a (C_{2-15}) alkynylene, a (C_{2-10}) alkynylene, a (C_{2-5}) alkynylene or a (C_{2-3}) alkynylene. Alternatively, "alkenylene," either alone or represented along with another radical, can be a (C_2) alkynylene, a (C_3) alkynylene or a (C_4) alkynylene.

[0042] "Amido" means the radical –C(=O)-NR-, –C(=O)-NRR′, -NR-C(=O)- and/or -NR-C(=O)R′, wherein each R and R′ are independently hydrogen or a further substituent.

[0043] "Amino" means a nitrogen moiety having two further substituents where, for example, a hydrogen or carbon atom is attached to the nitrogen. For example, representative amino groups include $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH((C_{1-10})alkyl), -N((C_{1-10})alkyl)$_2$, -NH(aryl), -NH(heteroaryl), -N(aryl)$_2$, -N(heteroaryl)$_2$, and the like. Optionally, the two substituents together with the nitrogen may also form a ring. Unless indicated otherwise, the compounds of the invention containing amino moieties may include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

[0044] "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).

[0045] "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").

[0046] "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 carbon atoms in the ring. In particular embodiments, "aryl," either alone or represented along with another radical, can be a (C_{3-14})aryl, a (C_{3-10})aryl, a (C_{3-7})aryl, a (C_{8-10})aryl or a (C_{5-7})aryl. Alternatively, "aryl," either alone or represented along with another radical, can be a (C_5)aryl, a (C_6)aryl, a (C_7)aryl, a (C_8)aryl., a (C_9)aryl or a (C_{10})aryl.

[0047] "Azaalkyl" means an alkyl, as defined above, except where one or more of the carbon atoms forming the alkyl chain are replaced with substituted or unsubstituted nitrogen atoms (-NR- or -NRR', wherein R and R' are each independently hydrogen or further substituents). For example, a (C_{1-10})azaalkyl refers to a chain comprising between 1 and 10 carbons and one or more nitrogen atoms.

[0048] "Bicycloalkyl" means a saturated or partially unsaturated fused, spiro or bridged bicyclic ring assembly. In particular embodiments, "bicycloalkyl," either alone or represented along with another radical, can be a (C_{4-15})bicycloalkyl, a (C_{4-10})bicycloalkyl,

a (C_{6-10})bicycloalkyl or a (C_{8-10})bicycloalkyl. Alternatively, "bicycloalkyl," either alone or represented along with another radical, can be a (C_8)bicycloalkyl, a (C_9)bicycloalkyl or a (C_{10})bicycloalkyl.

[0049] "Bicycloaryl" means a fused, spiro or bridged bicyclic ring assembly wherein 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. In particular embodiments, "bicycloaryl," either alone or represented along with another radical, can be a (a (C_{4-15})bicycloaryl, a (C_{4-10})bicycloaryl, a (C_{6-10})bicycloaryl or a (C_{8-10})bicycloaryl. Alternatively, "bicycloalkyl," either alone or represented along with another radical, can be a (C_8)bicycloaryl, a (C_9)bicycloaryl or a (C_{10})bicycloaryl.

[0050] "Bridging ring" and "bridged ring" as used herein refer to a ring that is bonded to another ring to form a compound having a bicyclic or polycyclic 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.

[0051] "Carbamoyl" means the radical -OC(O)NRR', wherein R and R' are each independently hydrogen or further substituents.

[0052] "Carbocycle" means a ring consisting of carbon atoms.

[0053] "Carbonyl" means the radical –C(=O)- and/or –C(=O)R, wherein R is hydrogen or a further substituent. 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.

[0054] "Carboxy" means the radical –C(=O)-O- and/or –C(=O)-OR, wherein R is hydrogen or a further substituent. 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.

[0055] "Cyano" means the radical -CN.

[0056] "Cycloalkyl" means a non-aromatic, saturated or partially unsaturated, monocyclic, bicyclic or 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. In particular embodiments, "cycloalkyl," either alone or represented along with another radical, can be a (C_{3-14})cycloalkyl, a (C_{3-10})cycloalkyl, a (C_{3-7})cycloalkyl, a (C_{8-10})cycloalkyl or a (C_{5-7})cycloalkyl. Alternatively, "cycloalkyl," either alone or represented along with another radical, can be a (C_5)cycloalkyl, a (C_6)cycloalkyl, a (C_7)cycloalkyl, a (C_8)cycloalkyl., a (C_9)cycloalkyl or a (C_{10})cycloalkyl.

[0057] "Cycloalkylene" means a divalent, saturated or partially unsaturated, monocyclic, bicyclic 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. In particular embodiments, "cycloalkylene," either alone or represented along with another radical, can be a (C_{3-14})cycloalkylene, a (C_{3-10})cycloalkylene, a (C_{3-7})cycloalkylene, a (C_{8-10})cycloalkylene or a (C_{5-7})cycloalkylene. Alternatively, "cycloalkylene," either alone or represented along with another radical, can be a (C_5)cycloalkylene, a (C_6)cycloalkylene, a (C_7)cycloalkylene, a (C_8)cycloalkylene., a (C_9)cycloalkylene or a (C_{10})cycloalkylene.

[0058] "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.

[0059] "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.

[0060] "Halo" means fluoro, chloro, bromo or iodo.

[0061] "Heteroalkyl" means alkyl, as defined in this Application, provided that one or more of the atoms within the alkyl chain is a heteroatom. In particular embodiments, "heteroalkyl," either alone or represented along with another radical, can be a hetero(C_{1-20})alkyl, a hetero(C_{1-15})alkyl, a hetero(C_{1-10})alkyl, a hetero(C_{1-5})alkyl, a hetero(C_{1-3})alkyl or a hetero(C_{1-2})alkyl. Alternatively, "heteroalkyl," either alone or

represented along with another radical, can be a hetero(C_1)alkyl, a hetero(C_2)alkyl or a hetero(C_3)alkyl.

[0062] "Heteroaryl" means a monocyclic, bicyclic or polycyclic aromatic group wherein at least one ring atom is a heteroatom and the remaining ring atoms are carbon. Monocyclic heteroaryl groups include, but are not limited to, cyclic aromatic groups 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. In particular embodiments, "heteroaryl," either alone or represented along with another radical, can be a hetero(C_{1-13})aryl, a hetero(C_{2-13})aryl, a hetero(C_{2-6})aryl, a hetero(C_{3-9})aryl or a hetero(C_{5-9})aryl. Alternatively, "heteroaryl," either alone or

represented along with another radical, can be a hetero(C_3)aryl, a hetero(C_4)aryl, a hetero(C_5)aryl, a hetero(C_6)aryl., a hetero(C_7)aryl, a hetero(C_8)aryl or a hetero(C_9)aryl.

[0063] "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.

[0064] "Heteroatom moiety" includes a moiety where the atom by which the moiety is attached is not a carbon. Examples of heteroatom moieties include -NR-, -$N^+(O^-)$=, -O-, -S- or -$S(O)_2$-, wherein R is hydrogen or a further substituent.

[0065] "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. In particular embodiments, "heterobicycloalkyl," either alone or represented along with another radical, can be a hetero(C_{1-14})bicycloalkyl, a hetero(C_{4-14})bicycloalkyl, a hetero(C_{4-9})bicycloalkyl or a hetero(C_{5-9})bicycloalkyl. Alternatively, "heterobicycloalkyl," either alone or represented along with another radical, can be a hetero(C_5)bicycloalkyl, hetero(C_6)bicycloalkyl, hetero(C_7)bicycloalkyl, hetero(C_8)bicycloalkyl or a hetero(C_9)bicycloalkyl.

[0066] "Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the atoms within the ring is a heteroatom. For example, hetero(C_{4-12})bicycloaryl as used in this Application includes, but is not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, tetrahydroisoquinolinyl, and the like. In particular embodiments, "heterobicycloaryl," either alone or represented along with another radical, can be a hetero(C_{1-14})bicycloaryl, a hetero(C_{4-14})bicycloaryl, a hetero(C_{4-9})bicycloarylor a hetero(C_{5-9})bicycloaryl. Alternatively, "heterobicycloaryl," either alone or represented along with another radical, can be a hetero(C_5)bicycloaryl, hetero(C_6)bicycloaryl, hetero(C_7)bicycloaryl, hetero(C_8)bicycloaryl or a hetero(C_9)bicycloaryl.

[0067] "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. In particular embodiments, "heterocycloalkyl," either alone or represented along with another radical, can be a hetero(C_{1-13})cycloalkyl, a

hetero(C_{1-9})cycloalkyl, a hetero(C_{1-6})cycloalkyl, a hetero(C_{5-9})cycloalkyl or a hetero(C_{2-6})cycloalkyl. Alternatively, "heterocycloalkyl," either alone or represented along with another radical, can be a hetero(C_2)cycloalkyl, a hetero(C_3)cycloalkyl, a hetero(C_4)cycloalkyl, a hetero(C_5)cycloalkyl, a hetero(C_6)cycloalkyl, hetero(C_7)cycloalkyl, hetero(C_8)cycloalkyl or a hetero(C_9)cycloalkyl.

[0068] "Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms is replaced by a heteroatom. In particular embodiments, "heterocycloalkylene," either alone or represented along with another radical, can be a hetero(C_{1-13})cycloalkylene, a hetero(C_{1-9})cycloalkylene, a hetero(C_{1-6})cycloalkylene, a hetero(C_{5-9})cycloalkylene or a hetero(C_{2-6})cycloalkylene. Alternatively, "heterocycloalkylene," either alone or represented along with another radical, can be a hetero(C_2)cycloalkylene, a hetero(C_3)cycloalkylene, a hetero(C_4)cycloalkylene, a hetero(C_5)cycloalkylene, a hetero(C_6)cycloalkylene, hetero(C_7)cycloalkylene, hetero(C_8)cycloalkylene or a hetero(C_9)cycloalkylene.

[0069] "Hydroxy" means the radical -OH.

[0070] "IC_{50}" means the molar concentration of an inhibitor that produces 50% inhibition of the target enzyme.

[0071] "Imino" means the radical –CR(=NR') and/or –C(=NR')-, wherein R and R' are each independently hydrogen or a further substituent.

[0072] "Isomers" means compounds having 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).

[0073] "Leaving group" means the group with the meaning conventionally associated with it in synthetic organic chemistry, *i.e.*, an atom or group displaceable under reaction (*e.g.*, alkylating) conditions. Examples of leaving groups include, but are not limited to, halo (*e.g.*, F, Cl, Br and I), alkyl (*e.g.*, methyl and ethyl) and sulfonyloxy (*e.g.*, mesyloxy, ethanesulfonyloxy, benzenesulfonyloxy and tosyloxy), thiomethyl, thienyloxy, dihalophosphinoyloxy, tetrahalophosphoxy, benzyloxy, isopropyloxy, acyloxy, and the like.

[0074] "Moiety providing X atom separation" and "linker providing X atom separation" between two other moieties mean that the chain of atoms directly linking the two other moieties is X atoms in length. When X is given as a range (*e.g.*, X_1-X_2), then the chain of atoms is at least X_1 and not more than X_2 atoms in length. It is understood that the chain of atoms can be formed from a combination of atoms including, for example, carbon, nitrogen, sulfur and oxygen atoms. Further, each atom can optionally be bound to one or more substituents, as valencies allow. In addition, the chain of atoms can form part of a ring. Accordingly, in one embodiment, a moiety providing X atom separation between two other moieties (R and R') can be represented by R-$(L)_X$-R' where each L is independently selected from the group consisting of CR"R'", NR"", O, S, CO, CS, C=NR"", SO, SO_2, and the like, where any two or more of R", R'", R"" and R"" can be taken together to form a substituted or unsubstituted ring.

[0075] "Nitro" means the radical -NO_2.

[0076] "Oxaalkyl" means an alkyl, as defined above, except where one or more of the carbon atoms forming the alkyl chain are replaced with oxygen atoms (-O- or –OR, wherein R is hydrogen or a further substituent). For example, an oxa(C_{1-10})alkyl refers to a chain comprising between 1 and 10 carbons and one or more oxygen atoms.

[0077] "Oxoalkyl" means an alkyl, as defined above, except where one or more of the carbon atoms forming the alkyl chain are replaced with carbonyl groups (-C(=O)- or –C(=O)-R, wherein R is hydrogen or a further substituent). The carbonyl group may be an

aldehyde, ketone, ester, amide, acid or acid halide. For example, an oxo(C_{1-10})alkyl refers to a chain comprising between 1 and 10 carbon atoms and one or more carbonyl groups.

[0078] "Oxy" means the radical -O- or –OR, wherein R is hydrogen or a further substituent. Accordingly, it is noted that the oxy radical may be further substituted with a variety of substituents to form different oxy groups including hydroxy, alkoxy, aryloxy, heteroaryloxy or carbonyloxy.

[0079] "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.

[0080] "Pharmaceutically acceptable salts" means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

[0081] 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.

[0082] "Polycyclic ring" includes bicyclic and multi-cyclic rings. The individual rings comprising the polycyclic ring can be fused, spiro or bridging rings.

[0083] "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 activity with respect to a given target protein. For example, a compound 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, phosphates, 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, a compound comprising an amine group may be administered as an amide that is converted by hydrolysis *in vivo* to the amine compound.

[0084] "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.

[0085] "Ring" and "ring assembly" means a carbocyclic or a heterocyclic system and includes aromatic and non-aromatic systems. The system can be monocyclic, bicyclic or polycyclic. In addition, for bicyclic and polycyclic systems, the individual rings comprising the polycyclic ring can be fused, spiro or bridging rings.

[0086] "Subject" and "patient" include 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).

[0087] "Substituent convertible to hydrogen *in vivo*" means any group that is convertible to a hydrogen atom by enzymological or chemical means including, but not limited to, hydrolysis and hydrogenolysis. Examples include hydrolyzable groups, such as acyl groups, groups having an oxycarbonyl group, amino acid residues, peptide residues, o-nitrophenylsulfenyl, trimethylsilyl, tetrahydro-pyranyl, diphenylphosphinyl, and the like. Examples of acyl groups include formyl, acetyl, trifluoroacetyl, and the like. Examples of groups having an oxycarbonyl group include ethoxycarbonyl, t-butoxycarbonyl [$(CH_3)_3C$-OCO-], benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, vinyloxycarbonyl, β-(p-toluenesulfonyl)ethoxycarbonyl, and the like. Examples of suitable amino acid residues

include amino acid residues *per se* and amino acid residues that are protected with a protecting group. Suitable amino acid residues include, but are not limited to, residues of Gly (glycine), Ala (alanine; $CH_3CH(NH_2)CO$-), Arg (arginine), Asn (asparagine), Asp (aspartic acid), Cys (cysteine), Glu (glutamic acid), His (histidine), Ile (isoleucine), Leu (leucine; $(CH_3)_2CHCH_2CH(NH_2)CO$-), Lys (lysine), Met (methionine), Phe (phenylalanine), Pro (proline), Ser (serine), Thr (threonine), Trp (tryptophan), Tyr (tyrosine), Val (valine), Nva (norvaline), Hse (homoserine), 4-Hyp (4-hydroxyproline), 5-Hyl (5-hydroxylysine), Orn (ornithine) and β-Ala. Examples of suitable protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethyloxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), t-butoxycarbonyl groups [$(CH_3)_3C$-OCO-], and the like. Suitable peptide residues include peptide residues comprising two to five, and optionally two to three, of the aforesaid amino acid residues. Examples of such peptide residues include, but are not limited to, residues of such peptides as Ala-Ala [$CH_3CH(NH_2)CO$-$NHCH(CH_3)CO$-], Gly-Phe, Nva-Nva, Ala-Phe, Gly-Gly, Gly-Gly-Gly, Ala-Met, Met-Met, Leu-Met and Ala-Leu. The residues of these amino acids or peptides can be present in stereochemical configurations of the D-form, the L-form or mixtures thereof. In addition, the amino acid or peptide residue may have an asymmetric carbon atom. Examples of suitable amino acid residues having an asymmetric carbon atom include residues of Ala, Leu, Phe, Trp, Nva, Val, Met, Ser, Lys, Thr and Tyr. Peptide residues having an asymmetric carbon atom include peptide residues having one or more constituent amino acid residues having an asymmetric carbon atom. Examples of suitable amino acid protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethyloxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), t-butoxycarbonyl groups [$(CH_3)_3C$-OCO-], and the like. Other examples of substituents "convertible to hydrogen *in vivo*" include reductively eliminable hydrogenolyzable groups. Examples of suitable reductively eliminable hydrogenolyzable groups include, but are not limited to, arylsulfonyl groups (such as o-toluenesulfonyl); methyl groups substituted with phenyl or benzyloxy (such as benzyl, trityl and benzyloxymethyl); arylmethoxycarbonyl groups (such as benzyloxycarbonyl and o-methoxy-benzyloxycarbonyl); and halogenoethoxycarbonyl groups (such as β,β,β-trichloroethoxycarbonyl and β-iodoethoxycarbonyl).

[0088] "Substituted or unsubstituted" means that a given moiety may consist of only hydrogen substituents through available valencies (unsubstituted) or may further comprise one or more non-hydrogen substituents through available valencies (substituted) that are not otherwise specified by the name of the given moiety. For example, isopropyl is an example of an ethylene moiety that is substituted by $-CH_3$. In general, a non-hydrogen substituent may be any substituent that may be bound to an atom of the given moiety that is specified to be substituted. Examples of substituents include, but are not limited to, aldehyde, alicyclic, aliphatic, (C_{1-10})alkyl, alkylene, alkylidene, amide, amino, aminoalkyl, aromatic, aryl, bicycloalkyl, bicycloaryl, carbamoyl, carbocyclyl, carboxyl, carbonyl group, cycloalkyl, cycloalkylene, ester, halo, heterobicycloalkyl, heterocycloalkylene, heteroaryl, heterobicycloaryl, heterocycloalkyl, oxo, hydroxy, iminoketone, ketone, nitro, oxaalkyl, and oxoalkyl moieties, each of which may optionally also be substituted or unsubstituted. In one particular embodiment, examples of substituents include, but are not limited to, hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, (C_{1-10})azaalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl. In addition, the substituent is itself optionally substituted by a further substituent. In one particular embodiment, examples of the further substituent include, but are not limited to, hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, (C_{1-10})azaalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl.

[0089] "Sulfinyl" means the radical –SO- and/or –SO-R, wherein R is hydrogen or a further substituent. 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.

[0090] "Sulfonyl" means the radical -SO_2- and/or –SO_2-R, wherein R is hydrogen or a further substituent. 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.

[0091] "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.

[0092] "Thio" denotes replacement of an oxygen by a sulfur and includes, but is not limited to, -SR, -S- and =S containing groups.

[0093] "Thioalkyl" means an alkyl, as defined above, except where one or more of the carbon atoms forming the alkyl chain are replaced with sulfur atoms (-S- or –S-R, wherein R is hydrogen or a further substituent). For example, a thio(C_{1-10})alkyl refers to a chain comprising between 1 and 10 carbons and one or more sulfur atoms.

[0094] "Thiocarbonyl" means the radical –C(=S)- and/or –C(=S)-R, wherein R is hydrogen or a further substituent. 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.

[0095] "Treatment" or "treating" means any administration of a compound of the present invention and includes:

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

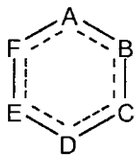
(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (*i.e.*, arresting further development of the pathology and/or symptomatology), or

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

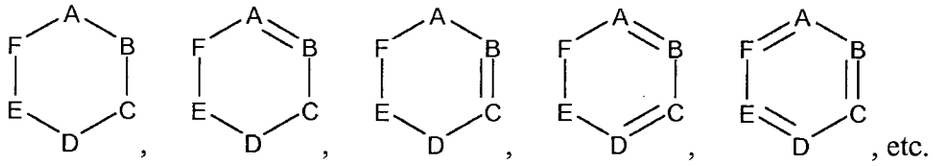
[0096] It is noted in regard to all of the definitions provided herein that the definitions should be interpreted as being open ended in the sense that further substituents beyond

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 -CRR'R" where R, R', and R" may each independently be hydrogen or a further 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. Similarly, terms such as alkylamino and the like comprise dialkylamino and the like.

[0097] A compound having a formula that is represented with a dashed bond is intended to include the formulae optionally having zero, one or more double bonds, as exemplified and shown below:



represents



, etc.

[0098] In addition, atoms making up the compounds of the present invention are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C.

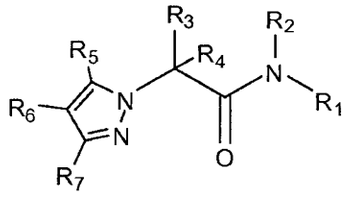
DETAILED DESCRIPTION OF THE INVENTION

[0099] The present invention relates to compounds that may be used to modulate a hexokinase and, in particular, compounds that activate glucokinase (referred to herein as "GK"). The present invention also relates to pharmaceutical compositions, kits and articles of manufacture comprising such compounds. In addition, the present invention relates to methods and intermediates useful for making the compounds. Further, the present invention relates to methods of using said compounds. It is noted that the compounds of the present invention may also possess activity for other hexokinase family

members and thus may be used to address disease states associated with these other family members.

Glucokinase Activators

[0100] In one embodiment, glucokinase activators of the present invention have the formula:



or a polymorph, solvate, ester, tautomer, enantiomer, pharmaceutically acceptable salt or prodrug thereof, wherein

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1-R_{22}$;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1$-R_{22};

or any two R_5, R_6 and R_7 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

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

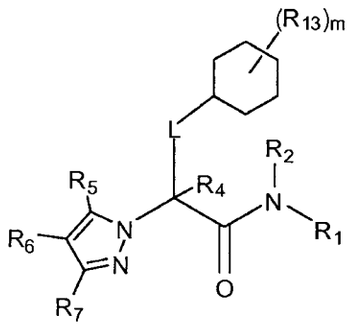
R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0101] In one variation of the above embodiment, R_1 is not 5-(3-acetamidocyclobutyl)-1H-pyrazol-3-yl when R_5 and R_6, together with the ring to which they are attached, form

an unsubstituted indazol-1-yl. In another variation of the above embodiment, R_1 is not 5-(2-chlorobenzyl)thiazol-2-yl when R_3 is phenyl and R_2, R_4, R_5, R_6 and R_7 are all hydrogen.

[0102] In another embodiment, glucokinase activators of the present invention have the formula:



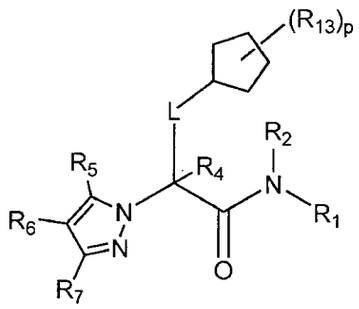
wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0103] In still another embodiment, glucokinase activators of the present invention have the formula:



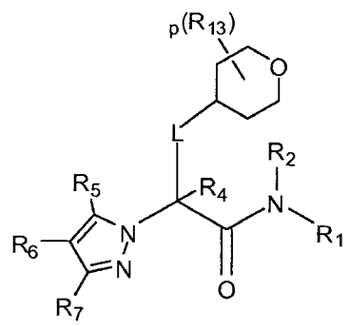
wherein

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0104] In yet another embodiment, glucokinase activators of the present invention have the formula:



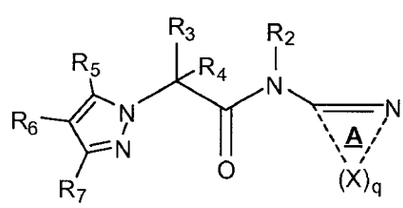
wherein

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0105] In a further embodiment, glucokinase activators of the present invention have the formula:



,

wherein

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

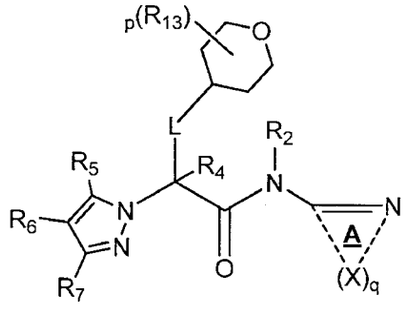
R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring, and

the remaining variables are as described above.

[0106] In one variation of the above embodiment, ring A is not 5-(3-acetamidocyclobutyl)-1H-pyrazol-3-yl when R_5 and R_6, together with the ring to which they are attached, form an unsubstituted indazol-1-yl. In another variation of the above embodiment, ring A is not 5-(2-chlorobenzyl)thiazol-2-yl when R_3 is phenyl and R_2, R_4, R_5, R_6 and R_7 are all hydrogen.

[0107] In another embodiment, glucokinase activators of the present invention have the formula:



wherein

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted

or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22};

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

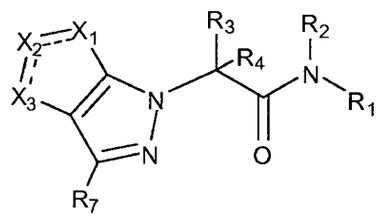
R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl,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

(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring, and

the remaining variables are as described above.

[0108] In another embodiment, glucokinase activators of the present invention have the formula:



wherein

X_1, X_2 and X_3 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_9 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,

(C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

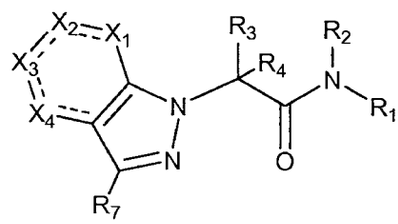
R_{11} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl,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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl,

thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring.

[0109] In a further embodiment, glucokinase activators of the present invention have the formula:



wherein

X_1, X_2, X_3 and X_4 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_9 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl,

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

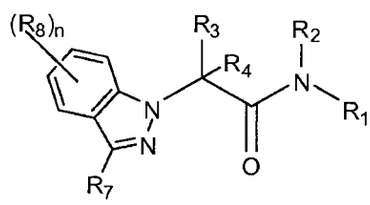
R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl,

(C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0110] In still a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

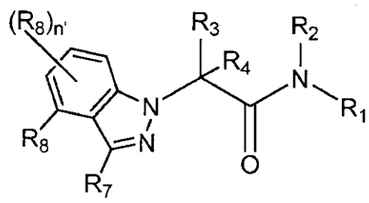
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl,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

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0111] In one variation of the above embodiment, R_1 is not 5-(3-acetamidocyclobutyl)-1H-pyrazol-3-yl when R_7 and each R_8 are all hydrogen.

[0112] In yet a further embodiment, glucokinase activators of the present invention have the formula:



wherein

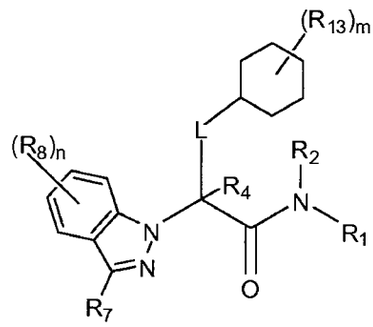
n′ is selected from the group consisting of 0, 1, 2 and 3;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0113] In one variation of the above embodiment, R_1 is not 5-(3-acetamidocyclobutyl)-1H-pyrazol-3-yl when R_7 and each R_8 are all hydrogen.

[0114] In still another embodiment, glucokinase activators of the present invention have the formula:



wherein

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

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11;

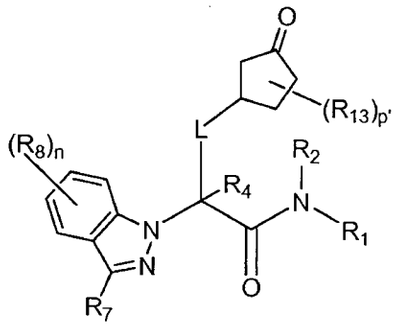
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0115] In yet another embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p′ is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6 and 7;

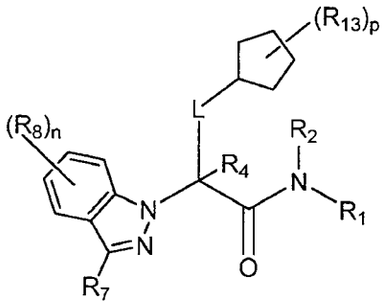
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$,

or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0116] In a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

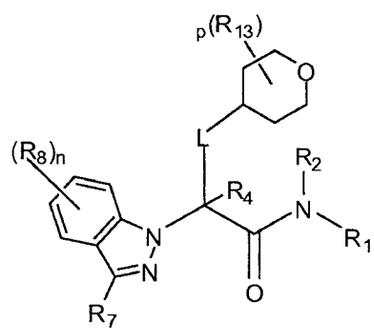
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl,

thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0117] In still a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

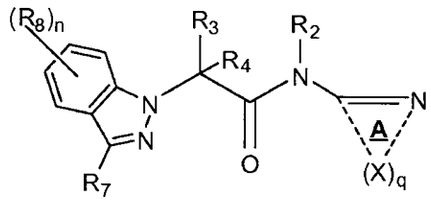
p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0118] In yet a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

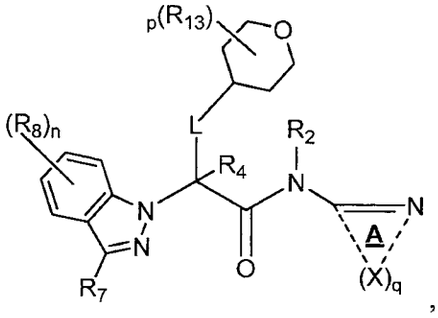
R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0119] In one variation of the above embodiment, ring A is not 5-(3-acetamidocyclobutyl)-1H-pyrazol-3-yl when R_7 and each R_8 are all hydrogen.

[0120] In yet a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22};

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

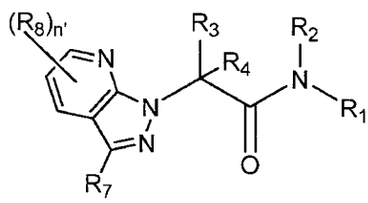
hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0121] In another embodiment, glucokinase activators of the present invention have the formula:



wherein

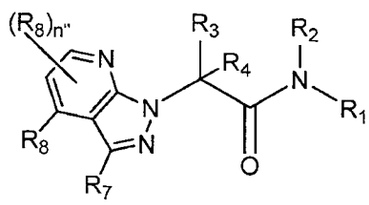
n′ is selected from the group consisting of 0, 1, 2 and 3;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl,

sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0122] In still another embodiment, glucokinase activators of the present invention have the formula:



wherein

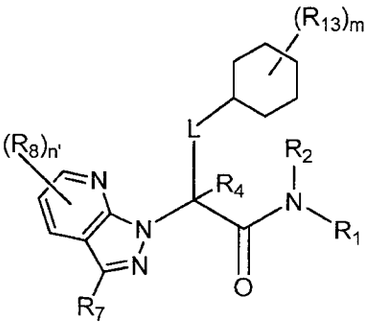
n'' is selected from the group consisting of 0, 1 and 2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$,

or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0123] In still another embodiment, glucokinase activators of the present invention have the formula:



wherein

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

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11;

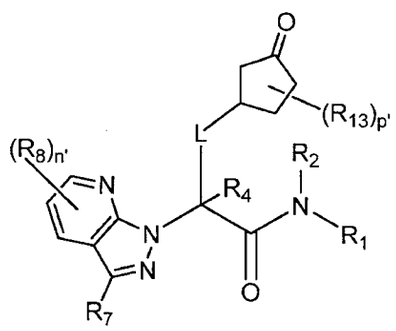
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl,

halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0124] In yet another embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p' is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6 and 7;

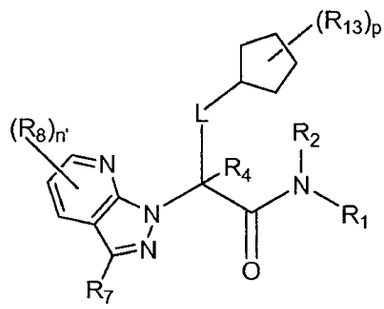
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl,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

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0125] In a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

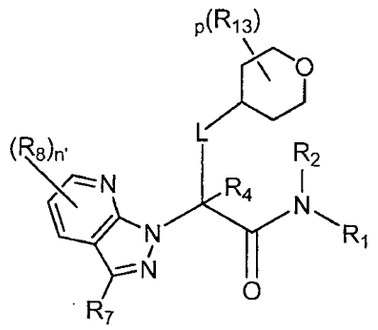
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0126] In still a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

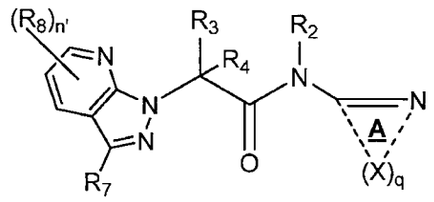
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0127] In yet a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22};

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

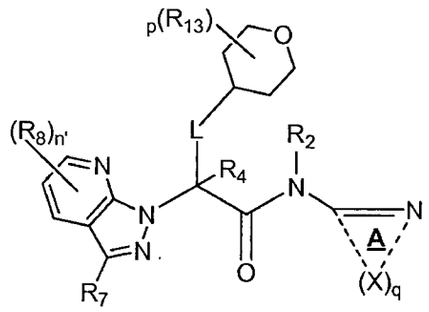
R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0128] In yet a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

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

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

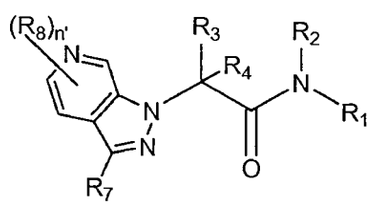
oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0129] In yet another embodiment, glucokinase activators of the present invention have the formula:



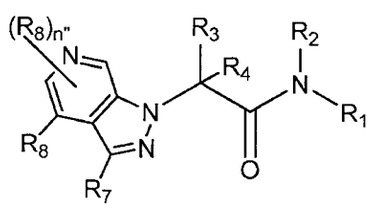
wherein

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

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0130] In a further embodiment, glucokinase activators of the present invention have the formula:



wherein

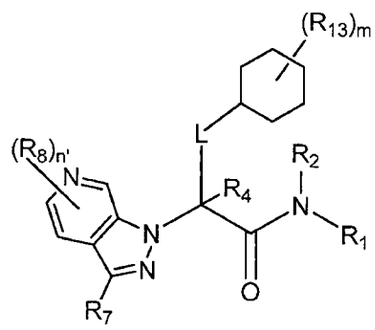
n'' is selected from the group consisting of 0, 1 and 2;

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

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0131] In still another embodiment, glucokinase activators of the present invention have the formula:



wherein

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

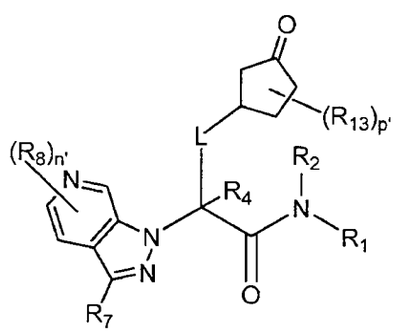
m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0132] In yet another embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p' is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6 and 7;

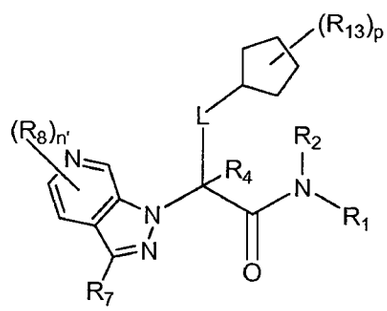
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0133] In a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

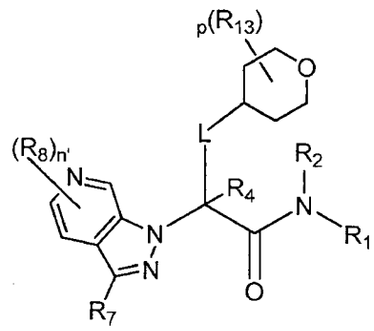
p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0134] In still a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

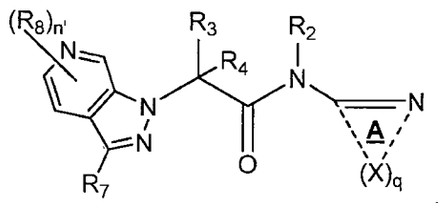
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0135] In yet a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22};

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

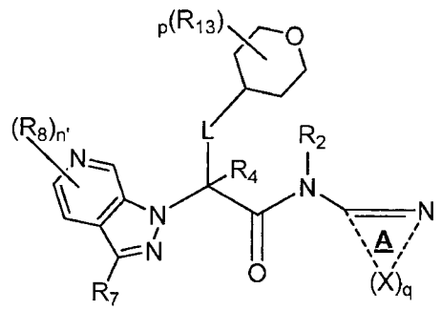
R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0136] In yet a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

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

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

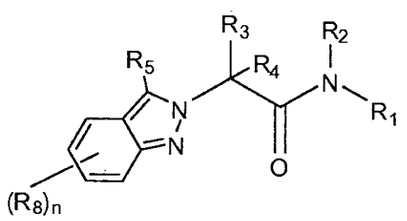
oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0137] In another embodiment, glucokinase activators of the present invention have the formula:



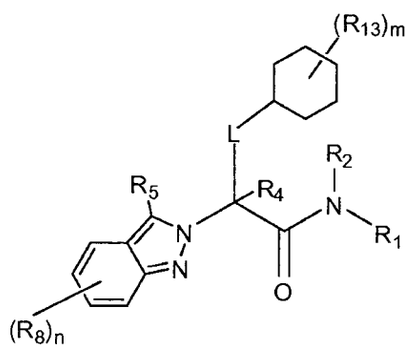
wherein

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

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_5 or two R_8 are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0138] In yet another embodiment, glucokinase activators of the present invention have the formula:



wherein

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

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11;

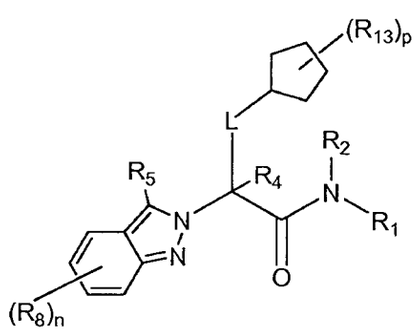
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl,

thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_5 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0139] In a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

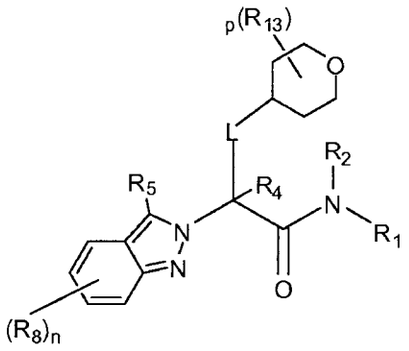
p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_5 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0140] In still a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

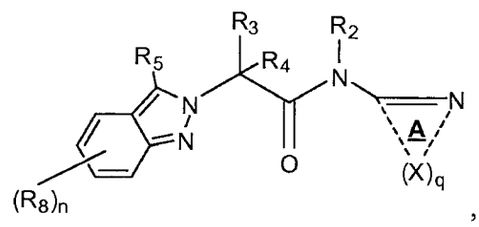
R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_5 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0141] In yet a further embodiment, glucokinase activators of the present invention have the formula:



,

wherein

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

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_5 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22};

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

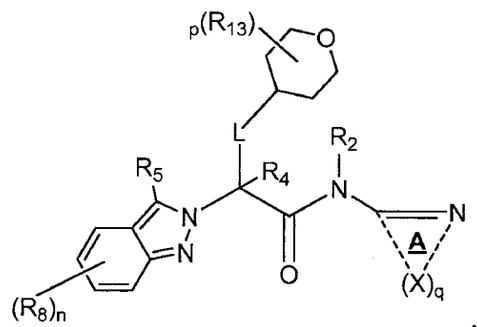
R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0142] In yet a further embodiment, glucokinase activators of the present invention have the formula:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

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

(C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_5 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl,

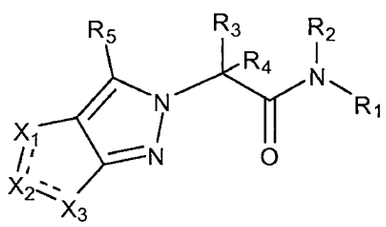
sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring; and

the remaining variables are as described above.

[0143] In still another embodiment, glucokinase activators of the present invention have the formula:



wherein

X_1, X_2 and X_3 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

R_{11} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, oxycarbonyl, amino,

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

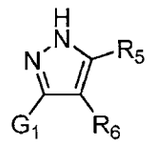
R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_5, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring; and

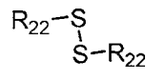
the remaining variables are as described above.

[0144] In another of its aspects, the present invention relates to methods of making compounds that are useful as glucokinase activators. In one embodiment, the methods comprise the steps of:

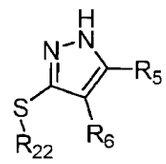
reacting a compound having the formula



with a compound having the formula

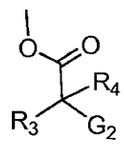


to form a first reaction product having the formula

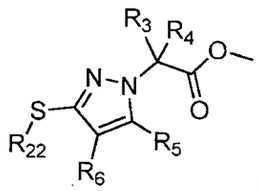


;

reacting the first reaction product with a compound having the formula

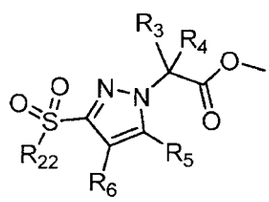


to form a second reaction product having the formula



;

treating the second reaction product to form a third reaction product having the formula

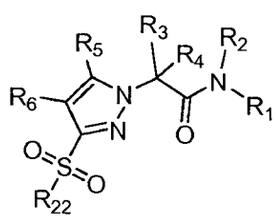


; and

reacting the third reaction product with a compound having the formula

NHR_1R_2

to form a fourth reaction product having the formula



,

wherein

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl,

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

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1$-R_{22};

or R_5 and R_6 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy,

carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is – $NR_{27}R_{28}$;

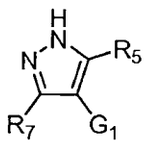
R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring; and

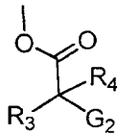
G_1 and G_2 are each independently a leaving group.

[0145] In another embodiment, the methods comprise the steps of:

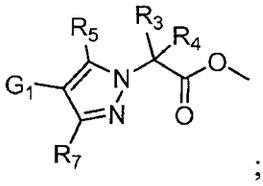
reacting a compound having the formula



with a compound having the formula



to form a first reaction product having the formula

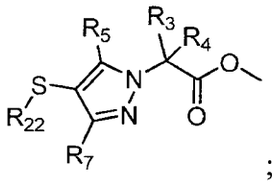


;

reacting the first reaction product with a compound having the formula

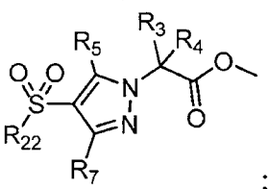
SHR_{22}

to form a second reaction product having the formula



;

treating the second reaction product to form a third reaction product having the formula

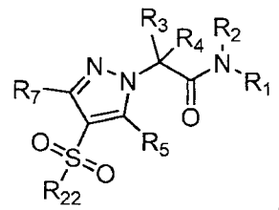


; and

reacting the third reaction product with a compound having the formula

NHR_1R_2

to form a fourth reaction product having the formula



,

wherein

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1$-R_{22};

or R_5 and R_7 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$;

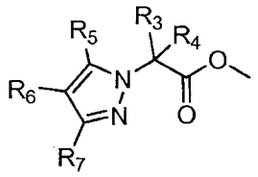
R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring; and

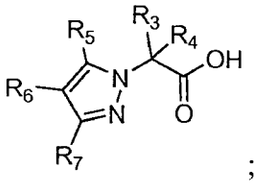
G_1 and G_2 are each independently a leaving group.

[0146] In still another embodiment, the methods comprise the steps of:

treating a compound having the formula

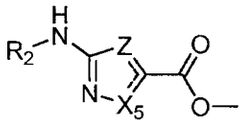


to form a first reaction product having the formula

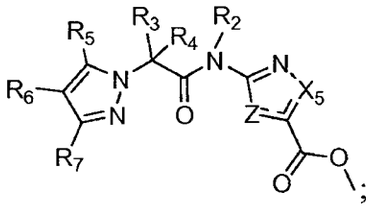


;

reacting the first reaction product with a compound having the formula

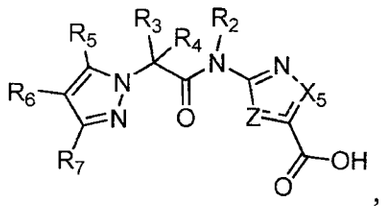


to form a second reaction product having the formula



; and

treating the second reaction product to form a third reaction product having the formula



wherein

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl,

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

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1-R_{22}$;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,

(C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1-R_{22}$;

or any two R_5, R_6 and R_7 are taken together to form a substituted or unsubstituted ring;

X_5 is selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and

hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond;

Z is selected from the group consisting of $CR_{14}R_{15}$, NR_{16}, O and S;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso

that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

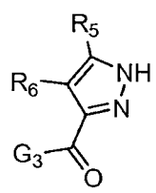
R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0147] In yet another embodiment, the methods comprise the steps of:

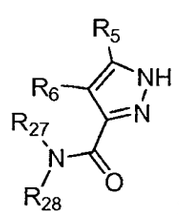
reacting a compound having the formula



with a compound having the formula

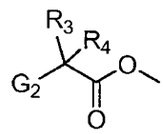
$NHR_{27}R_{28}$

to form a first reaction product having the formula

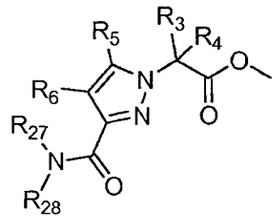


;

reacting the first reaction product with a compound having the formula

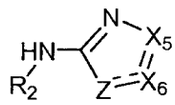


to form a second reaction product having the formula

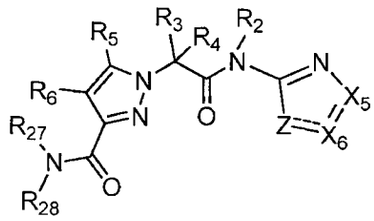


; and

reacting the second reaction product with a compound having the formula



to form a third reaction product having the formula



wherein

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is $-L-R_{18}$;

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1-R_{22}$;

or R_5 and R_6 are taken together to form a substituted or unsubstituted ring;

X_5 and X_6 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,

(C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond;

Z is selected from the group consisting of $CR_{14}R_{15}$, NR_{16}, O and S;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl,

(C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl,

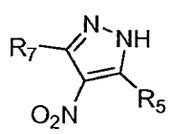
carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$;

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring; and

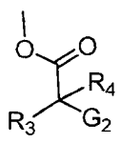
G_2 and G_3 are each independently a leaving group.

[0148] In a further embodiment, the methods comprise the steps of:

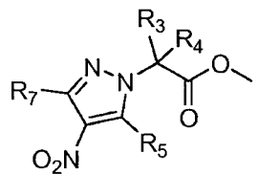
reacting a compound having the formula



with a compound having the formula

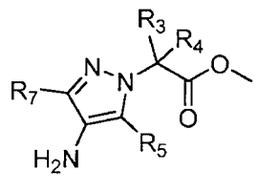


to form a first reaction product having the formula



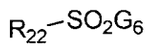
;

treating the first reaction product to form a second reaction product having the formula

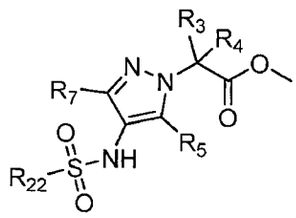


;

reacting the second reaction product with a compound having the formula

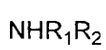


to form a third reaction product having the formula

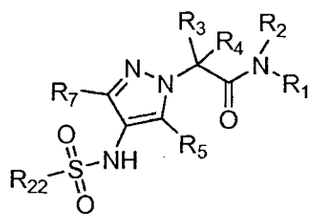


; and

reacting the third reaction product with a compound having the formula



to form a fourth reaction product having the formula



,

wherein

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1$-R_{22};

or R_5 and R_7 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl,

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

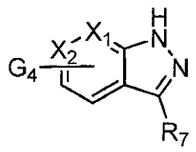
R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$;

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring; and

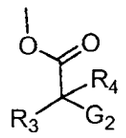
G_2 and G_6 are each independently a leaving group.

[0149] In still a further embodiment, the methods comprise the steps of:

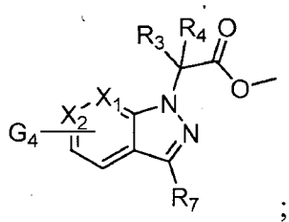
reacting a compound having the formula



with a compound having the formula

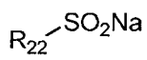


to form a first reaction product having the formula

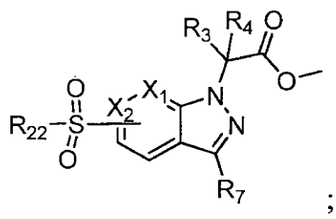


;

reacting the first reaction product with a compound having the formula

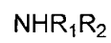


to form a second reaction product having the formula

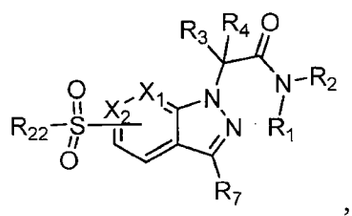


; and

reacting the second reaction product with a compound having the formula



to form a third reaction product having the formula



,

wherein

X_1 and X_2 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1-R_{22}$;

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

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

are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and

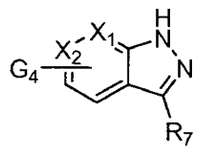
hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$;

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring; and

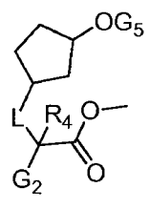
G_2 and G_4 are each independently a leaving group.

[0150] In yet a further embodiment, the methods comprise the steps of:

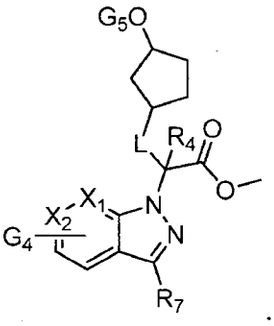
reacting a compound having the formula



with a compound having the formula

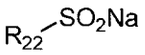


to form a first reaction product having the formula

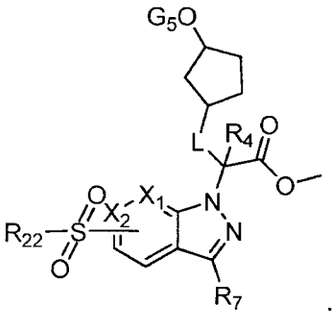


;

reacting the first reaction product with a compound having the formula

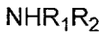


to form a second reaction product having the formula

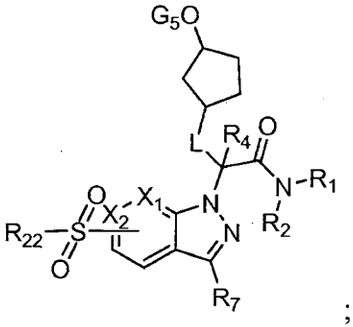


;

reacting the second reaction product with a compound having the formula

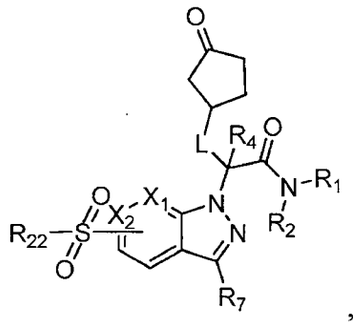


to form a third reaction product having the formula



; and

treating the third reaction product to form a fourth reaction product having the formula



wherein

X_1 and X_2 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

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

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl,

hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1-R_{22}$;

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

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

are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$;

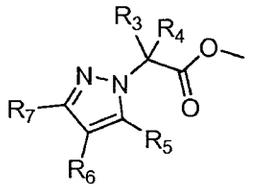
R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring;

G_2 and G_4 are each independently a leaving group; and

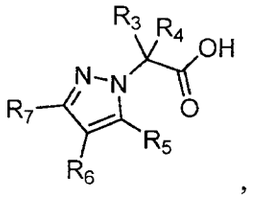
G_5 is a protecting group.

[0151] In another embodiment, the methods comprise the step of:

treating a first reaction product having the formula



under conditions sufficient to form a second reaction product having the formula



,

wherein

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is $-L-R_{18}$;

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted

or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1$-R_{22};

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl,

carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1$-R_{22};

or any two R_5, R_6 and R_7 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

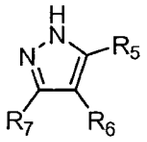
R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

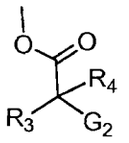
R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0152] In one variation of the above embodiment, the methods further comprise the step of:

reacting a compound having the formula



with a compound having the formula



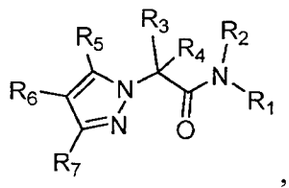
to form the first reaction, wherein G_2 is a leaving group.

[0153] In another variation of the above embodiment and variation, the methods further comprise the step of:

reacting the second reaction product with a compound having the formula

$$NHR_1R_2$$

to form a third reaction product having the formula



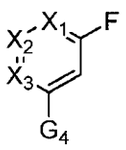
wherein

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

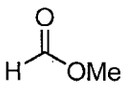
R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*.

[0154] In still another embodiment, the methods comprise the steps of:

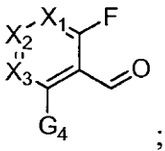
reacting a compound having the formula



with a compound having the formula

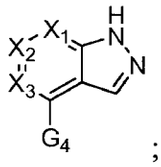


to form a first reaction product having the formula



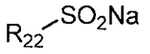
;

treating the first reaction product under conditions sufficient to form a second reaction product having the formula

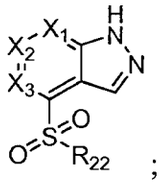


;

reacting the second reaction product with a compound having the formula

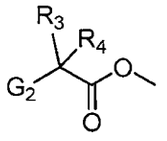


to form a third reaction product having the formula

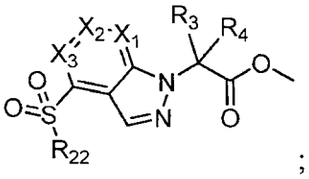


;

reacting the third reaction product with a compound having the formula



to form a fourth reaction product having the formula

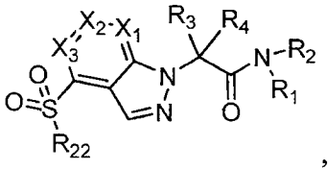


; and

reacting the fourth reaction product with a compound having the formula

NHR_1R_2

to form a fifth reaction product having the formula



,

wherein

X_1, X_2 and X_3 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is $-L-R_{18}$;

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_9 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl,

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

R_{11} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,

(C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

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

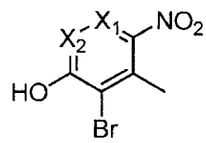
R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$;

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring; and

G_2 and G_4 are each independently a leaving group.

[0155] In yet another embodiment, the methods comprise the steps of:

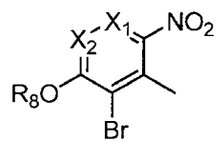
reacting a compound having the formula



with a compound having the formula

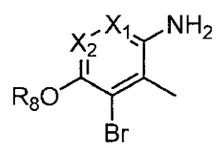


to form a first reaction product having the formula



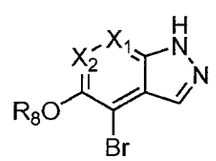
;

treating the first reaction product under conditions sufficient to form a second reaction product having the formula



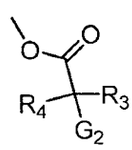
;

treating the second reaction product under conditions sufficient to form a third reaction product having the formula

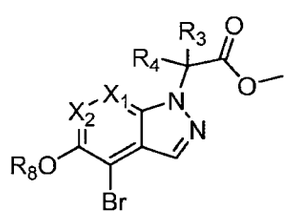


;

reacting the third reaction product with a compound having the formula

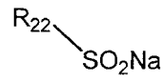


to form a fourth reaction product having the formula

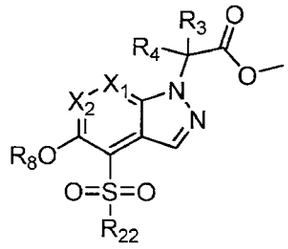


;

reacting the fourth reaction product with a compound having the formula



to form a fifth reaction product having the formula

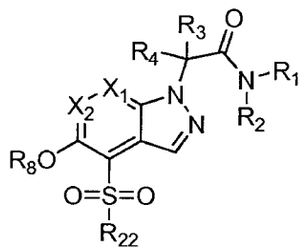


; and

reacting the fifth reaction product with a compound having the formula

NHR_1R_2

to form a sixth reaction product having the formula



,

wherein

X_1 and X_2 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

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

heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is –L_1-R_{22}, or two R_8 are taken together to form a substituted or unsubstituted ring;

R_9 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl,

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl,

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

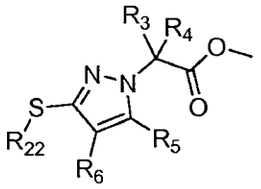
R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is – $NR_{27}R_{28}$;

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring;

G_2 is a leaving group; and

G_5 is a protecting group.

[0156] In still another of its aspects, the present invention relates to intermediates that are useful in making glucokinase activators. In one embodiment, the intermediates comprise:



wherein

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl,

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

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1-R_{22}$;

or R_5 and R_6 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

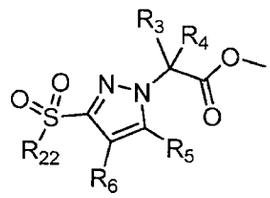
R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is – $NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl,

aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0157] In another embodiment, the intermediates comprise:



wherein

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1-R_{22}$;

or R_5 and R_6 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

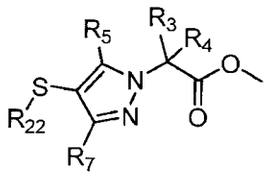
R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is – $NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0158] In still another embodiment, the intermediates comprise:



wherein

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl,

heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1-R_{22}$;

or R_5 and R_7 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

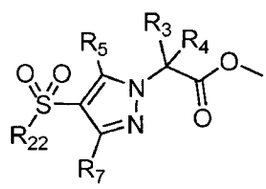
R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,

(C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0159] In yet another embodiment, the intermediates comprise:



wherein

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl,

sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,

(C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1-R_{22}$;

or R_5 and R_7 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

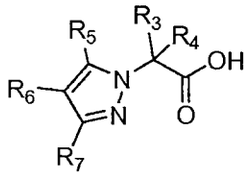
R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl,

hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0160] In a further embodiment, the intermediates comprise:



wherein

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is $-L-R_{18}$;

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl; hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1-R_{22}$;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1-R_{22}$;

or any two R_5, R_6 and R_7 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl,

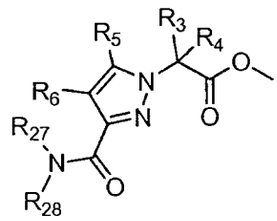
carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl,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

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted

or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0161] In still a further embodiment, the intermediates comprise:



wherein

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl,

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

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1-R_{22}$;

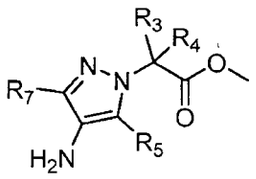
or R_5 and R_6 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0162] In yet a further embodiment, the intermediates comprise:



wherein

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1$-R_{22};

or R_5 and R_7 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

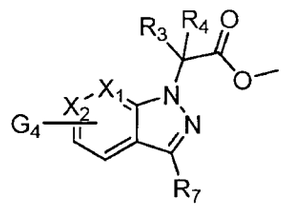
R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0163] In another embodiment, the intermediates comprise:



wherein

X_1 and X_2 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl,

aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1$-R_{22};

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

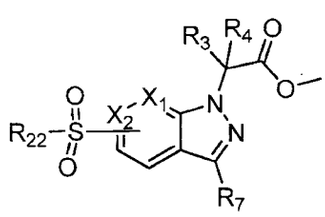
R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is – $NR_{27}R_{28}$;

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring; and

G_4 is a leaving group.

[0164] In still another embodiment, the intermediates comprise:



wherein

X_1 and X_2 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1-R_{22}$;

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

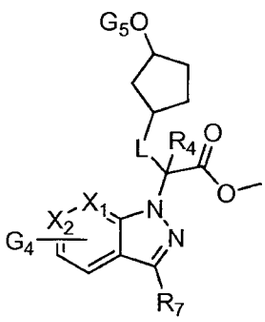
R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0165] In yet another embodiment, the intermediates comprise:



wherein

X_1 and X_2 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1-R_{22}$;

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl,

imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

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

that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$;

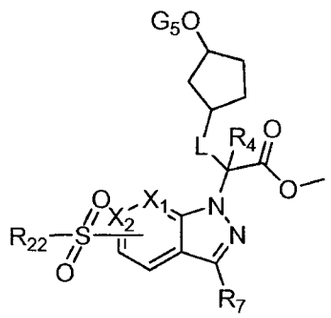
R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl,

aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring;

G_4 is a leaving group; and

G_5 is a protecting group.

[0166] In a further embodiment, the intermediates comprise:



wherein

X_1 and X_2 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy,

carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1-R_{22}$;

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl,

hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

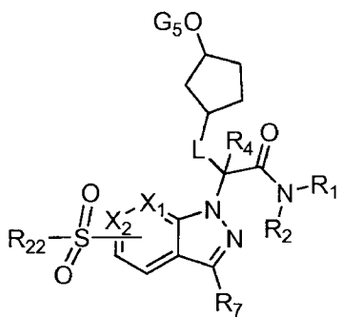
R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$;

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring; and

G_5 is a protecting group.

[0167] In still a further embodiment, the intermediates comprise:



wherein

X_1 and X_2 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1$-R_{22};

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl,

imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

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

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

that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is – $NR_{27}R_{28}$;

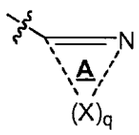
R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl,

aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring; and

G_5 is a protecting group.

[0168] In one variation of each of the above embodiments and variations containing R_1, R_1 is a substituted or unsubstituted heteroaryl. In another variation of each of the above embodiments and variations containing R_1, R_1 is selected from the group consisting of thiazolyl, pyrazinyl, pyrazolyl and pyridyl, each substituted or unsubstituted. In still another variation of each of the above embodiments and variations containing R_1, R_1 is selected from the group consisting of thiazol-2-yl; 2-pyridyl; 5-methyl-thiazol-2-yl; 6-methyl-pyrid-2-yl; 4-methyl-pyrid-2-yl; 5-bromo-6-methyl-pyrid-2-yl; 5-phenyl-pyrid-2-yl; benzothiazol-2-yl; a nictoinic acid methyl ester; and 5-bromo-pyrid-2-yl. In a further variation of each of the above embodiments and variations containing R_1, R_1 is a substituted or unsubstituted 2-pyrazinyl. In still a further variation of each of the above embodiments and variations containing R_1, R_1 is a substituted or unsubstituted 1-methyl-pyrazol-3-yl. In yet a further variation of each of the above embodiments and variations containing R_1, R_1 is a substituted or unsubstituted 5-fluoro-thiazol-2-yl.

[0169] In yet another variation of each of the above embodiments and variations containing R_1, R_1 comprises:



wherein

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22};

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso

that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring;

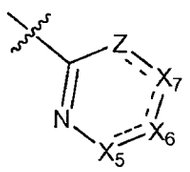
L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted

or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0170] In a further variation of each of the above embodiments and variations containing R_1, R_1 comprises:



wherein

X_5, X_6 and X_7 are each independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

Z is selected from the group consisting of $CR_{14}R_{15}$, NR_{16}, O and S;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22};

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring;

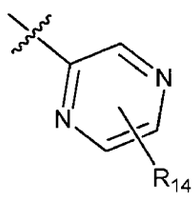
L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0171] In another variation of each of the above embodiments and variations containing R_1, R_1 comprises:

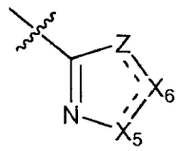


wherein

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$.

[0172] In still a further variation of each of the above embodiments and variations containing R_1, R_1 comprises:



wherein

X_5 and X_6 are each independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

Z is selected from the group consisting of $CR_{14}R_{15}$, NR_{16}, O and S;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond;

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring;

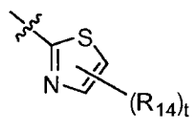
L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0173] In yet a further variation of each of the above embodiments and variations containing R_1, R_1 comprises:



wherein

t is selected from the group consisting of 0, 1 and 2; and

each R_{14} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$, or two R_{14} are taken together to form a substituted or unsubstituted ring;

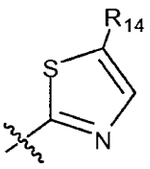
L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted

or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0174] In another variation of each of the above embodiments and variations containing R_1, R_1 comprises:



wherein

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

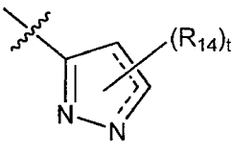
L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl,

hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0175] In a further variation of each of the above embodiments and variations containing R_1, R_1 comprises:



wherein

t is selected from the group consisting of 0, 1 and 2; and

each R_{14} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl,

(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$, or two R_{14} are taken together to form a substituted or unsubstituted ring;

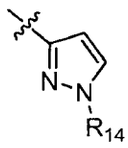
L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl,

heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0176] In still a further variation of each of the above embodiments and variations containing R_1, R_1 comprises:



wherein

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

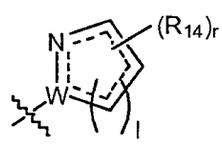
L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl,

hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0177] In yet another variation of each of the above embodiments and variations containing R_1, R_1 comprises:



wherein

l is selected from the group consisting of 1 and 2;

r is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8;

W is selected from the group consisting of CR_{17} or N;

each R_{14} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl,

sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$, or two R_{14} are taken together to form a substituted or unsubstituted ring;

R_{17} is selected from the group consisting of hydrogen, halo, (C_{1-3})alkyl, aryl and heteroaryl, each substituted or unsubstituted, or R_{17} and R_{14} are taken together to form a ring, with the proviso that R_{17} is absent when the atom to which it is attached forms part of a double bond;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

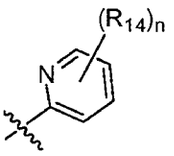
R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0178] In one variation of the above variations containing W, W is CR_{17}. In another variation of the above variations containing W, W is N.

[0179] In another variation of each of the above embodiments and variations containing R_1, R_1 comprises:



wherein

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

each R_{14} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22}, or two R_{14} are taken together to form a substituted or unsubstituted ring;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0180] In yet another variation of each of the above embodiments and variations containing ring **A**, ring **A** is a substituted or unsubstituted heteroaryl. In a further variation of each of the above embodiments and variations containing ring **A**, ring **A** is selected

from the group consisting of thiazolyl, pyrazinyl, pyrazolyl and pyridyl, each substituted or unsubstituted. In a further variation of each of the above embodiments and variations containing **A**, **A** is a substituted or unsubstituted 2-pyrazinyl. In still a further variation of each of the above embodiments and variations containing **A**, **A** is a substituted or unsubstituted 1-methyl-pyrazol-3-yl. In yet a further variation of each of the above embodiments and variations containing **A**, **A** is a substituted or unsubstituted 5-fluoro-thiazol-2-yl.

[0181] In still a further variation of each of the above embodiments and variations containing Z, Z is S.

[0182] In yet a further variation of each of the above embodiments and variations containing X_1, X_1 is –CH=. In yet another variation of each of the above embodiments and variations containing X_1, X_1 is –N=.

[0183] In another variation of each of the above embodiments and variations containing X_2, X_2 is –CH=. In yet another variation of each of the above embodiments and variations containing X_2, X_2 is –N=.

[0184] In a further variation of each of the above embodiments and variations containing X_3, X_3 is $-CR_9=$. In still another variation of each of the above embodiments and variations containing X_3, X_3 is –CH=.

[0185] In a further variation of each of the above embodiments and variations containing X_4, X_4 is $-CR_9=$. In still another variation of each of the above embodiments and variations containing X_4, X_4 is –CH=.

[0186] In a further variation of each of the above embodiments and variations containing X_1, X_2, X_3 and X_4, X_1 is –CH=, X_2 is –N=, X_3 is –CH= and X_4 is $-CR_9=$. In still a further variation of each of the above embodiments and variations containing X_1, X_2, X_3 and X_4, X_1 is –CH=, X_2 is –CH=, X_3 is $-C\ R_9=$ and X_4 is $-CR_9=$.

[0187] In still another variation of each of the above embodiments and variations containing X_5, X_5 is –CH=.

[0188] In still another variation of each of the above embodiments and variations containing X_6, X_6 is –CH=.

[0189] In still another variation of each of the above embodiments and variations containing X_7, X_7 is –CH=. In a further variation of each of the above embodiments and variations containing X_7, X_7 is –N=.

[0190] In yet another variation of each of the above embodiments and variations containing R_2, R_2 is hydrogen.

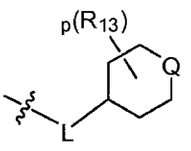
[0191] In a further variation of each of the above embodiments and variations containing R_3,

R_3 is –L-R_{18};

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0192] In still a further variation of each of the above embodiments and variations containing R_3, R_3 comprises:



wherein

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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;

Q is selected from the group consisting of O, S, CS, CO, SO, SO_2, $CR_{19}R_{20}$ and NR_{21};

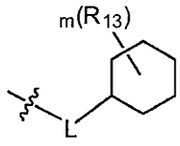
R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{21} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino

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

[0193] In yet a further variation of each of the above embodiments and variations containing R_3, R_3 comprises:



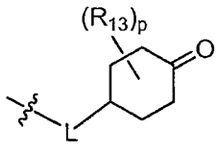
wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring.

[0194] In another variation of each of the above embodiments and variations containing R_3, R_3 comprises:



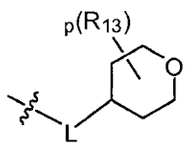
wherein

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring.

[0195] In still another variation of each of the above embodiments and variations containing R_3, R_3 comprises:



wherein

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

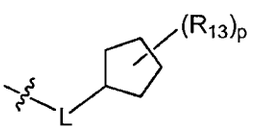
L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and the ring to which L is attached, wherein the atoms of the linker providing the

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

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring.

[0196] In yet another variation of each of the above embodiments and variations containing R_3, R_3 is selected from the group consisting of (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0197] In a further variation of each of the above embodiments and variations containing R_3, R_3 comprises:



wherein

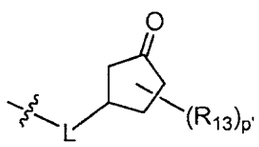
p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring.

[0198] In still a further variation of each of the above embodiments and variations containing R_3, R_3 comprises:



wherein

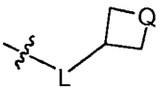
p′ is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6and 7;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl,

aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring.

[0199] In yet a further variation of each of the above embodiments and variations containing R_3, R_3 comprises:



wherein

Q is selected from the group consisting of O, S, CS, CO, SO, SO_2, $CR_{19}R_{20}$ and NR_{21};

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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;

R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{21} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl,

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

[0200] In another variation of each of the above embodiments and variations containing R_3, R_3 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, and heteroaryl(C_{1-5})alkyl, each substituted or unsubstituted. In still another variation of each of the above embodiments and variations containing R_3, R_3 is selected from the group consisting of butyl; hexylmethyl; benzyl; imidazol-4-ylmethyl, phenyl and (tetrahydro-2H-pyran-4-yl)methyl. In yet another variation of each of the above embodiments and variations containing R_3, R_3 is a substituted or unsubstituted (tetrahydro-2H-pyran-4-yl)methyl. In a further variation of each of the above embodiments and variations containing R_3, R_3 is selected from the group consisting of butyl; hexylmethyl; benzyl; imidazol-4-ylmethyl and phenyl. In still a further variation of each of the above embodiments and variations containing R_3, R_3 is selected from the group consisting of alkyl, cycloalkyl-alkyl, dihaloaryl-alkyl, alkoxyaryl-alkyl, alkoxycycloalkyl-alkyl, tetrahydrofuranyl-alkyl, furanyl-alkyl and tetrahydro-2H-pyranyl-alky, each substituted or unsubstituted.

[0201] In yet a further variation of each of the above embodiments and variations containing L, L is–CH_2-. In another variation of each of the above embodiments and variations containing L, L is selected from the group consisting of –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2C(O)$-, -CH_2-$C(O)CH_2$-, -$CH_2CH_2C(O)$-,-CH_2O-, -CH_2OCH_2-, -CH_2CH_2O-, -CH_2NH-, -CH_2NHCH_2-, -CH_2CH_2NH-, -$CH_2NHC(O)$-, -$CH_2C(O)NH$-, -CH_2S-, -CH_2SCH_2-, -CH_2CH_2S-,-$CH_2C(O)S$- and -$CH_2SC(O)$-, each substituted or unsubstituted. In still another variation of each of the above embodiments and variations containing L, 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.

[0202] In yet another variation of each of the above embodiments and variations containing L,

L is selected from the group consisting of $-(CR_{24}R_{25})_s$-;

s is selected from the group consisting from the group consisting of 1, 2, 3, 4, 5 and 6; and

R_{24} and R_{25} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0203] In a further variation of each of the above embodiments and variations containing Q, Q is $-CR_{19}R_{20}$-. In still a further variation of each of the above embodiments and variations containing Q, Q is -CH_2-. In yet a further variation of each of the above embodiments and variations containing Q, Q is $-NR_{21}$-. In another variation of each of the above embodiments and variations containing Q, Q is -NH-. In a further variation of each of the above embodiments and variations containing Q, Q is -O-.

[0204] In still another variation of each of the above embodiments and variations containing R_4, R_4 is selected from the group consisting of carbonyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl,

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

[0205] In yet another variation of each of the above embodiments and variations containing R_4, R_4 is selected from the group consisting of hydrogen, (C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, and heteroaryl(C_{1-5})alkyl, each substituted or unsubstituted. In a further variation of each of the above embodiments and variations containing R_4, R_4 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, and heteroaryl(C_{1-5})alkyl, each substituted or unsubstituted. In still a further variation of each of the above embodiments and variations containing R_4, R_4 is selected from the group consisting of hydrogen; butyl; cyclohexylmethyl; benzyl; imidazol-4-ylmethyl and phenyl. In yet a further variation of each of the above embodiments and variations containing R_4, R_4 is selected from the group consisting of butyl; cyclohexylmethyl; benzyl; imidazol-4-ylmethyl and phenyl. In another variation of each of the above embodiments and variations containing R_4, R_4 is hydrogen.

[0206] In still another variation of each of the above embodiments and variations containing R_5, R_5 is hydrogen. In yet another variation of each of the above embodiments and variations containing R_5, R_5 is halo. In a further variation of each of the above embodiments and variations containing R_5, R_5 is a substituted or unsubstituted (C_{1-3})alkyl.

[0207] In still a further variation of each of the above embodiments and variations containing R_6, R_6 is hydrogen. In yet a further variation of each of the above embodiments and variations containing R_6, R_6 is halo. In another variation of each of the above embodiments and variations containing R_6, R_6 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations containing R_6, R_6 is a substituted or unsubstituted (C_{1-3})alkylsulfonyl. In yet another variation of each of the above embodiments and variations containing R_6, R_6 is a substituted or unsubstituted (C_{1-6})cycloalkylsulfonyl. In yet a further variation of each of the above embodiments and variations containing R_6, R_6 is selected from the group consisting of methylsulfonyl, cyclopropylsulfonyl and cyclopentylsulfonyl, each substituted or unsubstituted.

[0208] In another variation of each of the above embodiments and variations containing R_6,

R_6 is $-L_1-R_{22}$;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0209] In still another variation of each of the above embodiments and variations containing R_6, R_6 is $-SO_2-R_{22}$; R_{22} is selected from the group consisting of hydrogen, halo,

nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0210] In yet another variation of each of the above embodiments and variations containing R_6, R_6 is $-CO-R_{22}$; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from

the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0211] In a further variation of each of the above embodiments and variations containing R_6, R_6 is -NH-SO_2-R_{22}; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0212] In still a further variation of each of the above embodiments and variations containing R_6, R_6 is -NH-CO-R_{22}; R_{22} is selected from the group consisting of hydrogen,

halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0213] In yet a further variation of each of the above embodiments and variations containing R_6, R_6 is -CO-NH-R_{22}; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from

the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0214] In another variation of each of the above embodiments and variations containing R_7, R_7 is hydrogen. In still another variation of each of the above embodiments and variations containing R_7, R_7 is halo. In yet another variation of each of the above embodiments and variations containing R_7, R_7 is a substituted or unsubstituted (C_{1-3})alkyl.

[0215] In a further variation of each of the above embodiments and variations containing R_7,

R_7 is $-L_1-R_{22}$;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and

hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0216] In a further variation of each of the above embodiments and variations containing R_7, R_7 is –CO-R_{22}; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl,

hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0217] In still a further variation of each of the above embodiments and variations containing R_7, R_7 is -NH-SO_2-R_{22}; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring..

[0218] In yet a further variation of each of the above embodiments and variations containing R_5 and R_6, R_5 and R_6, together with the atoms to which they are attached, form a substituted or unsubstituted aryl. In another variation of each of the above embodiments and variations containing R_5 and R_6, R_5 and R_6, together with the atoms to which they are attached, form a substituted or unsubstituted phenyl. In still another variation of each of the above embodiments and variations containing R_5 and R_6, R_5 and R_6, together with the atoms to which they are attached, form a substituted or unsubstituted heteroaryl.

[0219] In yet another variation of each of the above embodiments and variations containing R_6 and R_7, R_6 and R_7, together with the atoms to which they are attached, form a substituted or unsubstituted aryl. In a further variation of each of the above embodiments and variations containing R_6 and R_7, R_6 and R_7, together with the atoms to which they are attached, form a substituted or unsubstituted phenyl. In still a further variation of each of the above embodiments and variations containing R_6 and R_7, R_6 and R_7, together with the atoms to which they are attached, form a substituted or unsubstituted heteroaryl.

[0220] In yet a further variation of each of the above embodiments and variations containing R_8, R_8 is hydrogen. In another variation of each of the above embodiments and variations containing R_8, R_8 is halo. In another variation of each of the above embodiments and variations containing R_8, R_8 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations containing R_8, R_8 is a substituted or unsubstituted sulfonyl(C_{1-3})alkyl. In a further variation of each of the above embodiments and variations containing R_8, R_8 is a substituted or unsubstituted (C_{1-3})alkylsulfonyl. In still a further variation of each of the above embodiments and variations containing R_8, R_8 is a substituted or unsubstituted (C_{3-12})cycloalkylsulfonyl. In yet another variation of each of the above embodiments and variations containing R_8, R_8 is selected from the group consisting of sulfonylmethyl, methylsulfonyl, cyclopropylsulfonyl and cyclopentylsulfonyl, each substituted or unsubstituted. In a further variation of each of the above embodiments and variations containing R_8, R_8 is a substituted or unsubstituted cyclopropylsulfonyl. In still a further variation of each of the above embodiments and variations containing R_8, R_8 is cyano. In yet a further variation of each of the above embodiments and variations containing R_8, R_8 is a substituted or unsubstituted (C_{1-6})alkoxy. In another variation of each of the above embodiments and variations containing R_8, R_8 is methoxy.

[0221] In a further variation of each of the above embodiments and variations containing R_8,

R_8 is $-L_1$-R_{22};

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0222] In still a further variation of each of the above embodiments and variations containing R_8, R_8 is –SO_2-R_{22}; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl,

(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0223] In yet a further variation of each of the above embodiments and variations containing R_8, R_8 is $-CO-R_{22}$; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl,

(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0224] In another variation of each of the above embodiments and variations containing R_8, R_8 is -NH-SO_2-R_{22}; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0225] In still another variation of each of the above embodiments and variations containing R_8, R_8 is -NH-CO-R_{22}; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl,

(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0226] In yet another variation of each of the above embodiments and variations containing R_8, R_8 is -CO-NH-R_{22}; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl,

(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0227] In a further variation of each of the above embodiments and variations containing R_3 and R_8, R_3 is a substituted or unsubstituted(tetrahydro-2H-pyran-4-yl)methyl and R_8 is a substituted or unsubstituted cyclopropylsulfonyl.

[0228] In another variation of each of the above embodiments and variations containing R_9, R_9 is a substituted or unsubstituted cyclopropylsulfonyl. In still another variation of each of the above embodiments and variations containing R_9, R_9 is a substituted or unsubstituted (C_{1-3})alkoxy. In yet another variation of each of the above embodiments and variations containing R_9, R_9 is methoxy.

[0229] In still a further variation of each of the above embodiments and variations containing R_3 and R_9, R_3 is a substituted or unsubstituted(tetrahydro-2H-pyran-4-yl)methyl and R_9 is a substituted or unsubstituted cyclopropylsulfonyl.

[0230] In still another variation of each of the above embodiments and variations containing R_{10}, R_{10} is hydrogen. In yet another variation of each of the above embodiments and variations containing R_{10}, R_{10} is halo. In a further variation of each of the above embodiments and variations containing R_{10}, R_{10} is a substituted or unsubstituted (C_{1-3})alkyl.

[0231] In still another variation of each of the above embodiments and variations containing R_{11}, R_{11} is hydrogen. In a further variation of each of the above embodiments and variations containing R_{11}, R_{11} is a substituted or unsubstituted (C_{1-3})alkyl.

[0232] In still another variation of each of the above embodiments and variations containing R_{12}, R_{12} is hydrogen. In a further variation of each of the above embodiments and variations containing R_{12}, R_{12} is a substituted or unsubstituted (C_{1-3})alkyl.

[0233] In still another variation of each of the above embodiments and variations containing R_{13}, R_{13} is hydrogen. In yet another variation of each of the above embodiments and variations containing R_{13}, R_{13} is halo. In a further variation of each of the above embodiments and variations containing R_{13}, R_{13} is a substituted or unsubstituted (C_{1-3})alkyl.

[0234] In another variation of each of the above embodiments and variations containing R_{14}, each R_{14} is independently selected from the group consisting of hydrogen, halo, a

substituted or unsubstituted (C_{1-5})alkyl and a substituted or unsubstituted carboxamido. In a further variation of each of the above embodiments and variations containing R_{14}, at least one R_{14} is a substituted or unsubstituted carboxamido. In still a further variation of each of the above embodiments and variations containing R_{14}, at least one R_{14} is hydrogen. In yet a further variation of each of the above embodiments and variations containing R_{14}, at least one R_{14} is halo. In another variation of each of the above embodiments and variations containing R_{14}, at least one R_{14} is fluoro. In still another variation of each of the above embodiments and variations containing R_{14}, at least one R_{14} is chloro. In another variation of each of the above embodiments and variations containing R_{14}, at least one R_{14} is a substituted or unsubstituted (C_{1-5})alkyl. In another variation of each of the above embodiments and variations containing R_{14}, at least one R_{14} is methyl. In still another variation of each of the above embodiments and variations containing R_{14}, two R_{14}, together with the atoms to which they are attached, are taken together to form a substituted or unsubstituted ring.

[0235] In still another variation of each of the above embodiments and variations containing R_{14}, R_{14} is oxa(C_{1-5})alkyl. In yet another variation of each of the above embodiments and variations containing R_{14}, R_{14} is oxo(C_{1-5})alkyl. In a further variation of each of the above embodiments and variations containing R_{14}, R_{14} is $-L_1-R_{22}$, where L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl,

amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0236] In still a further variation of each of the above embodiments and variations containing R_{14}, R_{14} is selected from the group consisting of hydrogen, halo, cyano, -OR_{22}, -SO_2-R_{22}, -NH-SO_2-R_{22} and -SO_2-NH-R_{22}; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is –$NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring. In yet a further variation of each of the above embodiments and variations containing R_{14}, R_{14} is selected

from the group consisting of halo, (C_{1-5})alkyl, oxa(C_{1-5})alkyl and oxo(C_{1-5})alkyl, each substituted or unsubstituted.

[0237] In yet another variation of each of the above embodiments and variations containing R_{15}, R_{15} is hydrogen. In a further variation of each of the above embodiments and variations containing R_{15}, R_{15} is halo. In yet a further variation of each of the above embodiments and variations containing R_{15}, R_{15} is a substituted or unsubstituted (C_{1-5})alkyl.

[0238] In a further variation of each of the above embodiments and variations containing R_{16}, R_{16} is (C_{1-5})alkyl. In another variation of each of the above embodiments and variations containing R_{16}, R_{16} is methyl.

[0239] In another variation of each of the above embodiments and variations containing R_{17}, R_{17} is absent. In still another variation of each of the above embodiments and variations containing R_{17}, R_{17} is hydrogen. In yet another variation of each of the above embodiments and variations containing R_{17}, R_{17} is (C_{13})alkyl. In another variation of each of the above embodiments and variations containing R_{17}, R_{17} is methyl. In a further variation of each of the above embodiments and variations containing R_{17}, R_{17} is halo.

[0240] In another variation of each of the above embodiments and variations containing R_{18}, R_{18} is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, each substituted or unsubstituted.

[0241] In still another variation of each of the above embodiments and variations containing R_{19}, R_{19} is hydrogen. In yet another variation of each of the above embodiments and variations containing R_{19}, R_{19} is halo. In a further variation of each of the above embodiments and variations containing R_{19}, R_{19} is a substituted or unsubstituted (C_{1-3})alkyl.

[0242] In still another variation of each of the above embodiments and variations containing R_{20}, R_{20} is hydrogen. In yet another variation of each of the above embodiments and variations containing R_{20}, R_{20} is halo. In a further variation of each of the above embodiments and variations containing R_{20}, R_{20} is a substituted or unsubstituted (C_{1-3})alkyl.

[0243] In still another variation of each of the above embodiments and variations containing R_{21}, R_{21} is hydrogen. In a further variation of each of the above embodiments and variations containing R_{21}, R_{21} is a substituted or unsubstituted (C_{1-3})alkyl.

[0244] In still another variation of each of the above embodiments and variations containing R_{22}, R_{22} is a substituted or unsubstituted (C_{1-5})alkyl. In yet another variation of each of the above embodiments and variations containing R_{22}, R_{22} is a substituted or unsubstituted (C_{3-6})cycloalkyl. In a further variation of each of the above embodiments and variations containing R_{22}, R_{22} is a substituted or unsubstituted (C_{4-8})aryl. In still a further variation of each of the above embodiments and variations containing R_{22}, R_{22} is a substituted or unsubstituted phenyl. In yet a further variation of each of the above embodiments and variations containing R_{22}, R_{22} is a substituted or unsubstituted hetero(C_{1-6})aryl. In another variation of each of the above embodiments and variations containing R_{22}, R_{22} is cyclopropyl.

[0245] In still another variation of each of the above embodiments and variations containing R_{22},

R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

[0246] In yet a further variation of each of the above embodiments and variations containing L_1,

L_1 is selected from the group consisting of $-(CR_{24}R_{25})_s$-, $-NR_{26}$-, -O-, -S-, -CO-, -CS-, -SO-, $-SO_2$-, and combinations thereof;

s is selected from the group consisting from the group consisting of 1, 2, 3, 4, 5 and 6;

R_{24} and R_{25} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy,

(C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{26} is selected from the group consisting of hydrogen, cyano, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0247] In another variation of each of the above embodiments and variations containing L_1, L_1 is $-SO_2-$. In still another variation of each of the above embodiments and variations containing L_1, L_1 is $-C(O)-NR_{26}-$ and R_{26} is selected from the group consisting of hydrogen, cyano, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl,

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

[0248] In yet another variation of each of the above embodiments and variations containing L_1, L_1 is $-C(S)-NR_{26}-$ and R_{26} is selected from the group consisting of hydrogen, cyano, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0249] In a further variation of each of the above embodiments and variations containing R_{24}, R_{24} is selected from the group consisting of H and a substituted or unsubstituted (C_{1-5})alkyl.

[0250] In still a further variation of each of the above embodiments and variations containing R_{25}, R_{25} is selected from the group consisting of H and a substituted or unsubstituted (C_{1-5})alkyl.

[0251] In yet a further variation of each of the above embodiments and variations containing R_{26}, R_{26} is selected from the group consisting of hydrogen and a substituted or unsubstituted (C_{1-10})alkyl.

[0252] In yet another variation of each of the above embodiments and variations containing R_{27}, R_{27} is a substituted or unsubstituted (C_{3-12})cycloalkyl. In a further variation of each of the above embodiments and variations containing R_{27}, R_{27} is a substituted or unsubstituted cyclopropyl.

[0253] In still a further variation of each of the above embodiments and variations containing R_{28}, R_{28} is hydrogen.

[0254] In another variation of each of the above embodiments and variations containing l, l is 1.

[0255] In still another variation of each of the above embodiments and variations containing m, m is 0. In yet another variation of each of the above embodiments and variations containing m, m is 1. In a further variation of each of the above embodiments and variations containing m, m is 2.

[0256] In a further variation of each of the above embodiments and variations containing n, n is 0. In still a further variation of each of the above embodiments and variations containing n, n is 1. In yet a further variation of each of the above embodiments and variations containing n, n is 2.

[0257] In a further variation of each of the above embodiments and variations containing n′, n′ is 0. In still a further variation of each of the above embodiments and variations containing n′, n′ is 1. In yet a further variation of each of the above embodiments and variations containing n′, n′ is 2.

[0258] In a further variation of each of the above embodiments and variations containing n″, n″ is 0. In still a further variation of each of the above embodiments and variations containing n″, n″ is 1. In yet a further variation of each of the above embodiments and variations containing n″, n″ is 2.

[0259] In another variation of each of the above embodiments and variations containing p, p is 0. In still another variation of each of the above embodiments and variations containing p, p is 1. In yet another variation of each of the above embodiments and variations containing p, p is 2.

[0260] In another variation of each of the above embodiments and variations containing p′, p′ is 0. In still another variation of each of the above embodiments and variations containing p′, p′ is 1. In yet another variation of each of the above embodiments and variations containing p′, p′ is 2.

[0261] In a further variation of each of the above embodiments and variations containing q, q is 3. In still a further variation of each of the above embodiments and variations containing q, q is 4.

[0262] In another variation of each of the above embodiments and variations containing r, r is 1.

[0263] In a further variation of each of the above embodiments and variations containing s, s is 0. In still a further variation of each of the above embodiments and variations containing s, s is 1.

[0264] In another variation of each of the above embodiments and variations containing t, t is 1.

[0265] It is noted that the compounds of the present invention may be in the form of a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, solvate, hydrate or prodrug thereof. For example, the compound optionally comprises a substituent that is convertible *in vivo* to a different substituent, such as hydrogen. It is further noted that the compound may be present in a mixture of stereoisomers, or the compound may comprise a single stereoisomer.

[0266] The present invention also provides a pharmaceutical composition comprising as an active ingredient a compound according to any one of the above embodiments and variations. In one particular variation, the composition is a solid formulation adapted for oral administration. In another particular variation, the composition is a liquid formulation adapted for oral administration. In yet another particular variation, the composition is a tablet. In still another particular variation, the composition is a liquid formulation adapted for parenteral administration.

[0267] In another of its aspects, there is provided a pharmaceutical composition comprising a compound according to any one of the above embodiments and variations, wherein the composition is adapted for administration by a route selected from the group consisting of orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, and intrathecally.

[0268] In yet another of its aspects, there is provided a kit comprising a compound of any one of the above embodiments and variations; and instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the composition is to be administered, storage information for the composition, dosing information and instructions regarding how to administer the composition. In one particular variation, the kit comprises the compound in a multiple dose form.

[0269] In still another of its aspects, there is provided an article of manufacture comprising a compound of any one of the above embodiments and variations; and

packaging materials. In one variation, the packaging material comprises a container for housing the compound. In one particular variation, the container comprises a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the compound. In another variation, the article of manufacture comprises the compound in a multiple dose form.

[0270] In a further of its aspects, there is provided a therapeutic method comprising administering a compound of any one of the above embodiments and variations to a subject.

[0271] In another of its aspects, there is provided a method of activating glucokinase comprising contacting glucokinase with a compound of any one of the above embodiments and variations.

[0272] In yet another of its aspects, there is provided a method of activating glucokinase comprising causing a compound of any one of the above embodiments and variations to be present in a subject in order to activate glucokinase *in vivo*.

[0273] In a further of its aspects, there is provided a method of activating glucokinase comprising administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound activates glucokinase *in vivo*, the second compound being a compound according to any one of the above embodiments and variations.

[0274] In another of its aspects, there is provided a method of treating a disease state for which increasing glucokinase activity ameliorates the pathology and/or symptomology of the disease state, the method comprising causing a compound of any one of the above embodiments and variations to be present in a subject in a therapeutically effective amount for the disease state.

[0275] In yet another of its aspects, there is provided a method of treating a disease state for which increasing glucokinase activity ameliorates the pathology and/or symptomology of the disease state, the method comprising administering a compound of any one of the above embodiments and variations to a subject, wherein the compound is present in the subject in a therapeutically effective amount for the disease state.

[0276] In a further of its aspects, there is provided a method of treating a disease state for which increasing glucokinase activity ameliorates the pathology and/or symptomology of the disease state, the method comprising administering a first compound to a subject that is

converted *in vivo* to a second compound wherein the second compound activates glucokinase *in vivo*, the second compound being a compound according to any one of the above embodiments and variations.

[0277] In one variation of each of the above methods the disease state is selected from the group consisting of hyperglycemia, diabetes, dyslipidaemia, obesity, insulin resistance, metabolic syndrome X, impaired glucose tolerance, polycystic ovary syndrome, and cardiovascular disease.

Salts, Hydrates, and Prodrugs of Glucokinase Activators

[0278] 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.

[0279] 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.

[0280] When the compounds of the present invention possess a free acid form, a pharmaceutically acceptable base addition salt can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Examples of such bases are alkali metal hydroxides including potassium, sodium and lithium hydroxides; alkaline earth metal hydroxides such as barium and calcium hydroxides; alkali metal alkoxides, *e.g.*, potassium ethanolate and sodium propanolate; and various organic bases such as ammonium hydroxide, piperidine, diethanolamine and N-methylglutamine. Also included are the aluminum salts of the compounds of the present invention. Further base salts of the present invention include, but are not limited to: copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium and zinc salts. Organic base salts include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, *e.g.*, arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, iso-propylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)-methylamine (tromethamine). It should be recognized that the free acid forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid forms for the purposes of the present invention.

[0281] 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.

[0282] *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.

[0283] 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.

[0284] 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.

[0285] 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.

[0286] A "pharmaceutically acceptable salt", as used herein, is intended to encompass any compound according to the present invention that is utilized in the form of a salt thereof, especially where the salt confers on the compound improved pharmacokinetic properties as compared to the free form of compound or a different salt form of the compound. The

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

Compositions Comprising Glucokinase Activators

[0287] A wide variety of compositions and administration methods may be used in conjunction with the compounds of the present invention. Such compositions may include, in addition to the compounds of the present invention, conventional pharmaceutical excipients, and other conventional, pharmaceutically inactive agents. Additionally, the compositions may include active agents in addition to the compounds of the present invention. These additional active agents may include additional compounds according to the invention, and/or one or more other pharmaceutically active agents.

[0288] 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.

[0289] Compositions comprising compounds of the present invention may be administered or coadministered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, or

intrathecally. The compounds and/or compositions according to the invention may also be administered or coadministered in slow release dosage forms.

[0290] The glucokinase activators 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 glucokinase activator, 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.

[0291] 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.

[0292] When compounds according to the present invention exhibit insufficient solubility, methods for solubilizing the compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

[0293] Upon mixing or adding compounds according to the present invention to a composition, a solution, suspension, emulsion or the like may be formed. The form of the resulting composition will depend upon a number of factors, including the intended mode of administration, and the solubility of the compound in the selected carrier or vehicle. The effective concentration needed to ameliorate the disease being treated may be empirically determined.

[0294] 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.

[0295] In addition to one or more compounds according to the present invention, the composition may comprise: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acaciagelatin, glucose, molasses, polvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known in the

art, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a sufficient quantity of an activator of the present invention to increase glucokinase activity *in vivo*, thereby treating the disease state of the subject.

[0296] Dosage forms or compositions may optionally comprise one or more compounds according to the present invention in the range of 0.005% to 100% (weight/weight) with the balance comprising additional substances such as those described herein. For oral administration, a pharmaceutically acceptable composition may optionally comprise any one or more commonly employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate, sodium saccharin, talcum. Such compositions include solutions, suspensions, tablets, capsules, powders, dry powders for inhalers and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparing these formulations are known to those skilled in the art. The compositions may optionally contain 0.01%-100% (weight/weight) of one or more glucokinase activators, optionally 0.1-95%, and optionally 1-95%.

[0297] Salts, preferably sodium salts, of the activators may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. The formulations may further include other active compounds to obtain desired combinations of properties.

Formulations for Oral Administration

[0298] 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.

[0299] In certain embodiments, compounds according to the present invention are provided as solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like may optionally contain one or more of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

[0300] 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.

[0301] Examples of lubricants that may be used include, but are not limited to, talc, starch, magnesium or calcium stearate, lycopodium and stearic acid.

[0302] Examples of diluents that may be used include, but are not limited to, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate.

[0303] Examples of glidants that may be used include, but are not limited to, colloidal silicon dioxide.

[0304] 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.

[0305] 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.

[0306] 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.

[0307] 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.

[0308] 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.

[0309] 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.

[0310] Examples of film coatings that may be used include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0311] 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.

[0312] 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.

[0313] 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.

[0314] The compounds of the present invention may also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. For example, if a compound is used for treating asthma or hypertension, it may be used with other bronchodilators and antihypertensive agents, respectively.

[0315] Examples of pharmaceutically acceptable carriers that may be included in tablets comprising compounds of the present invention include, but are not limited to binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets may be compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets may be compressed tablets that have been coated with polymers or other suitable coating. Multiple compressed tablets may be compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also

be used in tablets. Flavoring and sweetening agents may be used in tablets, and are especially useful in the formation of chewable tablets and lozenges.

[0316] 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.

[0317] 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.

[0318] 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.

[0319] 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.

[0320] Examples of pharmaceutically acceptable substances that may be used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide.

[0321] Coloring and flavoring agents may optionally be used in all of the above dosage forms.

[0322] Particular examples of preservatives that may be used include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol.

[0323] Particular examples of non-aqueous liquids that may be used in emulsions include mineral oil and cottonseed oil.

[0324] Particular examples of emulsifying agents that may be used include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate.

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.

[0333] 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.

[0334] 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.

[0335] 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.

[0336] 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.

[0337] 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.

[0338] 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.

[0339] Antimicrobial agents in bacteriostatic or fungistatic concentrations may be added to parenteral preparations, particularly when the preparations are packaged in multiple-dose containers and thus designed to be stored and multiple aliquots to be removed. Examples of antimicrobial agents that may be used include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride.

[0340] 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 includes EDTA.

[0341] 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.

[0342] The concentration of an activator in the parenteral formulation may be adjusted so that an injection administers a pharmaceutically effective amount sufficient to produce the desired pharmacological effect. The exact concentration of an activator 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.

[0343] 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.

[0344] 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 glucokinase activator to the treated tissue(s). The activator 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.

[0345] The glucokinase activator may optionally be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease state and may be empirically determined.

Lyophilized Powders

[0346] The compounds of the present invention may also be prepared as lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. The lyophilized powders may also be formulated as solids or gels.

[0347] 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 glucokinase activator 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 activator.

Topical Administration

[0348] The compounds of the present invention may also be administered as topical mixtures. Topical mixtures may be used for local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[0349] The glucokinase activators may be formulated as aerosols for topical application, such as by inhalation (see, U.S. Pat. Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

[0350] The activators 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 glucokinase activator alone or in combination with other pharmaceutically acceptable excipients can also be administered.

Formulations for Other Routes of Administration

[0351] Depending upon the disease state being treated, other routes of administration, such as topical application, transdermal patches, and rectal administration, may also be used. For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum that melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients.

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

Examples of Formulations

[0352] The following are particular examples of oral, intravenous and tablet formulations that may optionally be used with compounds of the present invention. It is noted that these formulations may be varied depending on the particular compound being used and the indication for which the formulation is going to be used.

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

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

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

Kits Comprising Glucokinase Activators

[0353] The invention is also directed to kits and other articles of manufacture for treating diseases associated with glucokinase. It is noted that diseases are intended to cover all

conditions for which increasing glucokinase activity (*e.g.*, upregulation of glucokinase) ameliorates the pathology and/or symptomology of the condition.

[0354] In one embodiment, a kit is provided that comprises a composition comprising at least one activator 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.

[0355] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one activator 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.

[0356] 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.

[0357] 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.

[0358] 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.

Dosage, Host and Safety

[0359] The compounds of the present invention are stable and can be used safely. In particular, the compounds of the present invention are useful as glucokinase activators for a variety of subjects (*e.g.*, humans, non-human mammals and non-mammals). The optimal dose may vary depending upon such conditions as, for example, the type of subject, the body weight of the subject, the route of administration, and specific properties of the particular compound being used. In general, the daily dose for oral administration

to an adult (body weight of about 60 kg) is about 1 to 1000 mg, about 3 to 300 mg, or about 10 to 200 mg. It will be appreciated that the daily dose can be given in a single administration or in multiple (*e.g.*, 2 or 3) portions a day.

Combination Therapies

[0360] A wide variety of therapeutic agents may have a therapeutic additive or synergistic effect with GK activators according to the present invention. In particular, the present invention also relates to the use of the GK activators of the present invention in combination with one or more other antidiabetic compounds. Examples of such other antidiabetic compounds include, but are not limited to S9 proteases, like dipeptidyl peptidase IV (DPP-IV) inhibitors; insulin signaling pathway modulators, like protein tyrosine phosphatase (PTPase) inhibitors, and glutamine-fructose-6-phosphate amidotransferase (GFAT) inhibitors; compounds influencing a dysregulated hepatic glucose production, like glucose-6-phosphatase (G6Pase) inhibitors, fructose-1,6-bisphosphatase (F-1,6-BPase) inhibitors, glycogen phosphorylase (GP) inhibitors, glucagon receptor antagonists and phosphoenolpyruvate carboxykinase (PEPCK) inhibitors; pyruvate dehydrogenase kinase (PDHK) inhibitors; insulin sensitivity enhancers (insulin sensitizers); insulin secretion enhancers (insulin secretagogues); alpha-glucosidase inhibitors; inhibitors of gastric emptying; other glucokinase (GK) activators; GLP-1 receptor agonists; UCP modulators; RXR modulators; GSK-3 inhibitors; PPAR modulators; metformin; insulin; and α_2-adrenergic antagonists.

[0361] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be DPP-IV inhibitors selected from the group consisting of Alogliptin (Nesina; Takeda Pharmaceutical Company Limited), Sitagliptin (Januvia; Merck), Saxagliptin (Onglyza; Bristol Myers Squibb), and Vildagliptin (Galvus; Novartis). In addition, the one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be DPP-IV inhibitors combined with metformin such as, for example, Alogliptin plus metformin(Takeda Pharmaceutical Company Limited), Sitagliptin plus metformin (Janumet; Merck), Saxagliptin plus metformin (Bristol Myers Squibb), and Vildagliptin plus metformin (Eucreas; Novartis).

[0362] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be selected from the group

consisting of protein tyrosine phosphatase inhibitors, glutamine-fructose-6-phosphate amidotransferase inhibitors, glucose-6-phosphatase inhibitors, fructose-1,6-bisphosphatase inhibitors, glycogen phosphorylase inhibitors, glucagon receptor antagonists, phosphoenolpyruvate carboxykinase inhibitors, pyruvate dehydrogenase kinase inhibitors, alpha-glucosidase inhibitors, inhibitors of gastric emptying, glucokinase activators, GLP-1 receptor agonists, GLP-2 receptor agonists, UCP modulators, RXR modulators, GSK-3 inhibitors, PPAR modulators, metformin, insulin, and α_2-adrenergic antagonists.

[0363] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be selected from the group consisting of GSK-3 inhibitors, retinoid X receptor agonists, Beta-3 AR agonists, UCP modulators, antidiabetic thiazolidinediones, non-glitazone type PPAR gamma agonists, dual PPAR gamma/PPAR alpha agonists, antidiabetic vanadium containing compounds and biguanides.

[0364] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be thiazolidinediones selected from the group consisting of (S)-((3,4-dihydro-2-(phenyl-methyl)-2H-1-benzopyran-6-yl)methyl-thiazolidine-2,4-dione, 5-{[4-(3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxo-propyl)-phenyl]-methyl}-thiazolidine-2,4-dione, 5-{[4-(1-methyl-cyclohexyl)methoxy)-phenyl]methyl]-thiazolidine-2,4-dione, 5-{[4-(2-(1-indolyl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione, 5-{4-[2-(5-methyl-2-phenyl-4-oxazoly)-ethoxy)]benzyl}-thiazolidine-2,4-dione, 5-(2-naphthylsulfonyl)-thiazolidine-2,4-dione, bis{4-[(2,4-dioxo-5-thiazolidinyl)-methyl]phenyl}methane, 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]-benzyl}- -thiazolidine-2,4-dione, 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-benzyl]-thiazolidine-2,4-dione, 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenylmethyl)-thiazolidine-2,4-dione, 5-[3-(4-chloro-phenyl])-2-- propynyl]-5-phenylsulfonyl)thiazolidine-2,4-dione, 5-[3-(4-chlorophenyl])-- 2-propynyl]-5-(4-fluorophenyl-sulfonyl)thiazolidine-2,4-dione,5-{[4-(2-(methyl-2-pyridinyl-amino)-ethoxy)phenyl]methyl}-thiazolidine-2,4-dione, 5-{[4-(2-(5-ethyl-2-pyridyl)ethoxy)phenyl]-methyl}-thiazolidine-2,4-dione, 5-{[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-methyl)-thiazolidine-2,4-dione, 5-[6-(2-fluoro-benzyloxy)-naphthalen-2-ylmethyl]-thiazolidine-2,4-dione, 5-([2-(2-naphthyl)-benzoxazol-5-yl]-methyl}thiazolidine-2,4-dione and 5-(2,4-dioxothiazolidin-5-

ylmethyl)-2-methoxy-N-(4-trifluoromethyl-benzyl)benzamide, including any pharmaceutically acceptable salts thereof.

[0365] In one variation, the one or more antidiabetic compounds administered in combination with the GK activators of the present invention includes metformin. In one particular variation, the metformin in this combination comprises one or more pharmaceutically acceptable salts thereof. In another particular variation, the metformin in this combination comprises a metformin HCl salt. In still another particular variation, the metformin in this combination is administered in a daily dose of between 125 and 2550 mg. In yet another variation, the metformin in this combination is administered in a daily dose of between 250 and 2550 mg.

[0366] In another variation, the one or more antidiabetic compounds administered in combination with the GK activators of the present invention includes one or more sulphonyl urea derivatives.

[0367] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be selected from the group consisting of glisoxepid, glyburide, glibenclamide, acetohexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, glimepiride and gliclazide, including any pharmaceutically acceptable salts thereof. In one variation, the one or more antidiabetic compounds administered in combination with the GK activators of the present invention includes glimepiride.

[0368] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be selected from the group consisting of incretin hormones or mimics thereof, beta-cell imidazoline receptor antagonists, and short-acting insulin secretagogues.

[0369] In another variation, the one or more antidiabetic compounds administered in combination with the GK activators of the present invention includes insulin.

[0370] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be one or more GLP-1 agonists including, for example, extendatide.

[0371] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be one or more GLP-2 agonists including, for example, human recombinant GLP-2.

[0372] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be one or more antidiabetic D-phenylalanine derivatives.

[0373] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be selected from the group consisting of repaglinide, mitiglinide, and nateglinide, including any pharmaceutically acceptable salts thereof. In one variation, the one or more antidiabetic compounds administered in combination with the GK activators of the present invention includes mitiglinide calcium salt hydrate.

[0374] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be one or more alpha-Glucosidase inhibitors.

[0375] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be selected from the group consisting of acarbose, voglibose and miglitol, including any pharmaceutically acceptable salts thereof. In one variation, the one or more antidiabetic compounds administered in combination with the GK activators of the present invention includes voglibose. In another variation, the voglibose in this combination is administered in a daily dose of between 0.1 and 1 mg.

[0376] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be rosiglitazone, including any pharmaceutically acceptable salts thereof. In one variation, the rosiglitazone in this combination comprises a rosiglitazone maleate salt.

[0377] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be tesaglitazar, muraglitazar or naveglitazar, including any pharmaceutically acceptable salts thereof.

[0378] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally be pioglitazone, including any pharmaceutically acceptable salts thereof. In one variation, the pioglitazone in this combination comprises a pioglitazone HCl salt. In another variation, the pioglitazone in this combination is administered in a daily dose of between 7.5 and 60 mg. In still another variation, the pioglitazone in this combination is administered in a daily dose of between 15 and 45 mg.

[0379] The one or more antidiabetic compounds administered in combination with the GK activators of the present invention may also optionally comprise metformin and pioglitazone. In one variation, the pioglitazone in this combination comprises one or more pharmaceutically acceptable salts thereof. In another variation, the pioglitazone in this combination comprises a pioglitazone HCl salt. In still another variation, the pioglitazone in this combination is administered in a daily dose of between 7.5 and 60 mg. In yet another variation, the pioglitazone in this combination is administered in a daily dose of between 15 and 45 mg. In another variation of each of the above variations, the metformin in this combination comprises one or more pharmaceutically acceptable salts thereof. In one particular variation, the metformin in this combination comprises a metformin HCl salt. In another particular variation, the metformin in this combination is administered in a daily dose of between 125 and 2550 mg. In still another variation, the metformin in this combination is administered in a daily dose of between 250 and 2550 mg.

[0380] In the case of combination therapy with compounds of the present invention, the other antidiabetic compound may be administered (*e.g.*, route and dosage form) in a manner known per se for such compound. Compounds of the present invention and the other antidiabetic compound may be administered sequentially (*i.e.*, at separate times) or at the same time, either one after the other separately in two separate dose forms or in one combined, single dose form. In one particular embodiment, the other antidiabetic compound is administered with compounds of the present invention as a single, combined dosage form. The dose of the antidiabetic compound may be selected from the range known to be clinically employed for such compound. Any of the therapeutic compounds of diabetic complications, antihyperlipemic compounds or antiobestic compounds can be used in combination with compounds of the present invention in the same manner as the above antidiabetic compounds.

EXAMPLES

Preparation of Glucokinase Activators

[0381] 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.

[0382] It will be readily recognized that certain compounds according to the present invention have atoms with linkages to other atoms that confer a particular stereochemistry to the compound (*e.g.*, chiral centers). It is recognized that synthesis of compounds according to the present invention may result in the creation of mixtures of different stereoisomers (*i.e.*, enantiomers and diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

[0383] Various methods for separating mixtures of different stereoisomers are known in the art. For example, a racemic mixture of a compound may be reacted with an optically active resolving agent to form a pair of diastereoisomeric compounds. The diastereomers may then be separated in order to recover the optically pure enantiomers. Dissociable complexes may also be used to resolve enantiomers (*e.g.*, crystalline diastereoisomeric salts). Diastereomers typically have sufficiently distinct physical properties (*e.g.*, melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. For example, diastereomers can typically be separated by chromatography or by separation/resolution techniques based upon differences in solubility. A more detailed description of techniques that can be used to resolve stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

[0384] 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.

[0385] 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).

[0386] 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.

[0387] 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.

[0388] 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).

[0389] 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.

[0390] 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.

[0391] Compounds according to the present invention can also be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of

enantiomers can be carried out using covalent diastereomeric derivatives of compounds, dissociable complexes are preferred (*e.g.*, crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (*e.g.*, melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

[0392] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or thee-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

µL (microliters)	Ac (acetyl)
atm (atmosphere)	ATP (Adenosine Triphophatase)
BOC (tert-butyloxycarbonyl)	BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride)
BSA (Bovine Serum Albumin)	CBZ (benzyloxycarbonyl)
CDI (1,1-carbonyldiimidazole)	DCC (dicyclohexylcarbodiimide)
DCE (dichloroethane)	DCM (dichloromethane)
DMAP (4-dimethylaminopyridine)	DME (1,2-dimethoxyethane)
DMF (N,N-dimethylformamide)	DMPU (N,N'-dimethylpropyleneurea)
DMSO (dimethylsulfoxide)	EDCI (ethylcarbodiimide hydrochloride)
EDTA (Ethylenediaminetetraacetic acid)	Et (ethyl)
Et_2O (diethyl ether)	EtOAc (ethyl acetate)
FMOC (9-fluorenylmethoxycarbonyl)	g (grams)
h (hours)	HOAc or AcOH (acetic acid)
HOBT (1-hydroxybenzotriazole)	HOSu (N-hydroxysuccinimide)
HPLC (high pressure liquid chromatography)	Hz (Hertz)
i.v. (intravenous)	IBCF (isobutyl chloroformate)

i-PrOH (isopropanol)	L (liters)
M (molar)	mCPBA (meta-chloroperbenzoic acid)
Me (methyl)	MeOH (methanol)
mg (milligrams)	MHz (megahertz)
min (minutes)	mL (milliliters)
mM (millimolar)	mmol (millimoles)
mol (moles)	MOPS (Morpholinepropanesulfonic acid)
mp (melting point)	NaOAc (sodium acetate)
OMe (methoxy)	psi (pounds per square inch)
RP (reverse phase)	RT (ambient temperature)
SPA (Scintillation Proximity Assay)	TBAF (tetra-n-butylammonium fluoride)
TBS (t-butyldimethylsilyl)	tBu (tert-butyl)
TEA (triethylamine)	TFA (trifluoroacetic acid)
TFAA (trifluoroacetic anhydride)	THF (tetrahydrofuran)
TIPS (triisopropylsilyl)	TLC (thin layer chromatography)
TMS (trimethylsilyl)	TMSE (2-(trimethylsilyl)ethyl)
Tr (retention time)	

[0393] All references to ether or Et_2O are to diethyl ether; and brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at RT unless otherwise noted.

[0394] ^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).

[0395] 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).

[0396] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as the Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), or may be prepared by methods well known to a person of ordinary skill in the art, following procedures described in such standard references as Fieser and Fieser's *Reagents for Organic Synthesis*, vols. 1-17, John

Wiley and Sons, New York, NY, 1991; *Rodd's Chemistry of Carbon Compounds*, vols. 1-5 and supps., Elsevier Science Publishers, 1989; Organic Reactions, vols. 1-40, John Wiley and Sons, New York, NY, 1991; March J.: *Advanced Organic Chemistry*, 4th ed., John Wiley and Sons, New York, NY; and Larock: *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989.

[0397] The entire disclosures of all documents cited throughout this application are incorporated herein by reference.

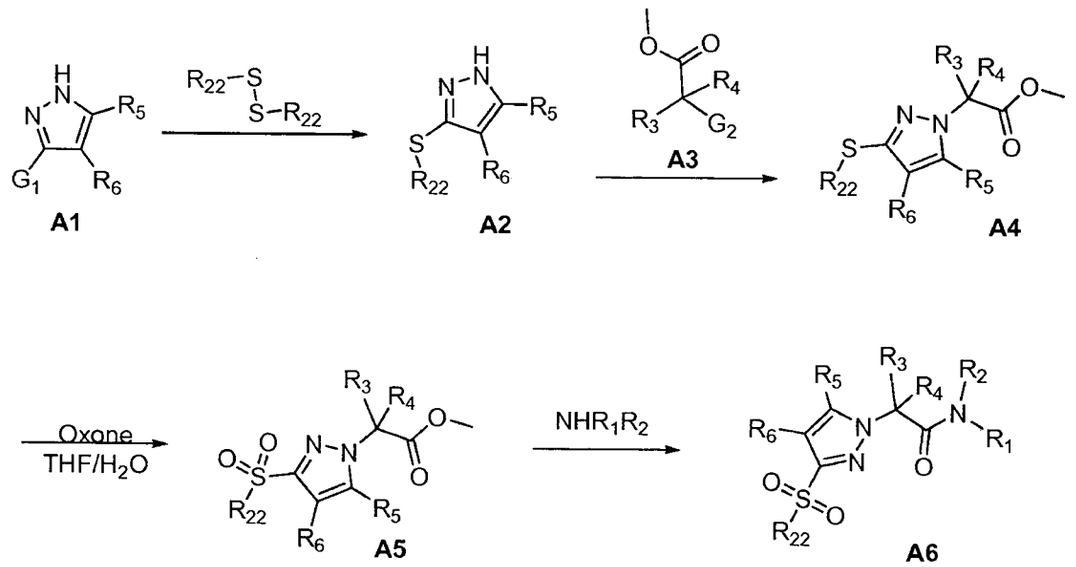
Synthetic Schemes for Compounds of the Present Invention

[0398] Compounds according to the present invention may be synthesized according to the reaction schemes shown below. Other reaction schemes could be readily devised by those skilled in the art. It should also be appreciated that a variety of different solvents, temperatures and other reaction conditions can be varied to optimize the yields of the reactions.

[0399] 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.

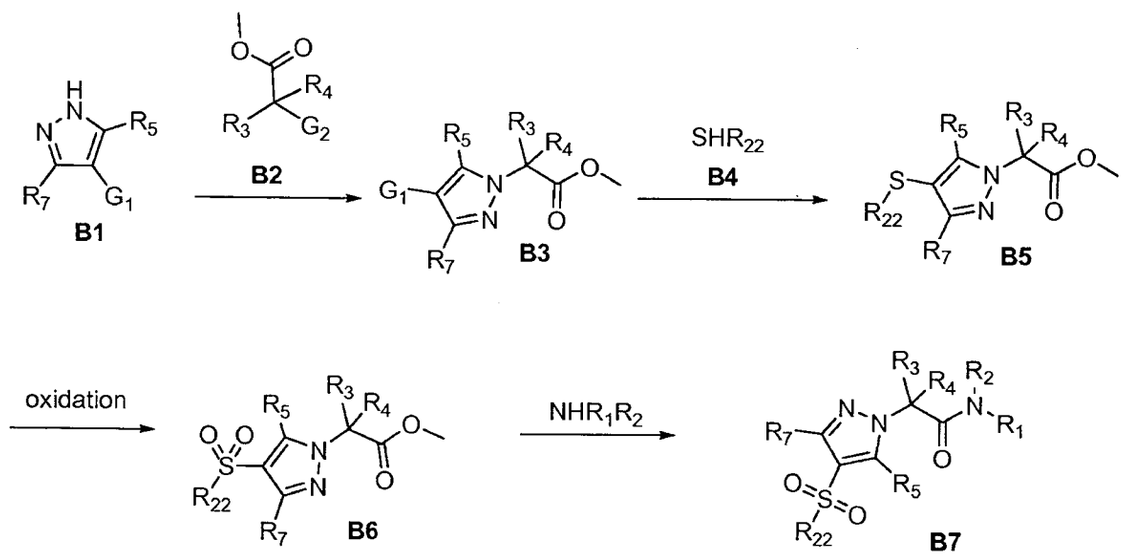
[0400] General synthetic routes for producing compounds of the present invention are shown below.

Scheme A



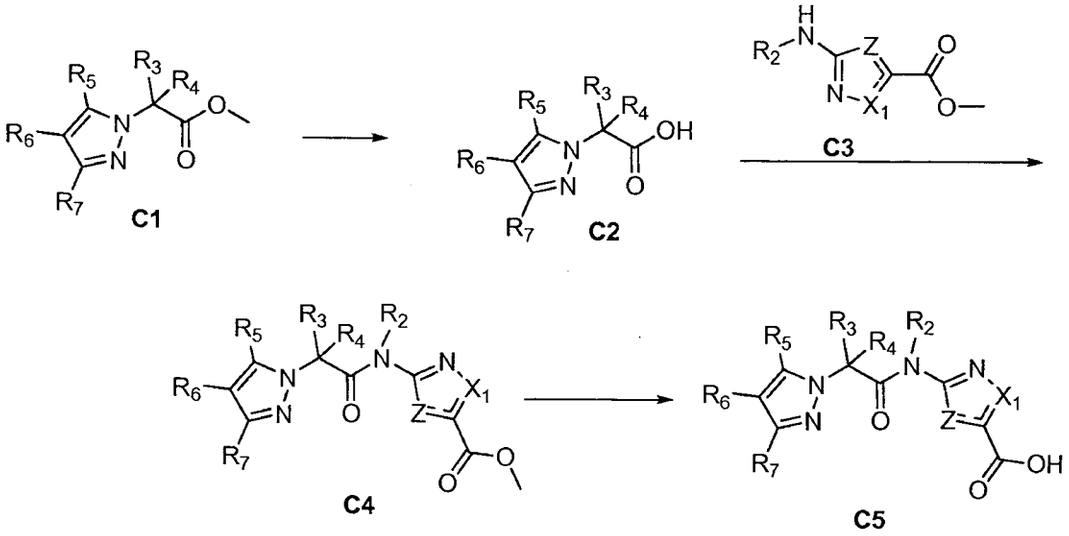
[0401] Referring to **Scheme A**, a halo-pyrazole (A1, wherein G_1 is a leaving group (*e.g.*, halo such as bromo)) and a disulfide are treated with NiBr and Zn in the presence of 2,2'-bipyridine to give intermediates A2. Subsequent treatment of A2 with base and reagent A3 (wherein G_2 is a leaving group (*e.g.*, halo such as bromo)) affords intermediates A4. Oxidation of the sulfur functionality of A4 with Oxone® gives analogs A5 which are then treated with various amine containing molecules to afford amides A6.

Scheme B



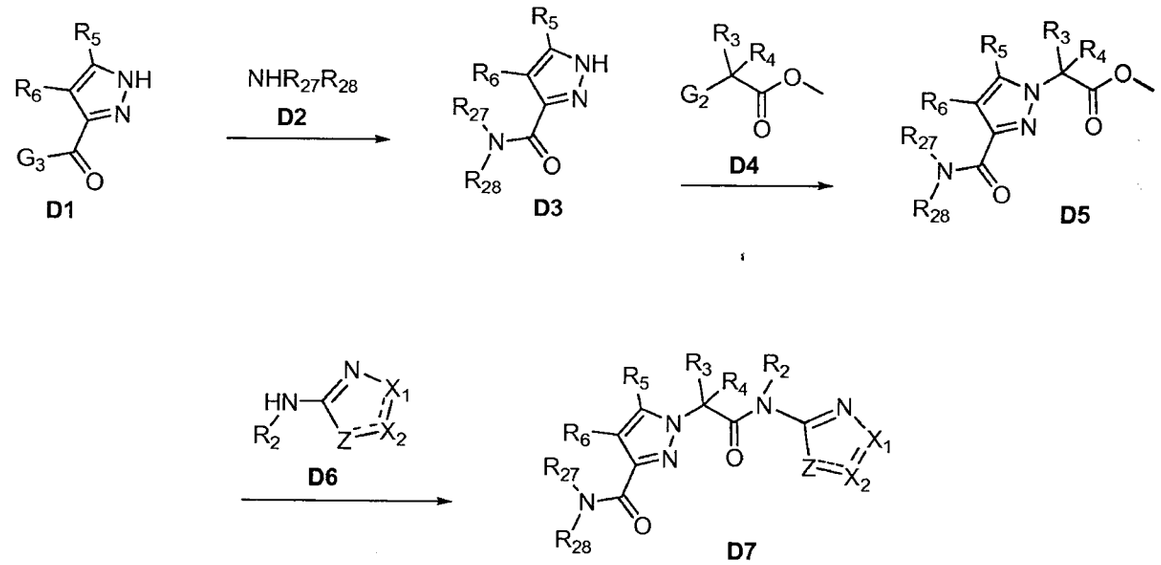
[0402] Referring to **Scheme B**, a halo-pyrazole (B1, wherein G_1 is a leaving group (*e.g.*, halo such as bromo)) is treated with base and reagent B2 (wherein G_2 is a leaving group (*e.g.*, halo such as bromo)) to afford intermediates B3. Subsequent treatment of this material with various mercaptans in the presence of tris(dibenzylacetone)dipalladium and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene affords B5. Oxidation of the sulfur functionality of B5 gives analogs B6 which are then treated with various amine containing molecules to give amides B7.

Scheme C



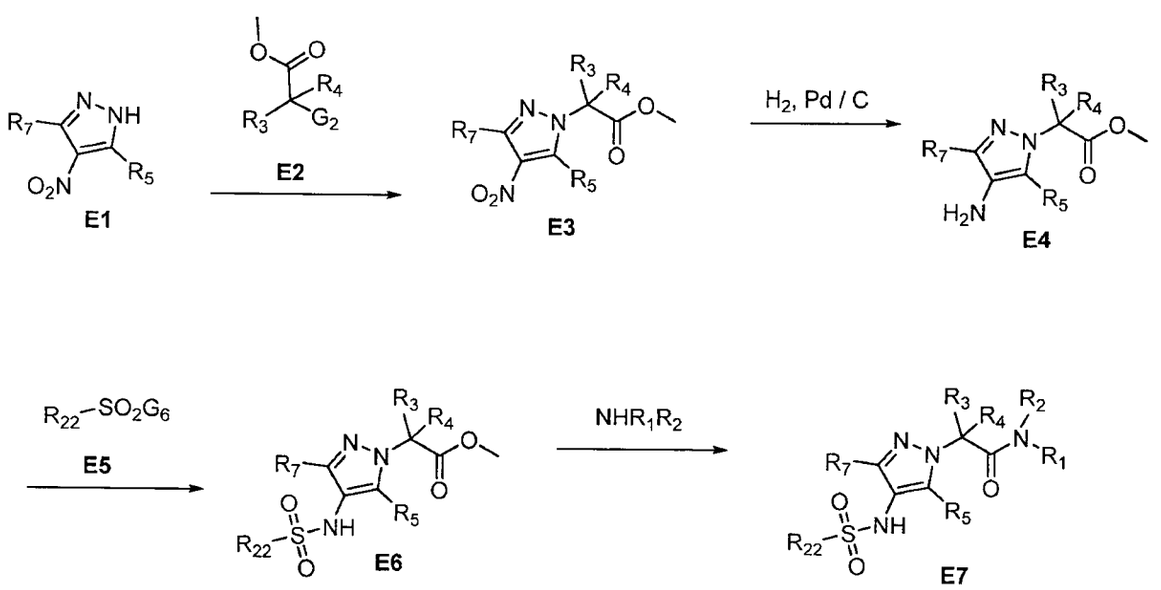
[0403] Referring to **Scheme C**, ester C1 which can be generated, for example, according to Scheme B is saponified to the acid C2 and coupled with an amino heterocycle C3 to obtain the intermediate C4. This intermediate on saponification gives the target compound C5.

Scheme D



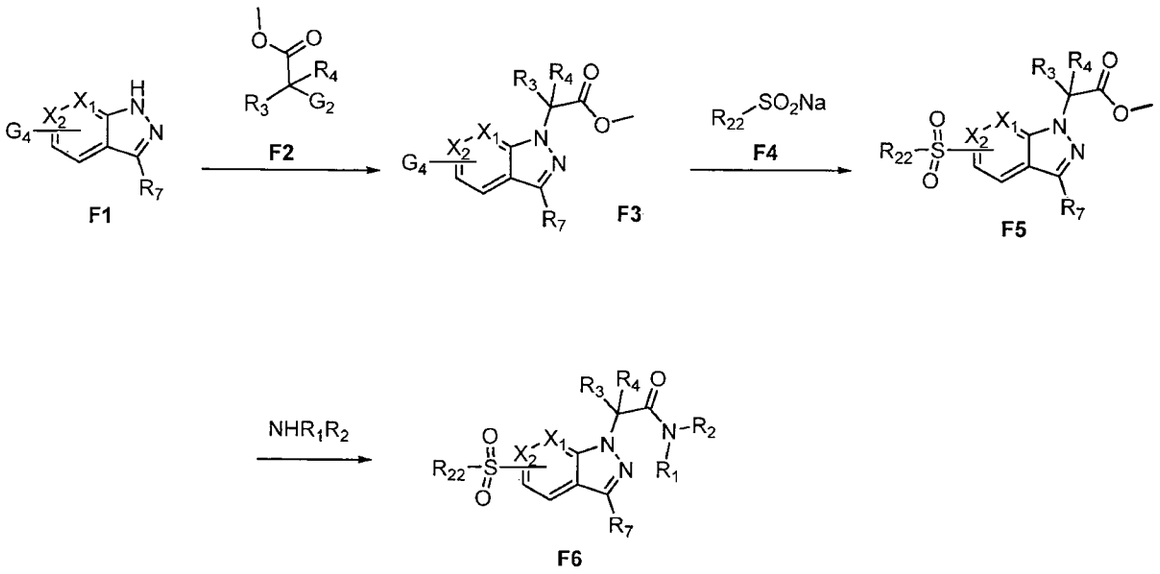
[0404] Referring to **Scheme D**, intermediate D3 can be obtained by treatment of a substituted pyrazole-3-carbonyl chloride (D1, wherein G_3 is a leaving group (*e.g.*, halo such as chloro)) with an amine D2 in the presence of a base. Alkylation followed by coupling with the amino heterocycle D6 can be done using an analogous procedure as in Scheme A to obtain the target compound D7.

Scheme E



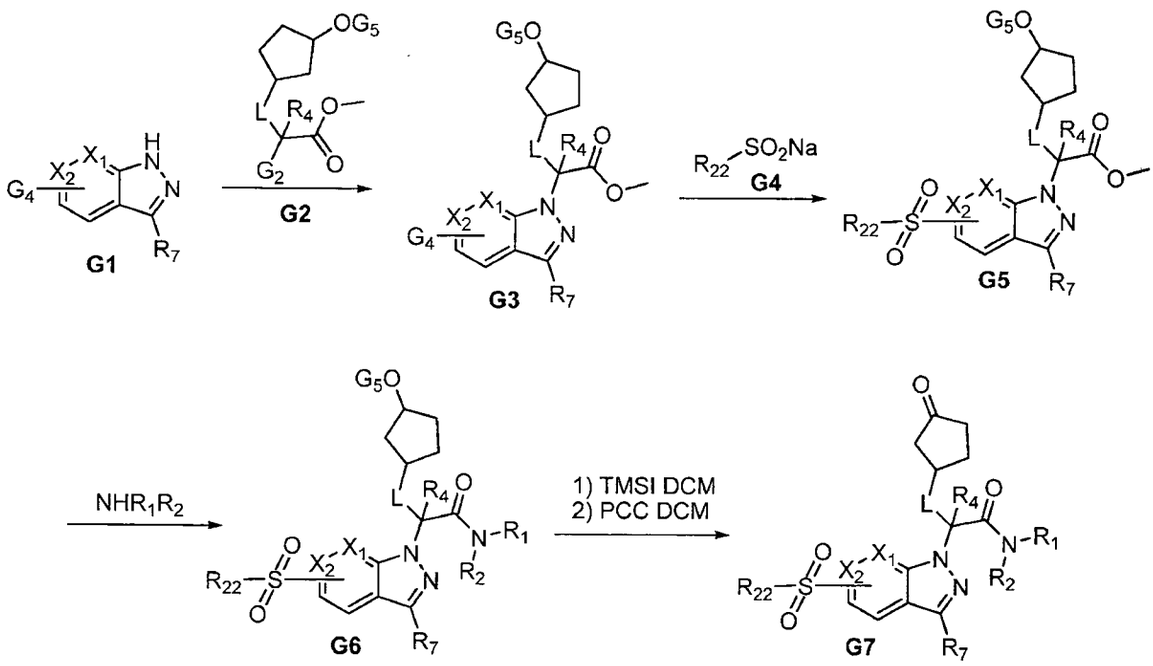
[0405] Referring to **Scheme E**, a nitro pyrazole E1 is treated with a base and reagent E2 (wherein G_2 is a leaving group (*e.g.*, halo such as bromo)) to afford intermediate E3. Reduction of the nitro group followed by treatment with an electrophile E5 (wherein G_6 is a leaving group (*e.g.*, halo such as chloro)) in the presence of a base gives the intermediate E6. Coupling with an amine gives the target compound E7.

Scheme F



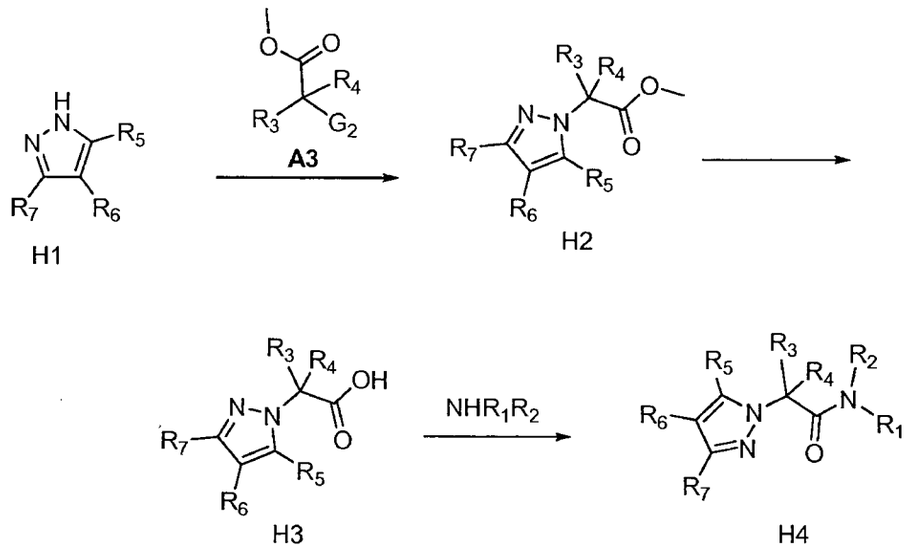
[0406] Referring to **Scheme F**, a substituted indazole (F1, wherein G_4 is a leaving group (*e.g.*, halo such as bromo)) is treated with reagent F2 (wherein G_2 is a leaving group (*e.g.*, halo such as bromo)) in the presence of a base to obtain a mixture of N-1 and N-2 alkylated products F3 which can be separated by flash column chromatography. Introduction of the sulfone group can be achieved by coupling in the presence of Pd or Cu to obtain intermediate F5, which is then treated with an amine to obtain the desired target F6.

Scheme G



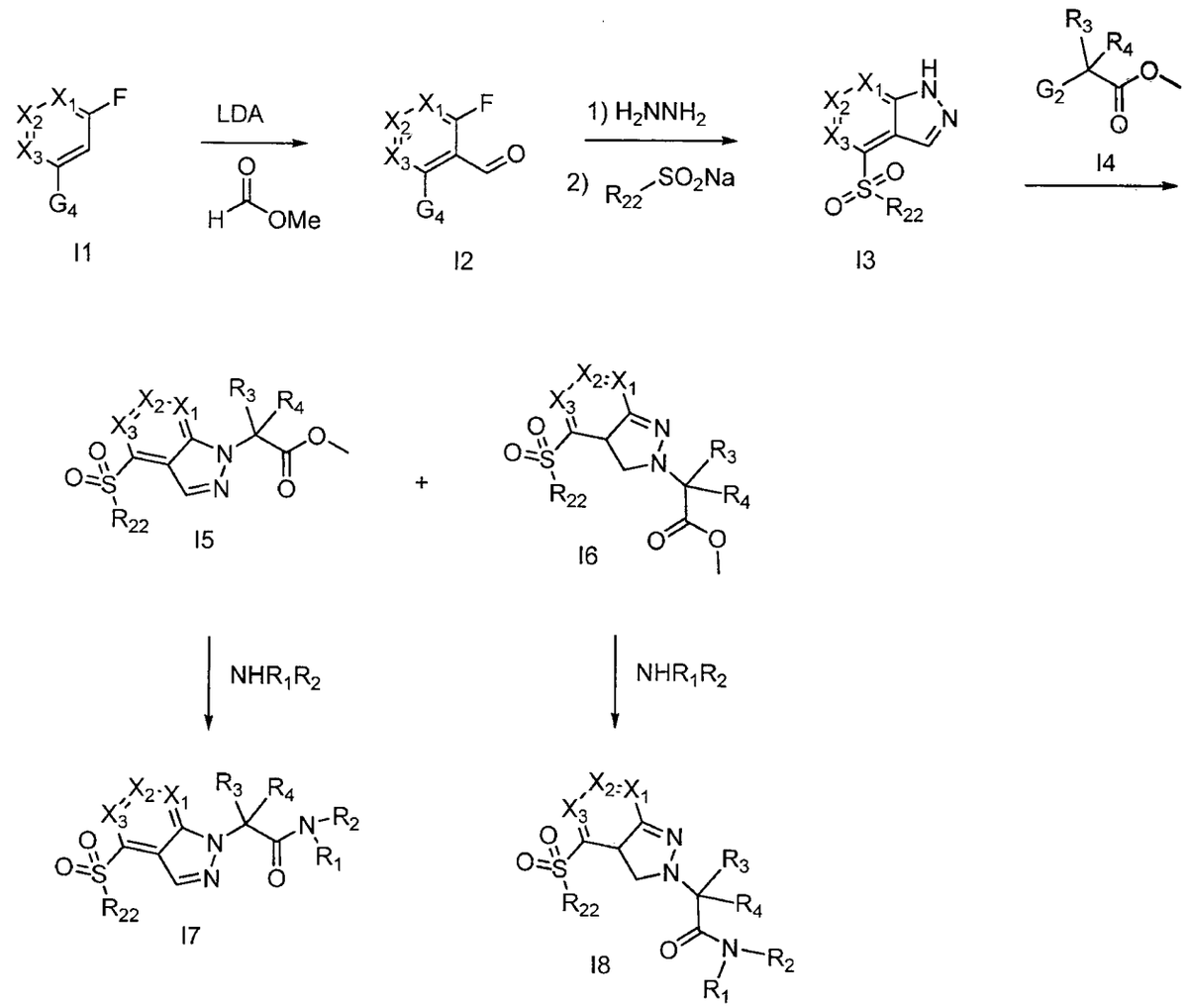
[0407] Referring to **Scheme G**, a substituted indazole (G1, wherein G_4 is a leaving group (*e.g.*, halo such as bromo)) is treated with an alkyl halide (G2, wherein G_2 is a leaving group (*e.g.*, halo such as bromo) and G_5 is a protecting group (*e.g.*, benzyl)) in the presence of a base to obtain a mixture of N-1 and N-2 alkylated products (G3) which can be separated by flash column chromatography. Introduction of the sulfone group can be achieved by coupling in the presence of Pd or Cu to obtain intermediate G5 which is then treated with an amine to obtain the intermediate (G6). Deprotection of the benzyl group followed by oxidation of the alcohol gives the desired target (G7).

Scheme H



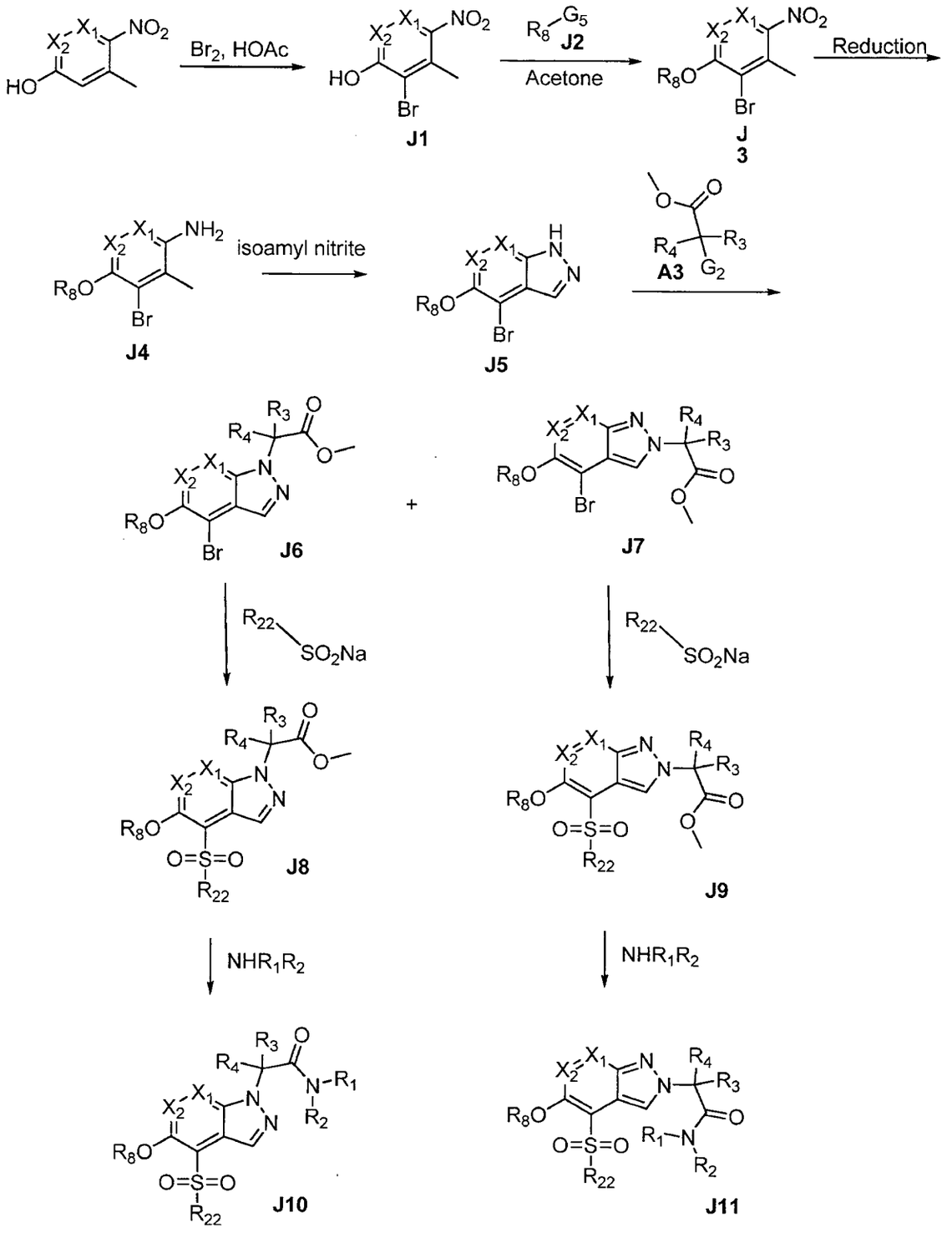
[0408] Referring to **Scheme H**, a substituted pyrazole H1, is treated with reagent A3 (wherein G_2 is a leaving group (*e.g.*, halo such as bromo)) in the presence of a base to obtain a mixture of alkylated products H2 which can be separated by column chromatography. Hydrolysis of the ester to H3, followed by coupling with an amine gives the target compound H4

Scheme I



[0409] Referring to **Scheme I**, ortho lithiation of I1, wherein G_4 is a leaving group (*e.g.*, halo such as fluoro), followed by introduction of the aldehyde ortho to the fluoride gives I2. Treatment with hydrazine gives the hydrazone which cyclizes to an intermediate indazole on heating. Introduction of the sulfone group can be achieved either by displacement with a sulfinate or by coupling in the presence of Pd or Cu to obtain intermediate I3. The indazole I3 is treated with reagent I4 (wherein G_2 is a leaving group (*e.g.*, halo such as bromo)) in the presence of a base to obtain a mixture of N-1 and N-2 alkylated products I5 and I6, which can be separated by flash column chromatography. Treatment of I5 and/or I6 with an amine gives the desired targets I7 and I8, respectively.

Scheme J



[0410] Referring to Scheme J, bromination of 3-methyl-4-nitrophenol gives a mixture of regioisomers which can be separated by column chromatography. Treatment of J1 with an

alkyl halide (J2, wherein G5 is a leaving group (e.g., halo such as bromine)) in the presence of a base gives J3. Reduction of the nitro group yields J4 which can then be treated with isoamyl nitrite in the presence of a base to obtain the substituted indazole J5. The substituted indazole J5 is treated with reagent A3 (wherein G_2 is a leaving group (*e.g.*, halo such as bromo)) in the presence of a base to obtain a mixture of N-1 and N-2 alkylated products J6 and J7, which can be separated by flash column chromatography. Introduction of a sulfone group on J6 and/or J7 can be achieved by coupling in the presence of Pd or Cu to obtain intermediates J8 and J9, respectively. J8 and/or J9 can then be treated with an amine to obtain J10 and J11, respectively.

[0411] Chiral components can be separated and purified using any of a variety of techniques known to those skilled in the art. For example, chiral components can be purified using supercritical fluid chromatography (SFC). In one particular variation, chiral analytical SFC/MS analyses are conducted using a Berger analytical SFC system (AutoChem, Newark, DE) which consists of a Berger SFC dual pump fluid control module with a Berger FCM 1100/1200 supercritical fluid pump and FCM 1200 modifier fluid pump, a Berger TCM 2000 oven, and an Alcott 718 autosampler. The integrated system can be controlled by BI-SFC Chemstation software version 3.4. Detection can be accomplished with a Waters ZQ 2000 detector operated in positive mode with an ESI interface and a scan range from 200-800 Da with 0.5 second per scan. Chromatographic separations can be performed on a ChiralPak AD-H, ChiralPak AS-H, ChiralCel OD-H, or ChiralCel OJ-H column (5μ, 4.6 x 250 mm; Chiral Technologies, Inc. West Chester, PA) with 10 to 40% methanol as the modifier and with or without ammonium acetate (10 mM). Any of a variety of flow rates can be utilized including, for example, 1.5 or 3.5 mL/min with an inlet pressure set at 100 bar. Additionally, a variety of sample injection conditions can be used including, for example, sample injections of either 5 or 10μL in methanol at 0.1 mg/mL in concentration.

[0412] In another variation, preparative chiral separations are performed using a Berger MultiGram II SFC purification system. For example, samples can be loaded onto a ChiralPak AD column (21 x 250 mm, 10 μ). In particular variations, the flow rate for separation can be 70 mL/min, the injection volume up to 2 mL, and the inlet pressure set at 130 bar. Stacked injections can be applied to increase the efficiency.

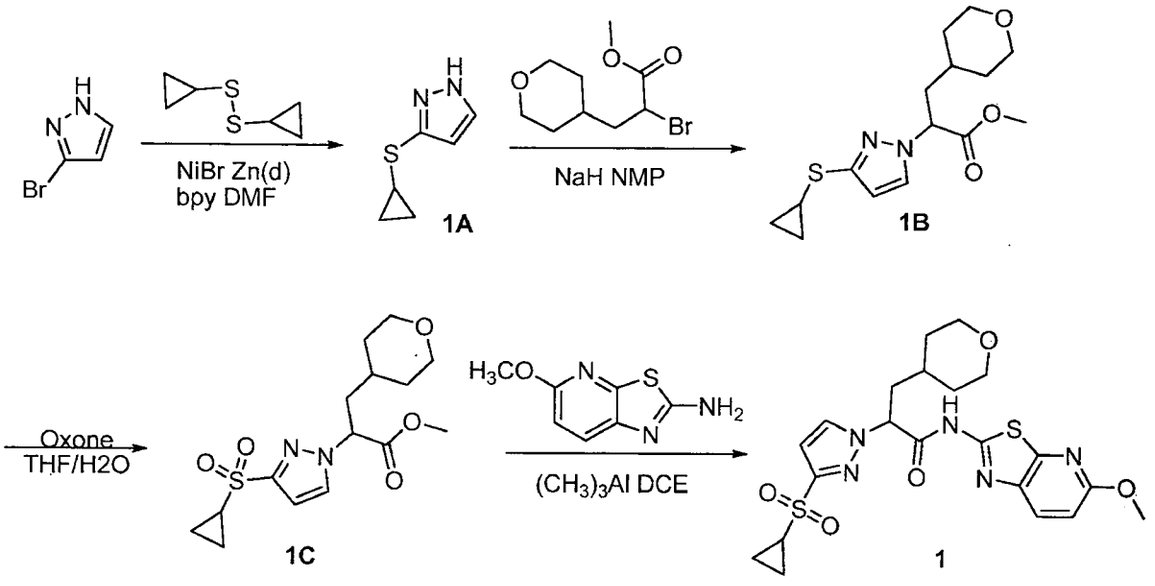
[0413] In each of the above reaction procedures or schemes, the various substituents may be selected from among the various substituents otherwise taught herein.

[0414] Descriptions of the syntheses of particular compounds according to the present invention based on the above reaction schemes are set forth herein.

Examples of Glucokinase Activators

[0415] The present invention is further exemplified, but not limited by, the following examples that describe the synthesis of particular compounds according to the invention.

Compound 1: 2-(3-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide



[0416] 3-bromo-1H-pyrazole (1.0 g, 6.8 mmole), NiBr (0.148 g, 0.68 mmole), 2,2'-bipyridine (0.106 g, 0.68 mmole), Zinc dust (0.993 g, 13.6 mmole) and 1,2-dicyclopropyldisulfane (0.993 g, 6.8 mmole) were added to a solution of DMF (20 mL) and the mixture was heated under N_2 for 18 h at 80 °C. The solvent was removed from the crude reaction mixture under vacuum and the orange gum was treated with MeOH. The resulting ppt was filtered and discarded. Purification of the filtrate with preparative scale HPLC afforded compound **1A** as light brown oil (367 mg). [M+H] calc'd for $C_6H_9N_2S$, 141.04; found 141.0. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.73 (q, *J*=5.05 Hz,

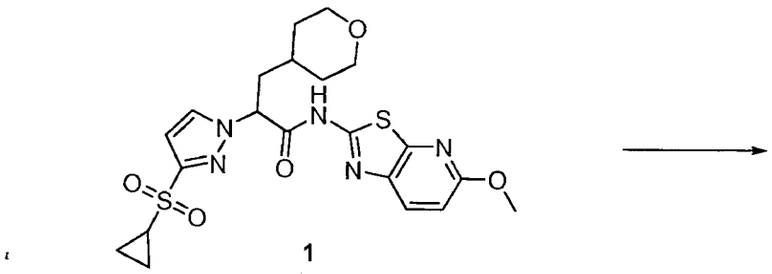
2 H) 1.02 - 1.17 (m, 2 H) 2.26 (ddd, *J*=7.58, 3.66, 3.41 Hz, 1 H) 6.48 (br. s., 1 H) 7.82 (br. s., 1 H).

[0417] 3-(cyclopropylthio)-1H-pyrazole (**1A**) (0.083 g, 0.6 mmole) was dissolved in NMP (2 mL) and the solution was chilled to 0 °C. NaH (0.060 g, 1.8 mmole) was added and when the reaction subsided methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate (0.060 g, 1.8 mmole) was introduced, and the reaction was heated at 80 °C for 1 h. The reaction was cooled and quenched with a small volume of MeOH and the crude mixture was purified using preparative scale HPLC. Compound **1B** as well as a small amount of the carboxylic acid of **1B** were collected. Removal of the solvent and treatment of the acid with $TMSCH_2N_2$ followed by combination with **1B** afforded title compound as oil (81mg). [M+H] calc'd for $C_{15}H_{23}N_2O_3S$ (**1B** ester), 311.14; found 311.0; [M+H] calc'd for $C_{14}H_{21}N_2O_3S$ (**1B** acid), 297.12; found 297.0.

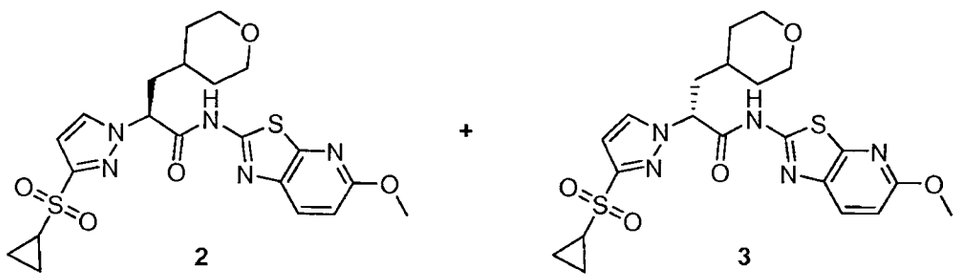
[0418] Compound **1B** used directly from the preceding step was treated with Oxone® (0.147 g, 0.24 mmole) in a 1:1 solution of THF/H_2O (10 mL). After oxidation was judged complete the solvent was removed and the residue was portioned between EtOAc and H_2O. The organic layer was separated, dried and concentrated to yield crude compound **1C** as oil. This material was purified using preparative scale HPLC and used directly in the next step, [M+H] calc'd for $C_{15}H_{23}N_2O_5S$, 343.12; found 343.3.

[0419] 5-Methoxythiazolo[5,4-b]pyridin-2-amine (0.048 g, 0.26 mmole) was added to a microwave vial followed by DCE (2 mL). The reaction mixture was cooled to 0°C under a N_2 atmosphere. Trimethyl aluminum (2M in hexanes) (0.13 mL, 0.26 mmole) was added and when the reaction subsided the cooling bath was removed, the solution was then stirred at RT for 15 min. To this was added a solution of methyl 2-(3-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanoate **1C** (0.015 g, 0.04 mmole) in DCE (2mL) and the reaction mixture was heated in a microwave at 110°C for 1h. The reaction was then quenched with 1N HCl and extracted 2x with DCM. The organic layers were pooled, dried over Na_2SO_4; the solvent was removed and the crude residue was purified by preparative scale HPLC to afford compound **1** (46mg). [M+H] calc'd for $C_{21}H_{26}N_5O_5S_2$, 492.13; found 492.0. ^{1}H NMR (400 MHz, MeOD) d ppm 1.07 (dd, *J*=7.96, 2.15 Hz, 2 H) 1.18 - 1.42 (m, 6 H) 1.52 (d, *J*=9.35 Hz, 1 H) 1.74 (d, *J*=2.02 Hz, 1 H) 2.14 (t, *J*=6.32 Hz, 1 H) 2.32 (t, *J*=10.48 Hz, 1 H) 2.61 - 2.80 (m, 1 H) 3.29 (m, 1 H, under MeOD signal) 3.79 - 3.98 (m, 5 H) 5.50 (ddd, *J*=10.80, 5.68, 5.49 Hz, 1 H) 6.81 - 6.90 (m, 2 H) 7.94 (d, *J*=8.84 Hz, 1 H) 8.10 (d, *J*=2.53 Hz, 1 H)

Compounds 2 and 3: (*S*)-2-(3-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide and (*R*)-2-(3-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide



1



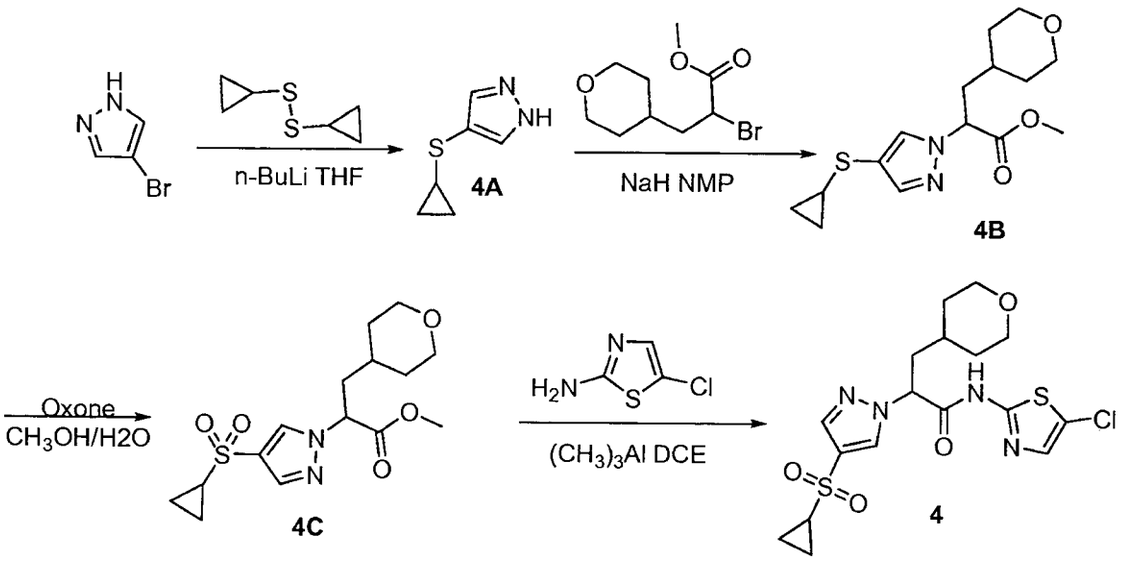
2 + 3

[0420] Compound 1 was subjected to chiral separation on a Berger SFC instrument. For this particular compound, it was found that using Chiralpak AD-H media eluting with 16% MeOH to afford **Compounds 2** and **3** was optimal.

[0421] Compound2: [M+H] calc'd for $C_{21}H_{26}N_5O_5S_2$, 492.13; found 492.0. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.07 (dd, *J*=7.96, 2.15 Hz, 2 H) 1.18 - 1.42 (m, 6 H) 1.52 (d, *J*=9.35 Hz, 1 H) 1.74 (d, *J*=2.02 Hz, 1 H) 2.14 (t, *J*=6.32 Hz, 1 H) 2.32 (t, *J*=10.48 Hz, 1 H) 2.61 - 2.80 (m, 1 H) 3.29 (m, 1 H, under MeOD signal) 3.79 - 3.98 (m, 5 H) 5.50 (ddd, *J*=10.80, 5.68, 5.49 Hz, 1 H) 6.81 - 6.90 (m, 2 H) 7.94 (d, *J*=8.84 Hz, 1 H) 8.10 (d, *J*=2.53 Hz, 1 H)

[0422] Compound 3: [M+H] calc'd for $C_{21}H_{26}N_5O_5S_2$, 492.13; found 492.0. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.07 (dd, *J*=7.96, 2.15 Hz, 2 H) 1.18 - 1.42 (m, 6 H) 1.52 (d, *J*=9.35 Hz, 1 H) 1.74 (d, *J*=2.02 Hz, 1 H) 2.14 (t, *J*=6.32 Hz, 1 H) 2.32 (t, *J*=10.48 Hz, 1 H) 2.61 - 2.80 (m, 1 H) 3.29 (m, 1 H, under MeOD signal) 3.79 - 3.98 (m, 5 H) 5.50 (ddd, *J*=10.80, 5.68, 5.49 Hz, 1 H) 6.81 - 6.90 (m, 2 H) 7.94 (d, *J*=8.84 Hz, 1 H) 8.10 (d, *J*=2.53 Hz, 1 H)

Compound 4: N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide



[0423] 4-bromo-1H-pyrazole (4.0 g, 26.9 mmole) was dissolved in THF (100 mL) and chilled to 0 °C. 1.6 M n-BuLi in THF was added and the reaction mixture was stirred for 1 h at RT The reaction was then cooled to 0 °C and 1,2-dicyclopropyldisulfane (3.9 g, 26.9 mmole) was added; the reaction was stirred for 1h at 0 °C and quenched with sat NH4Cl and extracted with EtOAc. The crude product was obtained as an oil and used directly in the next step. [M+H] calc'd for $C_6H_9N_2S$, 141.04; found 141.9.

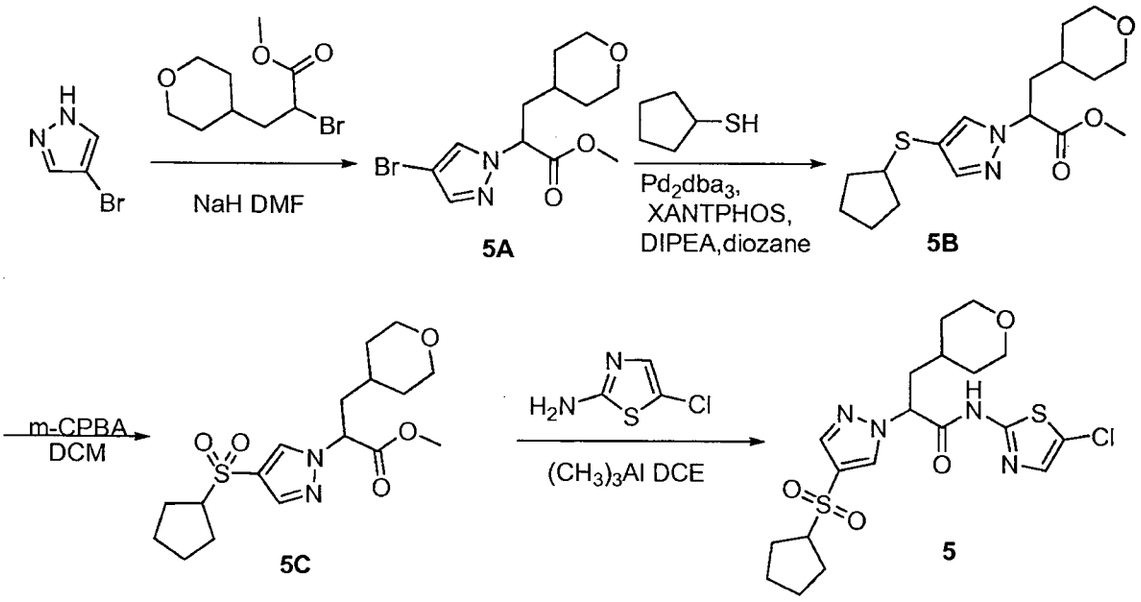
[0424] 4-(cyclopropylthio)-1H-pyrazole (**4A**) (1.0 g, 7.14 mmole) was dissolved in NMP (5 mL) and the solution was chilled to 0 °C. NaH (0.263 g, 7.9 mmole) was added and when the reaction subsided methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate (1.1 g, 7.9 mmole) was introduced, and the reaction was heated at 80 °C for 1 h. The reaction was cooled and quenched with a small volume of MeOH and the crude mixture was purified using preparative scale HPLC. Compound **4B** as well as a small amount of the carboxylic acid of **4B** were collected. Removal of the solvent and treatment of the acid with $TMSCH_2N_2$ followed by combination with **4B** afforded title compound as oil (0.68 g). [M+H] calc'd for $C_{15}H_{23}N_2O_3S$ (**4B** ester), 311.14; found 311.2; [M+H] calc'd for $C_{14}H_{21}N_2O_3S$ (**4B** acid), 297.12; found 297.1.

[0425] Compound **4B** (0.68 g, 1.9 mmole) was treated with Oxone® (2.4 g, 3.8 mmole) in a 1:1 solution of MeOH/H_2O (20 mL). After oxidation was judged complete the solvent

was removed and the residue was portioned between EtOAc and H_2O. The organic layer was separated, dried and concentrated to yield crude compound **4C** as oil (0.729 g). This material was purified using preparative scale HPLC and used directly in the next step, [M+H] calc'd for $C_{15}H_{23}N_2O_5S$, 343.12; found 343.0.

[0426] 5-chlorothiazol-2-amine (0.519 g, 3.03 mmole) was added to a microwave vial followed by DCE (3 mL). The reaction mixture was cooled to 0°C under a N_2 atmosphere. Trimethyl aluminum (2M in hexanes) (2.6 mmole) was added and when the reaction subsided the cooling bath was removed, the solution was then stirred at RT for 15 min. To this was added a solution of methyl 2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanoate **4C** (0.173 g, 0.51 mmole) in DCE (2mL) and the reaction mixture was heated in a microwave at 110°C for 1h. The reaction was then quenched with 1N HCl and extracted 2x with DCM. The organic layers were pooled, dried over Na_2SO_4 and the solvent was removed. This crude residue was purified by preparative scale HPLC to afford compound **4** (0.21g). [M+H] calc'd for $C_{17}H2_2ClN_4O_4S_2$, 445.07; found 445.2. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.93 - 1.75 (m, 9 H) 2.19 (br. s., 2 H) 2.55 (br. s., 1 H) 3.31 (br. s., 2 H) 3.94 (br. s., 2 H) 5.10 (br. s., 1 H) 7.32 (s, 1 H) 8.01 (d, *J*=9.35 Hz, 2 H) 10.35 (bs, 1 H)

Compound 5: N-(5-chlorothiazol-2-yl)-2-(4-(cyclopentylsulfonyl)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide



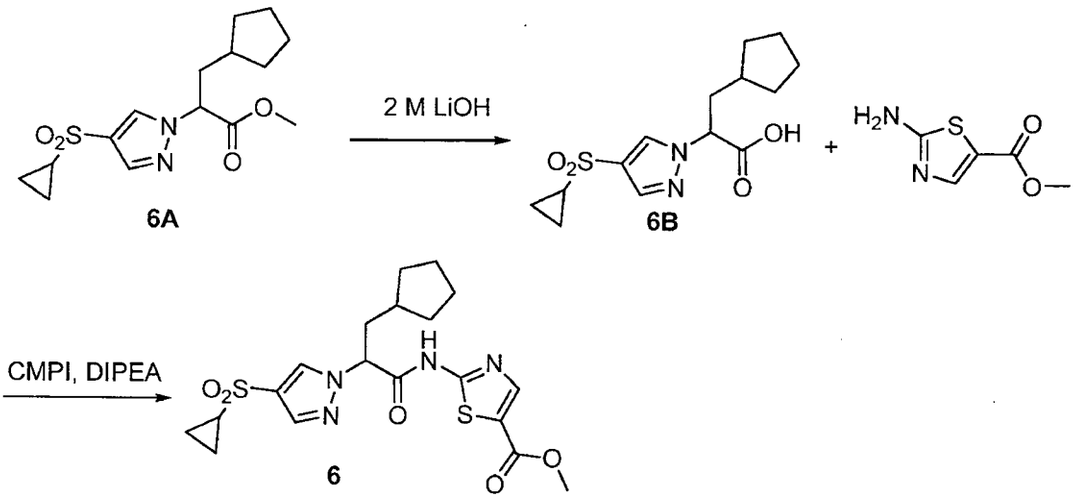
[0427] Sodium hydride (63 mg, 2.47 mmol) was suspend in DMF (5 ml), and was cooled to 0°C. A solution of 4-bromo-1H-pyrazole (300 mg, 2.06 mmole) in DMF(5 mL) was added dropwise. After stirring for 20 min at 0°C, methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate (620 mg, 2.47 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched with sat. ammonium chloride and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, concentrated by high vacuum to yield crude compound **5A** (492 mg). [M+H] calc'd for $C_{12}H_{17}BrN_2O_3$ 318.18; found 318.

[0428] Compound **5A** (492 mg, 1.56 mmol) was dissolved in dioxane (5 ml). Cyclopentylmercaptan (159 mg, 1.56 mmol) was added, followed by diisopropylethylamine (0.54 ml, 3.12 mmol) tris(dibenzylacetone)dipalladium (71 mg, 0.078 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (90 mg, 0.156 mmol). The reaction mixture was heated at 100°C in sealed vial over night. After cooling to room temperature, the solution was poured to water, extracted with ethyl acetate, washed with water, dried over $MgSO_4$, concentrated by high vacuum to crude compound **5B** (695 mg). [M+H] calc'd for $C_{17}H_{26}N_2O_3S$ 339.46; found 339.

[0429] Compound **5B** (695 mg, 2.06 mmol) was dissolved in dichloromethane (20 ml) and cooled to 0°C. m-chloroperoxybenzoic acid (1.84 g, 8.22 mmol) was added. After stirring 3 hours at room temperature, the reaction solution was diluted with dichloromethane, washed with 1 N NaOH, water, dried over $MgSO_4$, concentrated by vacuum to afford crude compound **5C** (593 mg). [M+H] calc'd for $C_{17}H_{26}N_2O_5S$ 371.46; found 371.

[0430] Compound **5** was synthesized according to the procedure described in connection with **Compound 4.** [M+H] calc'd for $C_{19}H_{25}FN_4O_4S_2$ 457.56.01; found 457. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.34 (m, 3H) 1.50 (m, 1H) 1.65 (m, 3H) 1.77 (m, 2H) 2.02 (m, 4H) 2.16 (m, 1H), 2.24 (m, 1H) 3.29 (m, 2H) 3.50 (m, 1H) 3.94 (t, J = 16, 16 Hz, 2H) 5.13 (m, 1H) 7.08 (d, J = 4 Hz, 1H) 7.98 (s, 1H) 8.06 (s, 1H)

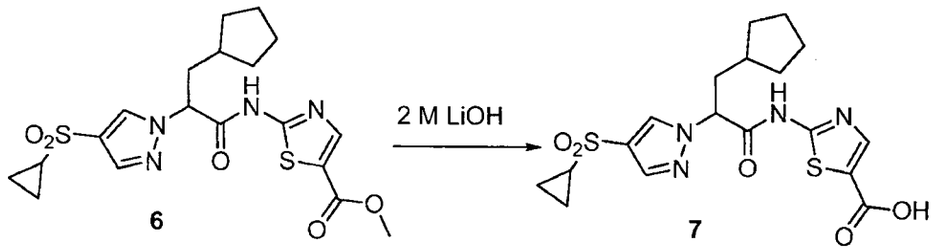
Compound 6: Methyl 2-(3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)propanamido)thiazole-5-carboxylate



[0431] Compound **6A** (1.663 g, 5.1 mmol), which was generated according to the procedure described in connection with **Compound 1**, was dissolved in dioxane (15 ml). 2 M LiOH (5.1 ml, 10.2 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction solution was concentrated, poured to water, acidified with 20% HCl, extracted with ethyl acetate, dried over Na_2SO_4, concentrated by vacuum to crude compound **6B** (1.494 g). [M+H] calc'd for $C_{14}H_{20}N_2O_4S$ 313.38; found 313.

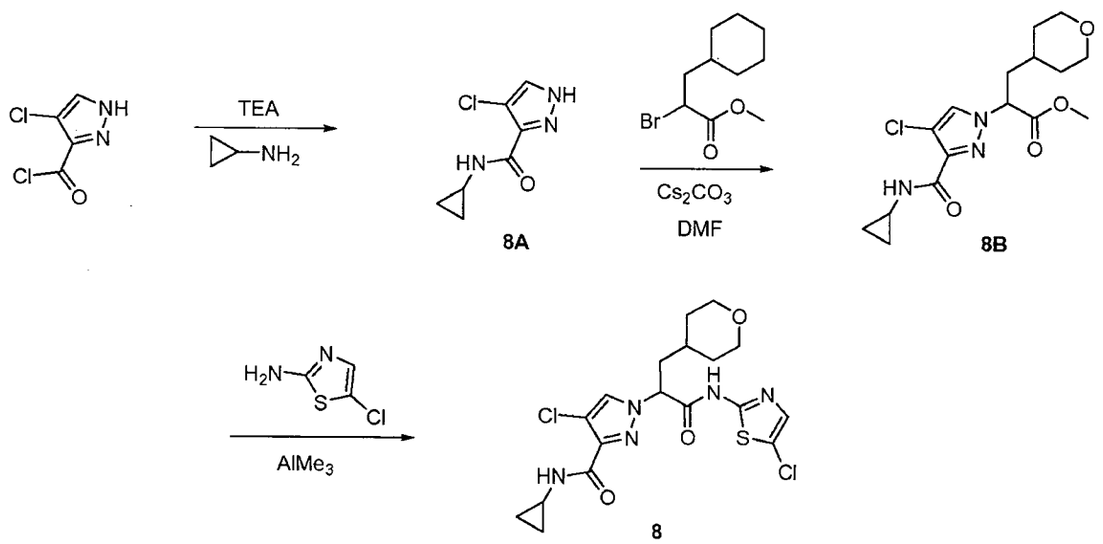
[0432] Compound **6B** (200 mg, 0.64 mmol) was dissolved in NMP (5 ml). Methyl 2-aminothioazole-5-carboxylate (184 mg, 1.282 mmol) was added, followed by 2-chloro-1-methylpyridinium iodide (360 mg, 1.41 mmol), diisopropylethylamine (0.25 ml, 1.41 mmol). The reaction mixture was heated at 90°C in sealed vial overnight. After cooling to room temperature, the reaction solution poured to water, extracted with ethyl acetate, concentrated. Residue was purified with HPLC to yield compound **6** (85 mg). [M+H] calc'd for $C_{19}H_{24}N_4O_5S_2$ 453.55; found 453. ^{1}H NMR (400 MHz, MeOD). δ ppm 1.23 (m, 6H) 1.60 (m, 6H) 1.82 (m, 1H) 2.20 (m, 1H) 2.34 (m, 1H) 2.75 (m, 1H), 3.86 (s, 3H) 5.34 (m, 1H) 7.90 (s, 1H) 8.10 (s, 1H) 8.47 (s, 1H)

Compound 7: 2-(3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)propanamido)thiazole-5-carboxylic acid



[0433] Compound **6** (67 mg, 0.149 mmol) was dissolved in dioxane (3 ml) and a 2 M LiOH (0.15 ml, 0.3 mmol) solution was added. After stirring at room temperature overnight, water (10 ml) was added and the reaction mixture was acidified with 20% HCl followed by extraction with ethyl acetate. The organic layer was separated, dried and concentrated. This material was purified using prep HPLC to afford compound **7** (36.3 mg). [M+H] calc'd for $C_{18}H_{22}N_4O_5S_2$ 439.52; found 439. ^{1}H NMR (400 MHz, MeOD). δ ppm 1.09 (m, 3H) 1.23 (m, 3H) 1.52 (m, 2H) 1.65 (m, 4H) 1.82 (m, 1H) 2.19 (m, 1H), 2.34 (m, 1H) 2.75 (m, 1H) 5.35 (m, 1H) 7.90 (s, 1H) 8.06 (s, 1H) 8.48 (s, 1H).

Compound 8: 4-chloro-1-(1-(5-chlorothiazol-2-ylamino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-N-cyclopropyl-1H-pyrazole-3-carboxamide



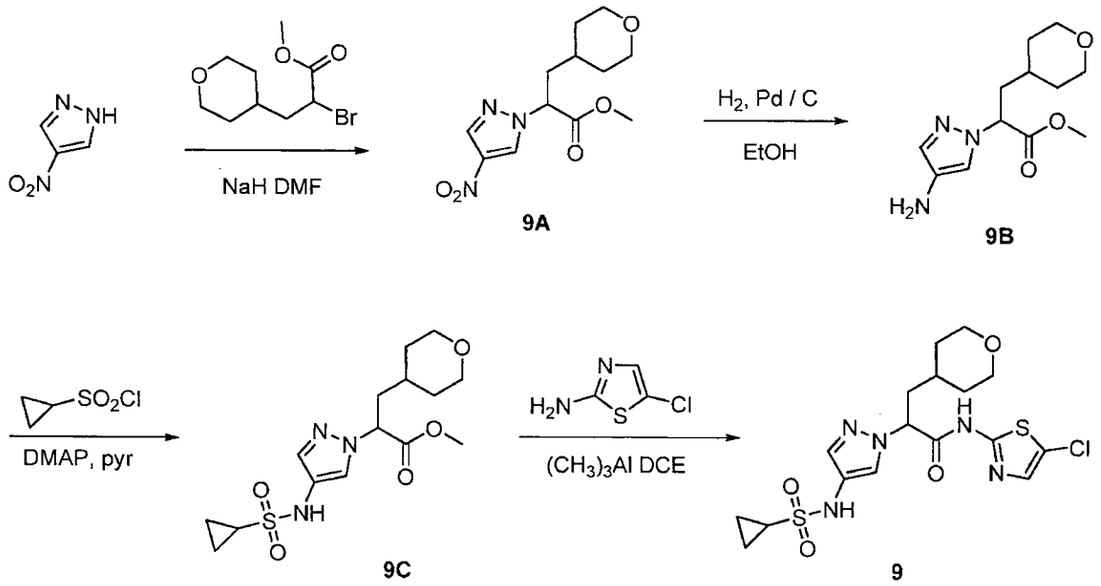
[0434] To 4-chloro-1H-pyrazole-3-carbonyl chloride (0.5 g, 3.03 mmol) in dichloromethane (10 ml) at 0°C was added TEA (0.46 ml, 3.33 mmol) followed by the dropwise addition of cyclopropylamine (0.419 ml, 6.06 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was

concentrated in vacuo, extracted into ethyl acetate and washed with sat. bicarbonate and brine solution. The organic layer was dried over Na_2SO_4, concentrated to obtain 0.55 g of **8A** as an oil and used as is in the next step. [M+H] calc'd for $C_7H_8ClN_3O$, 186.61; found 186.6

[0435] To compound **8A** (0.20 g, 1.08 mmol) in DMF (6 ml) was added Cs_2CO_3 (0.373g, 1.14 mmol) and methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate (0.271 g, 1.08 mmol) in 2 ml of DMF. The reaction mixture was stirred overnight at room temperature, extracted into ethyl acetate and washed with sat. brine solution. The organic layer was dried over Na_2SO_4 and concentrated to an oil. This material was purified by silica gel flash column (75 % ethyl acetate in hexanes) to obtain 0.3 g of compound **8B**. [M+H] calc'd for $C_{16}H_{22}ClN_3O_4$, 356.82; found 356.80

[0436] Compound 8 was synthesized using methyl 2-(4-chloro-3-(cyclopropylcarbamoyl)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanoate (**8B**) as starting material using the analogous procedure described in connection with **Compound 1**. [M+H] calc'd for $C_{18}H_{21}Cl_2N_5O_3S$, 459.36; found 459.30. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.52 - 0.60 (m, 2 H) 0.61 - 0.71 (m, 2 H) 1.13 - 1.38 (m, 3 H) 1.44 - 1.65 (m, 2 H) 1.89 - 2.05 (m, 1 H) 2.26 - 2.38 (m, 1 H) 2.76 (td, *J*=7.33, 4.04 Hz, 1 H) 3.19 (q, *J*=11.79 Hz, 2 H) 3.71 - 3.90 (m, 2 H) 5.35 (dd, *J*=10.99, 4.42 Hz, 1 H) 7.58 (s, 1 H) 8.18 (d, *J*=4.29 Hz, 1 H) 8.37 (s, 1 H) 13.01 (s, 1 H)

Compound 9: N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropanesulfonamido)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide



[0437] Compound 9A was synthesized using 4-nitro-1H-pyrazole and methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate as starting material using the analogous procedure described in connection with **Compound 1**.

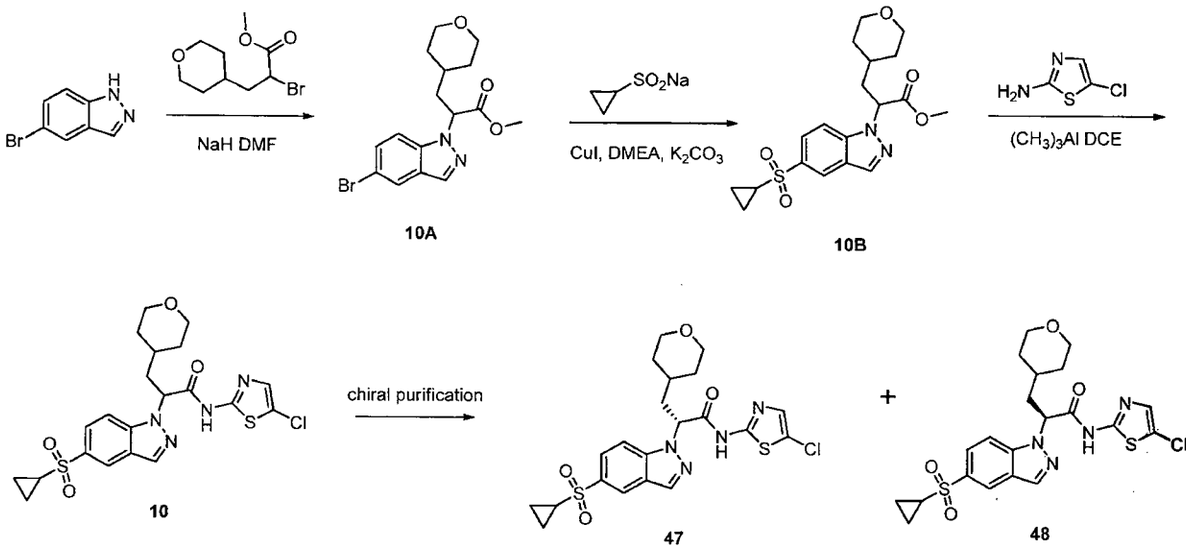
[0438] Compound **9A** (0.37 g) was dissolved in EtOH (15 mL). A catalytic amount of Pd-C was added. The suspension was purged with H_2 gas 3 times, and then stirred at room temperature under H_2 overnight. The suspension was then filtered and the filtrate was concentrated in vacuo to yield **9B** (0.121 g). [M+H] calc'd for $C_{12}H_{19}N_3O_3$, 254.3, found, 254.3

[0439] To the amine **9B** (0.120 g) in 10 ml of DCM at 0°C was added pyridine (0.038 ml), DMAP (0.057 g), followed by the dropwise addition of methane sulfonyl chloride (0.052 ml). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to obtain intermediate **9C** as an oil. [M+H] calc'd for $C_{15}H_{23}N_3O_5S$, 358.4 found, 358.4.

[0440] Compound **9** was synthesized using methyl 2-(4-(cyclopropanesulfonamido)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanoate (**9C**) as starting material using the analogous procedure described in connection with **Compound 1**. [M+H] calc'd for $C_{17}H_{22}ClN_5O_4S_2$ 460.97, found 461.0; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 - 0.87 (m, 2 H) 0.88 - 0.96 (m, 2 H) 1.14 - 1.31 (m, 3 H) 1.46 (d, *J*=10.36 Hz, 1 H) 1.59 (d,

J=9.35 Hz, 1 H) 1.92 - 2.02 (m, 1 H) 2.12 - 2.23 (m, 1 H) 2.54 - 2.57 (m, 1 H) 3.09 - 3.21 (m, 3 H) 3.74 - 3.86 (m, 2 H) 5.30 (dd, *J*=10.10, 5.31 Hz, 1 H) 7.36 (s, 1 H) 7.57 (s, 1 H) 7.82 (s, 1 H) 9.22 (s, 1 H) 12.87 (s, 1 H)

Compound 10: N-(5-chlorothiazol-2-yl)-2-(5-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide



[0441] Compound 10A was synthesized using 5-bromo-1H-indazole and methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate as starting material using the analogous procedure described in connection with **Compound 1**. A mixture (~ 4:1) of the N-1 vs. N-2 alkylated product was obtained. Purification using flash column chromatography (4:1, hexane:ethyl acetate) gave compound **10A**.

[0442] To methyl 2-(5-bromo-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanoate (0.22 g) in 10 ml of DMSO, was added sodium cyclopropanesulfinate (0.23g), copper iodide (0.011g), dimethylethylenediamine (0.013 ml) and K_2CO_3 (0.167 g). The reaction was heated at 100°C overnight. The reaction mixture was extracted into ethyl acetate, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to obtain intermediate **10B** as an oil. [M+H] calc'd for $C_{19}H_{24}N_2O_5S$, 393.47 found, 393.5

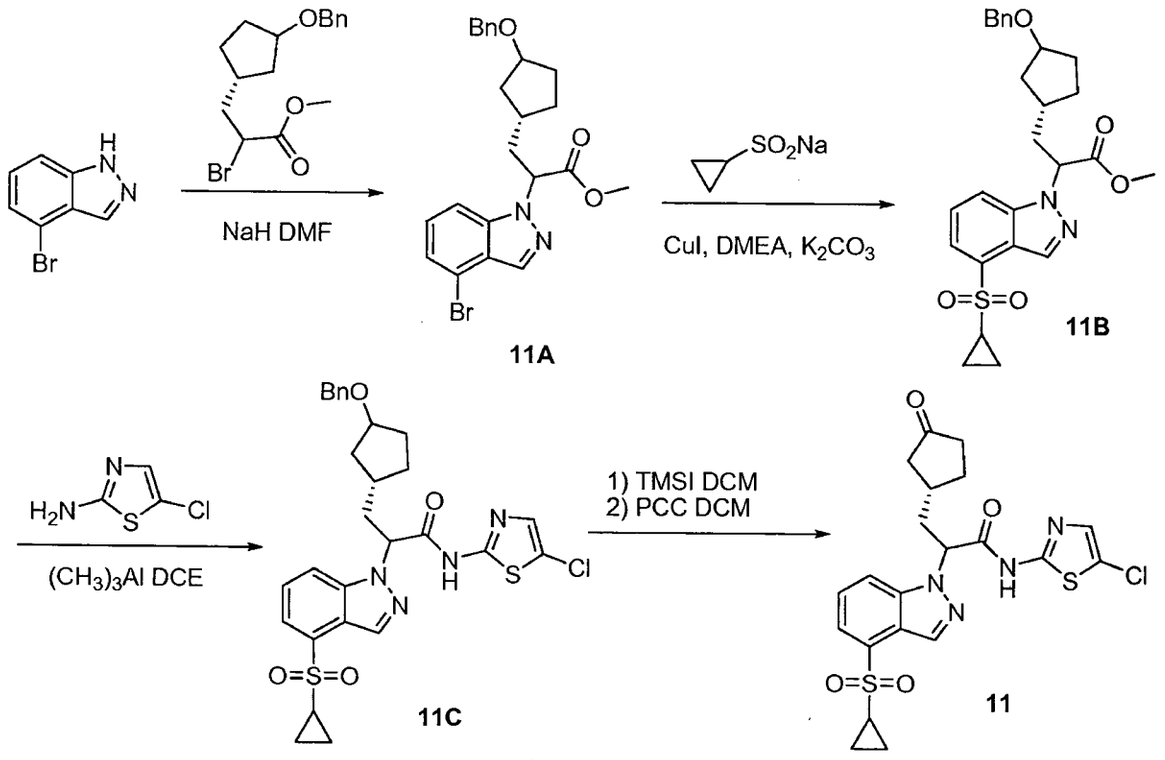
[0443] Compound 10 was synthesized using methyl 2-(5-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanoate (**10B**) as starting material using the analogous procedure described in connection with **Compound 1**. [M+H] calc'd for $C_{21}H_{23}ClN_4O_4S_2$ 496.01, found 496.1. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm

1.01 - 1.11 (m, 2 H) 1.18 - 1.29 (m, 1 H) 1.31 - 1.52 (m, 5 H) 1.59 - 1.71 (m, 1 H) 2.31 (ddd, *J*=14.02, 8.72, 4.80 Hz, 1 H) 2.45 - 2.59 (m, 2 H) 3.20 (m, *J*=19.48, 11.67, 11.67, 2.15 Hz, 2 H) 3.84 - 3.97 (m, 2 H) 5.51 (dd, *J*=10.36, 4.80 Hz, 1 H) 7.26 (s, 1 H) 7.61 (d, *J*=8.84 Hz, 1 H) 7.94 (dd, *J*=8.84, 1.52 Hz, 1 H) 8.35 (s, 1 H) 8.44 (s, 1 H)

[0444] Compound 10 was subjected to chiral separation on a Berger SFC instrument using Chiralpak AD-H media eluting with 40% MeOH to afford **Compounds 47** and **48**.

[0445] Compound 70 was obtained using an analogous procedure with the N-2 isomer of an indazole related to Compound **10B**.

Compound 11: N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-((R)-3-oxocyclopentyl)propanamide



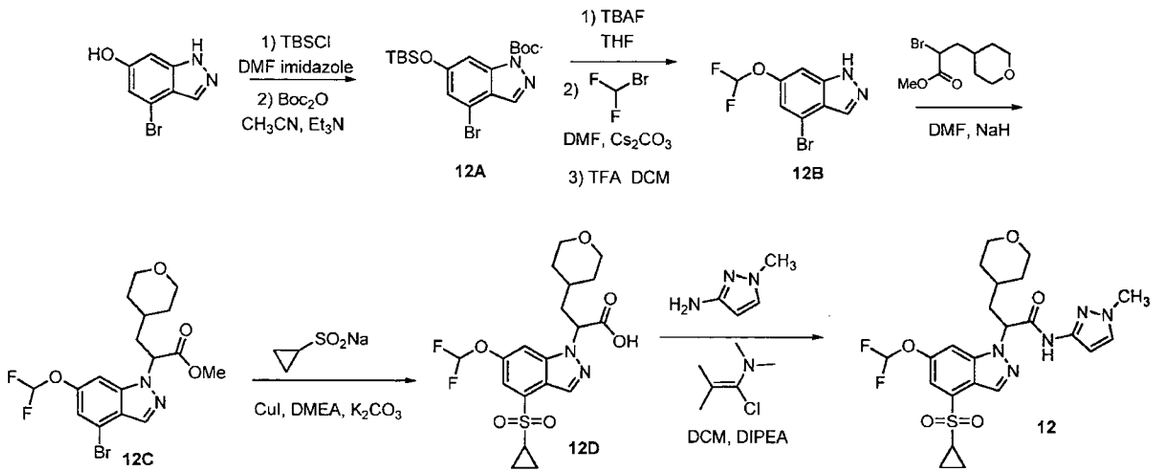
[0446] Compound 11A was synthesized using 4-bromo-1H-indazole and methyl 3-((1R)-3-(benzyloxy)cyclopentyl)-2-bromopropanoate as starting material using the analogous procedure described in connection with **Compound 1**. A mixture of the N-1 vs. N-2 alkylated product was obtained. Purification using flash column chromatography (3:1, hexane:ethyl acetate) gave compound **11A**. [M+H] calc'd for $C_{23}H_{26}BrN_2O_3$, 457.1 found 457.1.

[0447] To methyl 3-((1R)-3-(benzyloxy)cyclopentyl)-2-(4-bromo-1H-indazol-1-yl)propanoate (0.327 g) in 10 ml of DMSO, was added sodium cyclopropanesulfinate (0.57g), copper iodide (0.085g), dimethylethylenediamine (0.096 ml). The reaction was heated at 150°C overnight. The reaction mixture was cooled and washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford 11B. [M+H] calc'd for $C_{26}H_{31}N_2O_5S$, 483.19 found 483.2

[0448] 5-chlorothiazol-2-amine (0.35 g, 2.04 mmole) was added to a microwave vial followed by DCE (3 mL). The reaction mixture was cooled to 0°C under a N_2 atmosphere. Trimethyl aluminum (2M in hexanes) (2.0 mmole) was added and when the reaction subsided the cooling bath was removed, the solution was then stirred at RT for 15 min. To this was added a solution of methyl 3-((1R)-3-(benzyloxy)cyclopentyl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)propanoate **11B** (0.165 g, 0.34 mmole) in DCE (2mL) and the reaction mixture was heated in a microwave at 110°C for 1h. The reaction was then quenched with 1N HCl and extracted 2x with DCM. The organic layers were pooled, dried over Na_2SO_4 and the solvent was removed. This crude residue was purified by preparative scale HPLC to afford compound **11C** as a yellow oil (0.193g). [M+H] calc'd for $C_{28}H_{29}ClN_4O_4S_2$, 585.13; found 585.2.

[0449] Compound 11 was synthesized by treating compound 11C (0.142g) with an excess of TMSI at 50°C for 0.5h. The reaction mixture was quenched with MeOH, the solvent was the removed in vacuo and the residue was portioned between EtOAc and $NaHCO_3$ soln., the organics were dried over Na_2SO_4 and concentrated in vacuo. The crude material was subsequently redisolved in DCM and treated with pyridinium chlorochromate 20% on basic aluminum. After oxidation was complete the reaction mixture was filtered through a pad of celite and concentrated. Purification by preparative scale HPLC afforded compound **11** (0.040g). [M+H] calc'd for $C_{21}H_{31}ClN_4O_4S_2$, 493.07; found 493.1. ^1H NMR (MeOD) δ ppm: 8.48 (s, 1H), 8.07 (dd, J = 8.6, 3.0 Hz, 1H), 7.75 (d, J = 7.1 Hz, 1H), 7.64 (dd, J = 8.6, 7.3 Hz, 1H), 7.30 (s, 1H), 5.59 - 5.73 (m, 1H), 2.73 - 2.85 (m, 1H), 2.52 - 2.70 (m, 1H), 2.24 - 2.42 (m, 1H), 1.76 - 1.87 (m, 2H), 1.57 - 1.75 (m, 3H), 1.42 - 1.56 (m, 1H), 1.18 - 1.35 (m, 3H), 0.98 - 1.11 (m, 2H).

Compound 12: 2-(4-(cyclopropylsulfonyl)-6-(difluoromethoxy)-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide



[0450] Compound 12A was synthesized by treating 4-bromo-1H-indazol-6-ol (1.0 g, 4.7 mmol) with TBSCl (0.78 g, 5.2 mmol) and imidazole (0.35 g, 5.2 mmol) in 5 ml of DMF and stirring the solution at RT overnight. The reaction mixture was worked up using standard protecting group introduction protocol and the resulting orange red oil crystallized on standing (1.2g). This material was dissolved in CH_3CN (10mL) and treated with Boc_2 (0.88 g, 4.03 mmol), Et_3N (0.48 g, 4.8 mmol) and a catalytic amount of DMAP. The reaction was stirred at RT overnight, concentrated under vacuum and partitioned between DCM and 1N HCl. The organic layer was dried over $MgSO_4$ and concentrated. Purification using flash column chromatography afforded the title material as a clear oil (519 mg, 33% yield) [M+H] calc'd for $C_{18}H_{28}BrN_2O_3Si$, 427.1 found 427.1.

[0451] Compound 12B was synthesized by treating **12A** (0.52 g, 1.2 mmol) in THF (5mL) with 1M TBAF (2.4 mmol) at 0°C for 15 min. The reaction mixture was poured into NH_4Cl sat and extracted with EtOAc. The organics were dried over Na_2SO_4 and concentrated under vacuum. The resulting material was dried under high vacuum prior to use in the next step. Transfer of this compound to a pressure bottle was achieved with 1-2 mL of DMF; followed by the addition of Cs_2CO_3 (0.39 g, 1.2 mmol). This suspension was chilled and an excess of difluorobromomethane was condensed into the reaction mixture. The pressure bottle was sealed, allowed to warm to RT and stirred continuously for 2d. Subsequent warming to 50°C for 1d afforded a 70/30 mixture of the product and starting material, which was separated with flash column chromatography. This material was

treated with a 1:1 mixture of TFA/DFCM at RT for 1 h. Removal of solvent and portioning of the residue between EtOAc and sat. $NaHCO_3$ gave the title compound (0.18g, 57% yield).

[0452] Compound 12C was synthesized from **12B** (0.18 g, 0.67 mmol) and methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate (0.25 g, 1.0 mmol) using an analogous procedure described in connection with **Compound 1**. The title compound (yellow oil) was isolated as a crude N1 & N2 mixture (70/30) with the desired N1 material dominant. The regioisomers were separated with flash column chromatography; [M+H] calc'd for $C_{17}H_{20}BrF_2N_2O_4$, 433.1 found 433.2.

[0453] Compound 12D was synthesized from **12C** using an analogous procedure described in connection with **Compound 10**. The title material was isolated and purified using preparative HPLC; [M+H] calc'd for $C_{19}H_{23}F_2N_2O_6S$ 445.1 found 445.3.

[0454] Compound 12 was synthesized from **12D** (0.08 g, 0.17 mmol) which was dissolved in DCM (5 mL). To this solution was added 1-chloro-N,N,2-trimethylprop-1-en-1-amine (0.04 g, 0.3 mmol) at RT and the mixture was stirred for 30 min. 1-methyl-1H-pyrazol-3-amine (0.03 g, 0.3 mmol) was subsequently added along with DIPEA (0.04g, 0.3 mmol). The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and sat. bicarbonate soln. The organics were dried and purified by flash column chromatography to afford compound **12** (0.044g). [M+H] calc'd for $C_{23}H_{28}F_2N_5O_5S$, 524.2; found 524.4. ^1H NMR (MeOD) δ ppm: 0.94 - 1.13 (m, 2 H) 1.22 - 1.46 (m, 5 H) 1.52 (dd, J=9.47, 1.89 Hz, 1 H) 1.72 (dd, J=9.98, 1.89 Hz, 1 H) 2.05 - 2.29 (m, 1 H) 2.54 (ddd, J=14.15, 10.23, 4.17 Hz, 1 H) 2.84 (tt, J=7.96, 4.80 Hz, 1 H) 3.12 - 3.29 (m, 2 H) 3.65 (s, 1 H) 3.73 - 3.80 (m, 3 H) 3.80 - 3.96 (m, 2 H) 5.63 (dd, J=10.36, 5.31 Hz, 1 H) 6.45 (d, J=2.27 Hz, 1 H) 7.42 (d, J=2.27 Hz, 1 H) 7.54 (d, J=1.77 Hz, 1 H) 7.89 (d, J=2.27 Hz, 1 H) 8.46 (s, 1 H).

[0456] Compound 13B: To a solution of 3,5-difluoroisonicotinaldehyde (10.15 g , 70.60 mmol) in NMP (50 ml) at 0°C was added anhydrous hydrazine (2.3 ml, 70.69 mmol) dropwise. The reaction solution was stirred at R.T. for 2 hrs (monitored by LC-MS for completion of reaction to hydrazone). The reaction mixture was then heated at 140°C overnight for conversion to the indazole (monitored by LC-MS for completion of reaction). Cyclopropylsulfinic acid sodium salt (18.1g, 141.38 mmol) was then added to the reaction mixture and it was heated at 180°C overnight. When reaction was complete (monitored by LC-MS), the reaction mixture was concentrated using a high vacuum pump to remove NMP and then extracted into ethyl acetate. The organic layer was washed with water and any solid obtained was filtered through celite. The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. The oil was purified by flash column chromatography (80 % EtOAc in hexanes to 100% EtOAc) to yield 5.492 g (54% yield) of compound 13B. [M+H] calc'd for $C_9H_9N_3O_2S$ 224.2; found, 224.25.

[0457] Compound 13C: Sodium hydride (557 mg, 22.0 mmol) was suspended in DMF (5 ml), and cooled to 0°C. A solution of **Compound 13B** (3.77 g, 16.92 mmole) in DMF (15 mL) was added dropwise to it. After stirring for 20 min at 0°C, methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate (5.52 g, 22.0 mmol) was added dropwise to the reaction mixture and it was allowed to warm at room temperature and stirred for 2 hours. The reaction mixture was quenched with sat. ammonium chloride and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield crude compound **13C** (5.94 g; 89% yield). [M+H] calc'd for $C_{18}H_{23}N_3O_5S$ 394.4; found, 394.46.

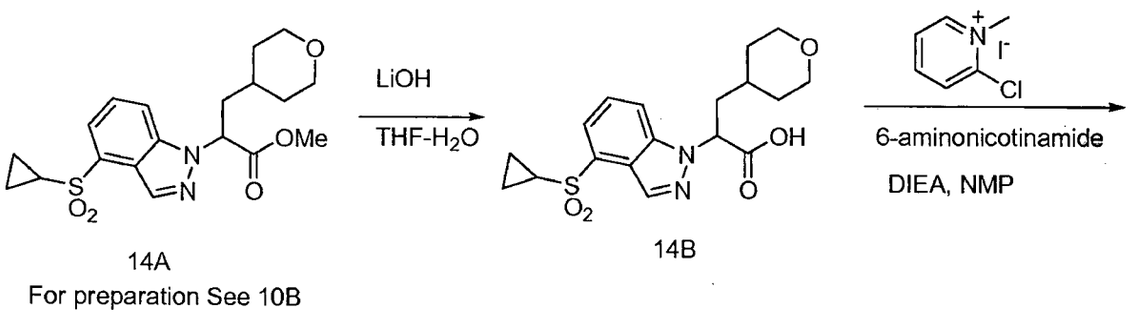
[0458] Compound 13D: To a suspension of 5-fluorothiazol-2-amine hydrochloride (9.36 g, 60.5 mmole) in DCE (30 mL) at 0°C under a N_2 atmosphere was added trimethyl aluminum (2M in hexanes) (30.3 mL, 60.5 mmole) dropwise. After stirring at room temperature for 30 minutes, a solution of **Compound 13C** (5.94 g; 15.12 mmol) in DCE (30 ml) was added dropwise and the reaction mixture was heated at 100°C for 2 hours. After cooling to 0°C, the reaction mixture was quenched with 1N HCl and extracted 2X with DCM. The organic layers was combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude **Compound 13D**.

[0459] Compounds 13 and **140** were obtained from compound 13D as a TFA salt, after purification using prep HPLC (Waters System: Column is Phenomenex C18, 5 μ, 150X50 mm, mobile phase A: 0.05% TFA in H2O and mobile phase B is 0.035% TFA in acetonitrile, Solvent gradient is 40-55 %B); [M+H] calc'd for $C_{20}H_{22}FN_5O_4S_2$ 480.5; found, 480.55.

[0460] Compound 13 was obtained as a free base by concentration of the HPLC fractions, followed by extraction into ethyl acetate and washing with satd. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain **compound 13** .

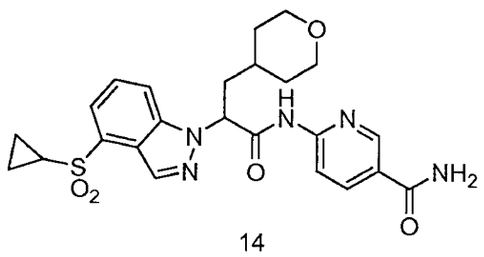
[0461] Compound 13 was subjected to chiral separation on a Berger SFC instrument using Chiralpak AD-H media eluting with 40% MeOH to afford **Compounds 84** and **85**.

Compound 14: 6-(2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamido)nicotinamide



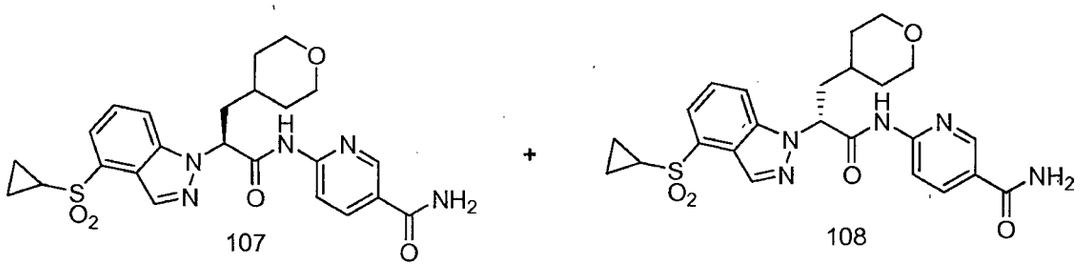
14A
For preparation See 10B

14B



14

chiral seperation



107 + 108

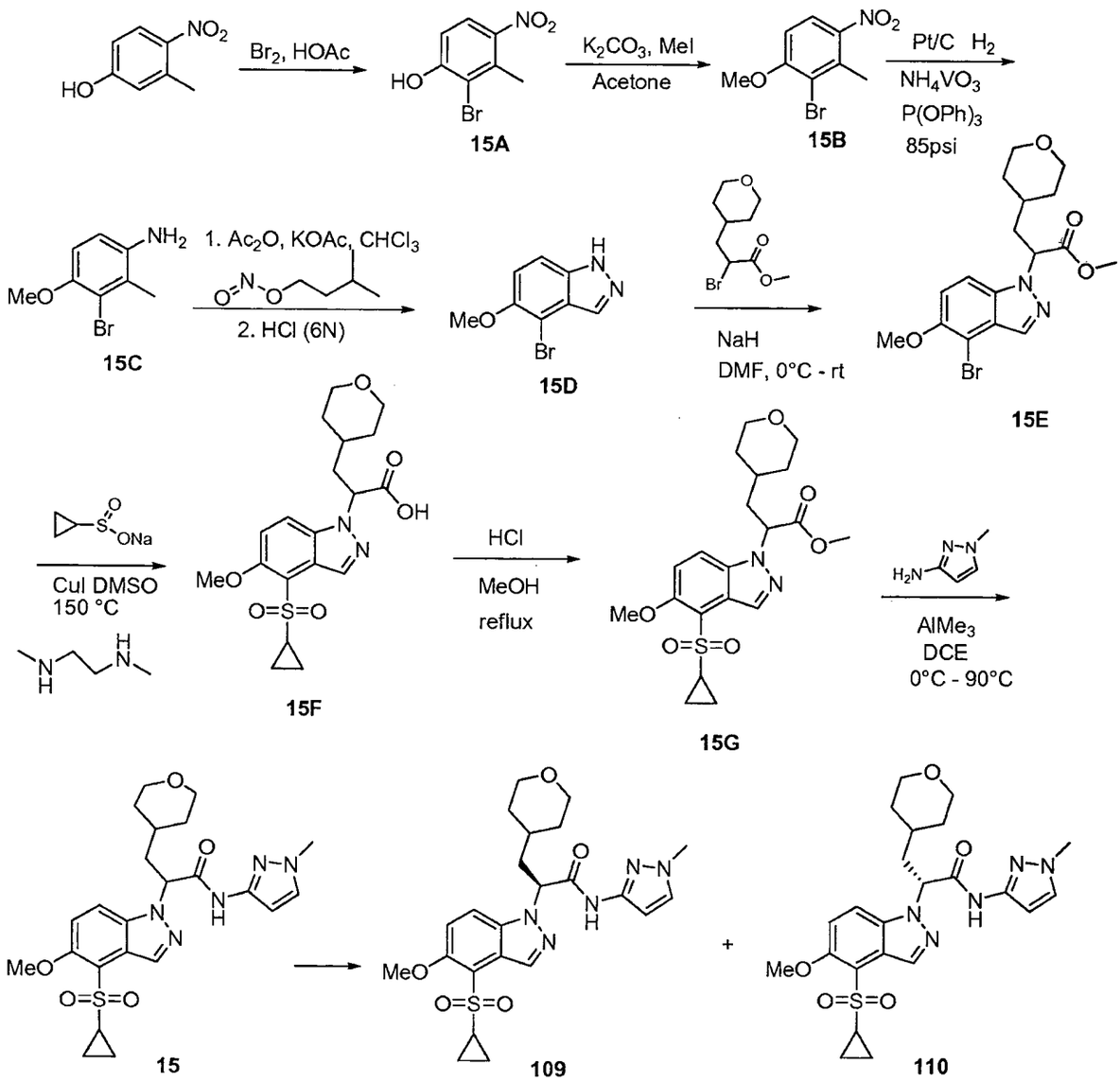
[0462] Compound 14A was synthesized using 4-bromo-1H-indazole and methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate as starting material using the analogous procedure described in connection with **Compound 10**. A mixture (~ 3:1) of the N-1 vs. N-2 alkylated product was obtained. Purification using flash column chromatography (4:1, hexane:ethyl acetate) gave compound **14A**.

[0463] Compound 14B was synthesized by treating **14A** (0.4 g, 1.0 mmol) in THF-H_2O (5:1, 10mL) with 1M LiOH (3.0 mmol) at 0°C for 15 min. and the mixture was stirred for 18h at room temperature. The reaction mixture was acidified with 1N HCl and extracted with EtOAc. The organics were dried over Na_2SO_4 and concentrated under vacuum. The resulting material was dried under high vacuum prior to use in the next step.

[0464] Compound 14 was synthesized from **14B** (0.15 g, 0.39 mmol) which was dissolved in NMP (5 mL). To this solution was added 6-aminonicotinamide (0.109 g, 0.79 mmol). 2-chloro-1-methylpyridiniumidodide (0.15 g, 0.58 mmol) was subsequently added along with DIPEA (0.092mL, 0.53 mmol) at RT and the mixture was stirred for 18h at 80°C. The reaction mixture was cooled and partitioned between EtOAc and sat. NaCl soln. The organic layer were dried and purified by prep HPLC (Waters System: Column is SunFire C18, 5 μ, 30 X 75 mm, mobile phase A: 0.05% TFA in H2O and mobile phase B is 0.035% TFA in acetonitrile, Solvent gradient is 30-45 %B); to afford compound **14** (158 mg). [M+H] calc'd for $C_{24}H_{28}N_5O_5S$, 498.3; found 498.6. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.94 - 1.13 (m, 2 H) 1.13 - 1.43 (m, 5 H) 1.43 - 1.67 (m, 2 H) 2.12 - 2.28 (m, 1 H) 2.50 (ddd, *J*=14.21, 10.42, 5.18 Hz, 1 H) 2.93 - 3.22 (m, 3 H) 3.79 - 3.95 (m, 2 H) 5.89 (dd, *J*=9.47, 4.93 Hz, 1 H) 7.48 (br. s., 1 H) 7.61 - 7.77 (m, 2 H) 7.95 - 8.12 (m, 2 H) 8.12 - 8.28 (m, 2 H) 8.43 (s, 1 H) 8.83 (d, *J*=1.77 Hz, 1 H) 11.32 (s, 1 H).

[0465] Compound 14 was subjected to chiral separation on a Berger SFC instrument using Chiralpak AD-H media eluting with 40% MeOH to afford **Compounds 107** and **108**.

Compound 15: 2-(4-(cyclopropylsulfonyl)-5-methoxy-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide



[0466] Compound **15A**: A solution of bromine (15.69 g, 0.097 mol) in acetic acid (8.88 ml) was added dropwise to a solution of 3-methyl-4-nitrophenol (14.8 g, 0.097 mol) in acetic acid (118 ml) over 45 min, and the mixture stirred for another 3h hour. Since the reaction was not complete as monitored for completeness using LC-MS, 1ml Bromine in acetic acid (2ml) was added to the reaction mixture, and the mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was suspended in water and extracted with ethyl acetate. The mixture was filtered through Celite. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to afford

crude compound **Compound 15A** (15 g) and the other regioisomer (3-methyl-4-nitro-6-bromophenol) in a 2:1 ratio. The crude compound is taken on to the next step without purification.

[0467] Compound **15B**: To the crude compound **15A** (104g, 0.45mol) in acetone (1000 ml), K_2CO_3 (68g, 0.49mol) and methyl iodide (74g, 0.52 mol) were added at room temperature. The mixture was refluxed for 1.5 hour. Since the reaction was not complete as monitored for completeness by LC-MS, K_2CO_3 (325 mesh) (22.6g, 0.16mol) and MeI (10ml, 0.16mol) was added to the reaction mixture, and the mixture was allowed to reflux overnight. The reaction was again monitored for completeness by LC-MS. Additional K_2CO_3 (325 mesh) (8g, 0.058mol) and MeI (4ml) was added to the reaction mixture, and the mixture allowed to reflux for another hour. The reaction mixture was then cooled to room temperature, filtered, and concentrated. The residue was portioned between EtOAc and H_2O. The organic layer was separated, dried and concentrated to yield crude compound **15B** (152g) as a brown solid.

[0468] Compound **15C**: To a solution of compound **15B** (76.4g, 0.311mol) in DCM (160ml) was added NH_4VO_3 (2.18g, 0.0186mol), $P(OPh)_3$ (0.964g, 0.00311mol) and Pt/C (5%) (15.5g). The mixture was stirred under H_2 at 85psi overnight. The reaction mixture was filtered through Celite and concentrated to give 64.9g crude compound **15C**. The crude compound **15C** containing the other regioisomer (5-bromo-4-methoxy-2-methylaniline) was separated at this stage by flash column chromatography (0-100 % ethyl acetate in hexanes) to afford compound **15C** (34.66g)..

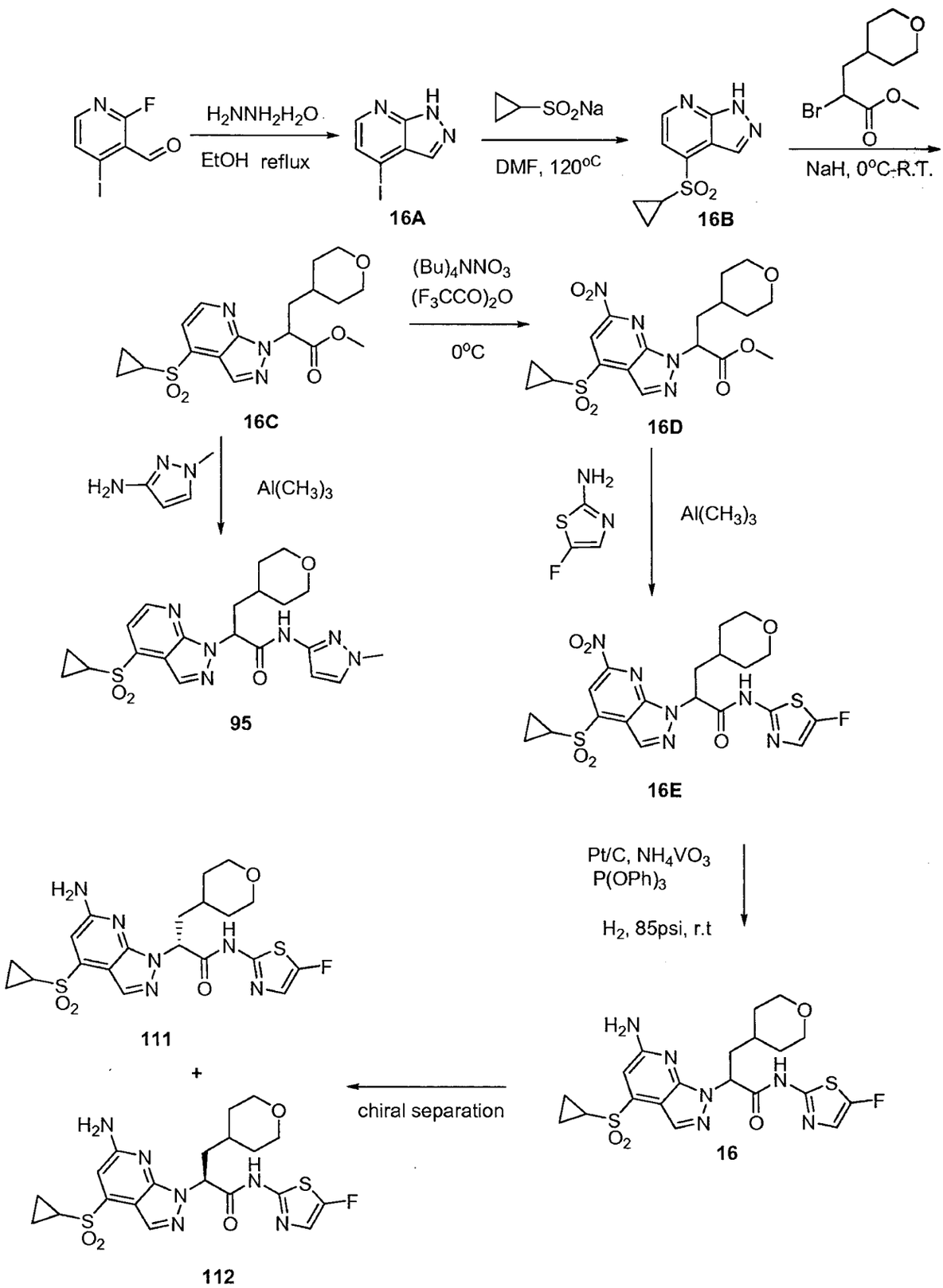
[0469] Compound **15D**: To compound **15C** (32.2g, 0.149mol) in $CHCl_3$ (470ml) was added Ac_2O (32.65ml, 0.345mol). The reaction mixture was stirred at room temperature for 40min. KOAc (4.47g, 0.0455mol) and isoamyl nitrite (44.3ml, 0.331mol) was added to the reaction mixture. The reaction mixture was refluxed overnight, cooled in an ice bath and neutralized with 1N NaOH. The organic layer was separated from the aqueous layer, washed with brine and dried over Na_2SO_4 and concentrated. The residue was taken up in a methanol (296ml) and 6N HCl solution (90ml). The reaction mixture was heated to reflux for one hour. After cooling, the reaction mixture was concentrated. The solid was neutralized with a saturated aqueous $NaHCO_3$ solution, isolated by filtration, washed with water and dried to afford compound **15D** (23g)

[0470] Compound **15E**: Compound **15D** (12g, 0.0529mol) was dissolved in DMF (140 mL) and the solution was chilled to 0 °C. NaH (2.65 g, 0.0663mole) was added and when

the reaction subsided, methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate (15.9g, 0.0635mole) was added to the reaction mixture. The reaction mixture was then warmed to room temperature and stirred overnight. When the reaction was complete as monitored by LC-MS (N1:N2 ratio was 3:1), the reaction mixture was cooled in an ice bath, quenched with a small volume of water and extracted into EtOAc. The organic layer was dried over Na_2SO_4 , filtered and concentrated to obtain an oil which was purified by flash column chromatography to afford Compound **15E** (7.54g).

[0471] Compound **15G**: To compound **15E** (7g, 0.0177mol) in 48 ml of DMSO was added sodium cyclopropanesulfinate (6.93g, 0.0546mol), copper iodide (3.46g, 0.0182mol) and dimethylethylenediamine (1.96ml, 0.0182mol). The reaction was heated at 150°C for 40 min. The reaction mixture was then cooled in an ice bath, diluted with EtOAc and filtered through celite.. The organic layer was dried over Na_2SO_4 and concentrated to afford a mixture of compound **15F** and compound **15G**. The residue was dissolved in MeOH (100ml) and HCl (6N, 10ml) was added to it. The reaction mixture was heated to reflux and stirred overnight. After the reaction mixture was cooled to room temperature, it was concentrated under vacuum, and extracted into EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated to obtain an oil. The crude oil was purified by flash column chromatography to give compound **15G** (2.7g).

[0472] Compound **15:** To a solution of 1-methyl-1H-pyrazol-3-amine (2.50g, 25.78mmol) in DCE (25 ml) at 0°C under a N_2 atmosphere was added trimethyl aluminum (2M in hexanes) (12.89 mL, 25.8 mmole). After 15 min, a solution of compound **15G** (2.72g, 6.46 mmole) in DCE (12 ml) was added to the reaction mixture and the solution was heated at 90°C for 2h. The reaction mixture was then cooled in ice bath, quenched with 1N HCl and extracted 2X with EtOAc. The organic layer was dried over Na_2SO_4 and the crude residue was purified by flash column chromatography (Hexanes/ EtOAc, 30%-100%)to afford compound **15** (2.7g). [M+H] calc'd for $C_{23}H_{29}N_5O_5S$ 488, found 488, ^1H NMR (CHLOROFORM-d ,400MHz): δ = 8.72 (s, 1 H), 8.64 (s, 1 H), 7.67 (d, *J*=9.3 Hz, 1 H), 7.30 (d, *J*=9.1 Hz, 1 H), 7.22 (d, *J*=2.5 Hz, 1 H), 6.61 (d, *J*=2.3 Hz, 1 H), 5.27 (dd, *J*=10.6, 4.8 Hz, 1 H), 4.07 (s, 3 H), 3.82 - 3.92 (m, 2 H), 3.75 (s, 3 H), 3.09 - 3.29 (m, 3 H), 2.44 - 2.56 (m, 1 H), 2.28 (d, *J*=5.1 Hz, 1 H), 1.42 - 1.52 (m, 2 H), 1.29 - 1.40 (m, 3 H), 1.21 (d, *J*=6.1 Hz, 2 H), 0.95 - 1.09 ppm (m, 2 H)


H2NNH2H2O
EtOH reflux
SO2Na
DMF, 120oC
NaH, 0oC-R.T.
16A
16B
16C
16D
(Bu)4NNO3
(F3CCO)2O
0oC
Al(CH3)3
Al(CH3)3
95
16E
Pt/C, NH4VO3
P(OPh)3
H2, 85psi, r.t
chiral separation
111
+
112
16

[0475] Compound **16A**: To a solution of 2-fluoro-4-iodonicotinaldehyde (3.0 g, 11.95 mmol) in ethanol (45 ml) was added hydrazine monohydrate (1.12 g, 14.34 mmol) and the reaction mixture was heated at 120°C in a sealed vial overnight. The reaction mixture was cooled to room temperature, and then was concentrated under reduced pressure. The residue was treated with water (30 ml) and 1 N NaOH (20 ml) and extracted with $CHCl_3$ (40x4 ml). The organic layer was separated, dried over $MgSO_4$ and concentrated to yield crude compound **16A** as solid (2.74 g). [M+H] calc'd for $C_6H_4IN_3$ 246; found 246.

[0476] Compound **16B**: To a solution of **16A** (1.00 g, 4.02 mmol) in DMF (12 ml) was added sodium cyclopropanesulfinate (1.57 g, 12.2 mmol) and the reaction was heated at 120°C for 4 hours. After cooling to room temperature, the reaction mixture was concentrated and the residue was treated with water, followed by extracted into ethyl acetate. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to yield crude **16B** (0.98 g). [M+H] calc'd for $C_9H_9N_3O_2S$ 224; found 224.

[0477] Compound **16C** was synthesized from compound **16B** using an analogous procedure described in connection with **Compound 10** to yield crude **16C** as solid (1.496 g, 86%). [M+H] calc'd for $C_{18}H_{23}N_3O_5S$ 394; found 394.

[0478] Compound **16D**: To a solution of compound **16C** (878 mg, 2.23 mmol) in DCM (10 ml) was added tetrabutylammonium nitrate (1.021 g, 3.35 mmol) and the solution was cooled to 0°C. Trifluoroacetic anhydride (0.47 ml, 3.35 mmol) was then added dropwise to the reaction mixture and it was stirred at 0°C for 1.5 h. after which another 1.5 eq. of tetrabutylammonium nitrate and trifluoroacetic anhydride was added to the reaction mixture at 0°C and stirred for 1.5 h. The reaction mixture was diluted with DCM and washed with water. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by prep. HPLC (Waters System: Column is Phenomenex C18, 5 μ, 150X50 mm, mobile phase A: 0.05% TFA in H2O and mobile phase B is 0.035% TFA in acetonitrile, Solvent gradient is 40-55 %B); to yield **16D** as solid (176 mg, 18%). [M+H] calc'd for $C_{18}H_{22}N_4O_7S$ 439; found 439.

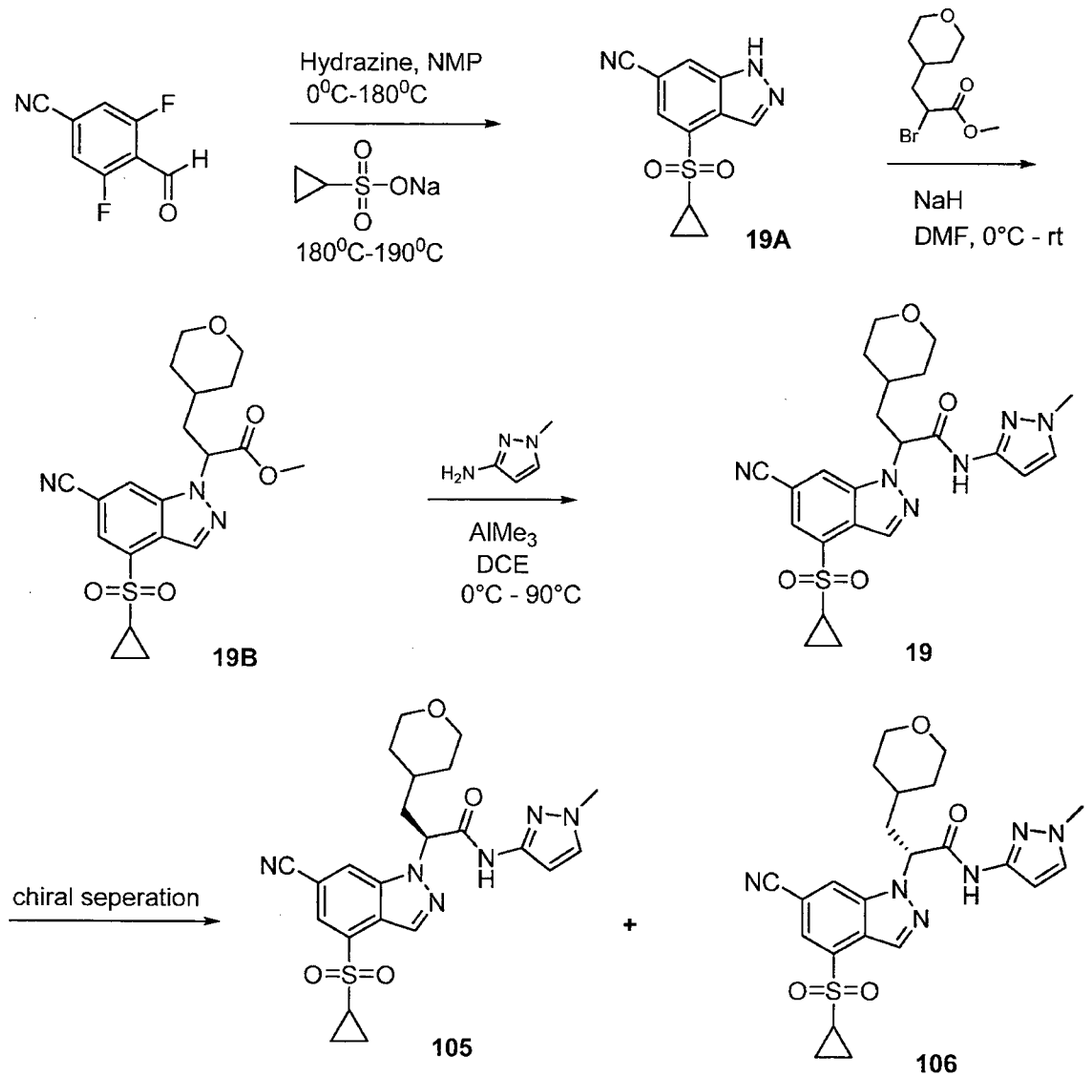
[0479] Compound **16E** was synthesized from compound **16D** using an analogous procedure described in connection with **Compound 10** to yield crude **16E** (233 mg). [M+H] calc'd for $C_{20}H_{21}FN_6O_6S_2$ 525; found 525.

[0480] Compound **16**: To a vial charged with ammonium metavanadate (5 mg, 0.032 mmol) and triphenylphosphite (2 mg, 0.05 mmol) was added a solution of compound **16E** (233 mg, 0.54 mmol) in THF (12 ml), followed by a catalytic mount of Pt/C (5%). The reaction mixture was stirred under hydrogen (85 psi) for 24 hours. The reaction mixture was then filtered through Celite and concentrated under reduced pressure to obtain a residue which was purified via prep. HPLC (Waters System: Column is Phenomenex C18, 5 μ, 150X50 mm, mobile phase A: 0.05% TFA in H2O and mobile phase B is 0.035% TFA in acetonitrile, Solvent gradient is 40-55 %B); to yield compound **16** (54 mg). [M+H] calc'd for $C_{20}H_{23}FN_6O_4S_2$ 496, found 496. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.99 - 1.07 (m, 9 H) 1.29 - 1.42 (m, 22 H) 1.47 - 1.54 (m, 4 H) 1.71 - 1.78 (m, 4 H) 2.09 - 2.19 (m, 4 H) 2.52 - 2.63 (m, 5 H) 2.90 (tt, *J*=8.08, 4.80 Hz, 5 H) 3.12 - 3.28 (m, 9 H) 3.80 - 3.90 (m, 9 H) 5.86 (dd, *J*=10.99, 4.42 Hz, 5 H) 7.08 (d, *J*=2.53 Hz, 4 H) 8.15 (s, 4 H) 8.32 (s, 4 H).

[0481] Compound 16 was subjected to chiral separation on a Berger SFC instrument. For this particular compound it was found that using Chiralpak AD-H media eluting with 40% MeOH afforded **Compounds 111** and **112**

[0482] Compound 95 was synthesized from compound **16C** using an analogous procedure described in connection with **Compound 10.** The crude compound was purified by prep. HPLC (Waters System: Column is Phenomenex C18, 5 μ, 150X50 mm, mobile phase A: 0.05% TFA in H2O and mobile phase B is 0.035% TFA in acetonitrile, Solvent gradient is 40-55 %B) to yield compound **95.** [M+H] calc'd for $C_{21}H_{27}N_6O_4S$ 459, found 459. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.08 - 1.18 (m, 2 H) 1.28 - 1.44 (m, 5 H) 1.54 (d, *J*=9.35 Hz, 1 H) 1.74 (dd, *J*=10.11, 1.77 Hz, 1 H) 2.17 - 2.27 (m, 1 H) 2.67 (ddd, *J*=14.21, 10.93, 3.66 Hz, 1 H) 2.89 (tt, *J*=7.86, 4.77 Hz, 1 H) 3.10 - 3.28 (m, 2 H) 3.76 (s, 3 H) 3.85 (dd, *J*=10.74, 4.93 Hz, 2 H) 5.99 (dd, *J*=10.99, 4.67 Hz, 1 H) 6.42 (d, *J*=2.53 Hz, 1 H) 7.42 (d, *J*=2.27 Hz, 1 H) 7.69 (d, *J*=4.80 Hz, 1 H) 8.51 (s, 1 H) 8.81 (d, 1 H)

Compound 19: 2-(6-cyano-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl) propanamide



[0483] Compound **19A:** To a solution of 3, 5-difluoro-4-formylbenzonitrile (9.76g, 0.058mol) in N-Methyl-2-pyrrolidinone (100ml) at 0°C was added anhydrous hydrazine (2.06g, 0.064mol) and the reaction mixture was stirred at 0°C for 1h. The solution was then allowed to warm to room temperature and stirred for 2h (monitored by LC-MS for completion of reaction to hydrazone). The reaction mixture was then heated to 180°C for 4h. The solution was cooled to room temperature and sodiumcyclopropanesulfinate (9.73g, 0.076mol) was added. The reaction mixture was then heated overnight at 180°C followed by heating at 190°C for another 5h. The reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through a pad of Celite. The filtrate was

washed with brine solution, dried over Na_2SO_4 and concentrated to obtain a residue which was purified by flash column chromatography to yield compound **19A** (8.5g). [M+H] calc'd for $C_{11}H_9N_3O_2S$ 248, found 248

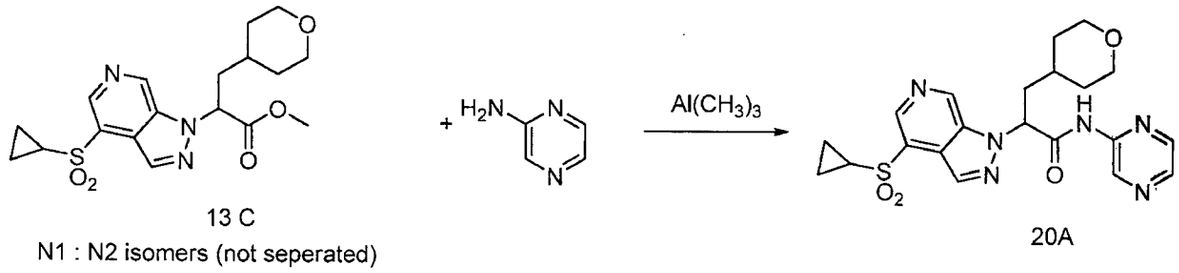
[0484] Compound 19B: Compound **19A** (4.2g, 16.99mmol) was dissolved in DMF (50 mL) and the solution was chilled to 0 °C. NaH (0.88 g, 22.08 mmol) was added and when the reaction subsided, methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate (5.54, 22.08 mmol) was added to the reaction mixture. The reaction mixture was then warmed to room temperature and stirred overnight. When the reaction was complete as monitored by LC-MS (N1:N2 ratio was 3;1), the reaction mixture was cooled in an ice bath, quenched with a small volume of water and extracted into EtOAc. The organic layer was dried over Na_2SO_4 , filtered and concentrated to obtain an oil which was purified by flash column chromatography to afford the N1 isomer as Compound **19B (1.8g, 25 %)** [M+H] calc'd for $C_{20}H_{23}N_3O_5S$ 418, found 418

[0485] Compound 19: To a solution of 1-methyl-1H-pyrazol-3-amine (5.21g, 53.7 mmol) in DCE (70 ml) at 0°C under a N_2 atmosphere was added trimethyl aluminum (2M in hexanes) (26.8 mL, 53.7 mmole). After 15 min, a solution of compound **19B** (5.6g, 13.41 mmole) in DCE (15 ml) was added to the reaction mixture and the solution was heated overnight at 90°C. The reaction mixture was then cooled in ice bath, quenched with 1N HCl and extracted 2X with EtOAc. The organic layer was dried over Na_2SO_4 and the crude residue was purified by flash column chromatography (Hexanes/ EtOAc, 40%-100%) to afford compound **19** as a free base (4.47g, 69%). [M+H] calc'd for $C_{23}H_{26}N_6O_4S$ 483, found 483. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.60 - 8.71 (m, 2H), 8.24 (s, 1H), 7.96 (d, J = 1.01 Hz, 1H), 7.22 - 7.28 (m, 1H), 6.62 (d, J = 2.27 Hz, 1H), 5.45 (dd, J = 5.56, 9.85 Hz, 1H), 3.84 - 3.98 (m, 2H), 3.77 (s, 3H), 3.13 - 3.32 (m, 2H), 2.55 - 2.67 (m, 1H), 2.44 - 2.55 (m, 1H), 2.35 (dd, J = 7.71, 13.77 Hz, 1H), 1.63 (d, J = 12.13 Hz, 1H), 1.31 - 1.58 (m, 6H), 1.06 - 1.19 (m, 2H)

[0486] Compound 19 was also purified via prep. HPLC (Waters System: Column is Phenomenex C18, 5 μ, 150X50 mm, mobile phase A: 0.05% TFA in H2O and mobile phase B is 0.035% TFA in acetonitrile, Solvent gradient is 40-55 %B); to yield compound **19** as a TFA salt.

[0487] Compound 19 was subjected to chiral separation on a Berger SFC instrument using Chiralpak AD-H media eluting with 20% IPOH to afford **Compounds 105** and **106**.

Compound 20: 2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide



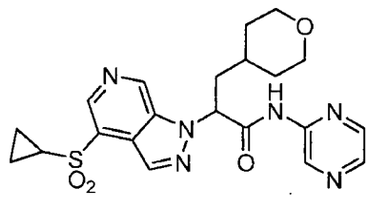
13 C

N1 : N2 isomers (not seperated)

20A

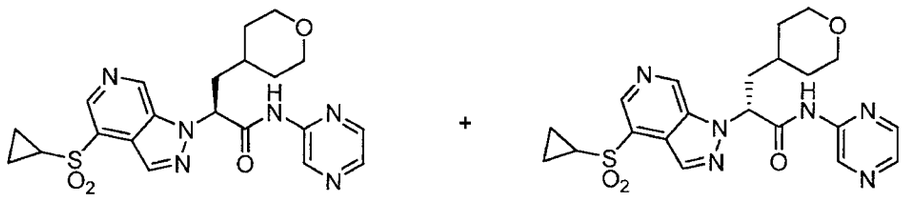
N1 : N2 isomers seperated

Prep HPLC



20

Chiral Purification



171 172

[0488] Compound 20A: To a solution of amino-pyrazine (3.4g, 35.8 mmol) in DCE (40 ml) at 0°C under a N_2 atmosphere was added trimethyl aluminum (2M in hexanes) (17.89 mL, 35.8 mmole). After 15 min, a solution of compound **13C** (3.52g, 8.95 mmole) in DCE (20 ml) was added to the reaction mixture and the solution was heated overnight at 90°C. The reaction mixture was then cooled in ice bath, quenched with 1N HCl and extracted 2X with EtOAc. The organic layer was dried over Na_2SO_4 and the crude residue as compound 20A

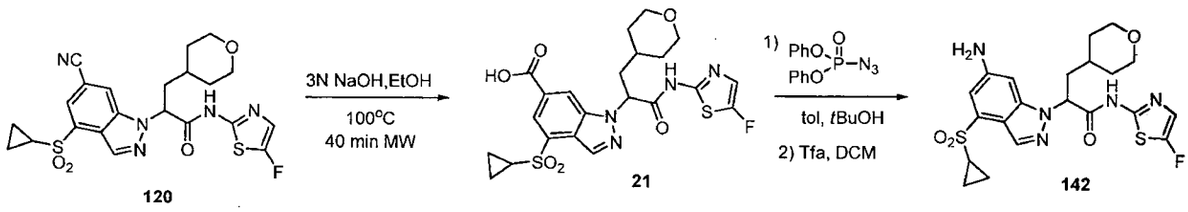
[0489] Compound 20 was obtained from **compound 20A** as a TFA salt after purification using prep HPLC (Waters System: Column is Phenomenex C18, 5 μ, 150X50 mm, mobile phase A: 0.05% TFA in H_2O and mobile phase B is 0.035% TFA in acetonitrile, Solvent gradient is 40-55 %B); [M+H] calc'd for $C_{21}H_{24}N_6O_4S$ 457.5; found, 457.55 ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.12 (m, 2 H) 1.20 - 1.37 (m, 5 H) 1.50 (d, J=11.62 Hz, 1 H) 1.66 (d, J=11.12 Hz, 1 H) 2.25 - 2.35 (m, 1 H) 2.52 - 2.58 (m, 1 H) 3.04 - 3.17

(m, 3 H) 3.71 - 3.83 (m, 2 H) 6.06 (dd, *J*=10.11, 5.31 Hz, 1 H) 8.40 (d, *J*=2.53 Hz, 1 H) 8.42 - 8.46 (m, 1 H) 8.55 (s, 1 H) 8.70 (s, 1 H) 9.24 (d, *J*=1.26 Hz, 1 H) 9.68 (s, 1 H).

[0490] Compound 20 was obtained as a free base after purification using prep HPLC (Waters System: Column is Phenomenex C18, 5 μ, 150X50 mm, mobile phase A: 10mM NH_4HCO_3 in H_2O and mobile phase B is 10mM NH_4HCO_3 in 80%acetonitrile, Solvent gradient is 30-35 % B).

[0491] Compound 20 was subjected to chiral separation on a Berger SFC instrument using Chiralpak AD-H media eluting with 40% MeOH to afford **Compounds 171** and **172**.

Compound 21: 4-(cyclopropylsulfonyl)-1-(1-(5-fluorothiazol-2-ylamino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-1H-indazole-6-carboxylic acid



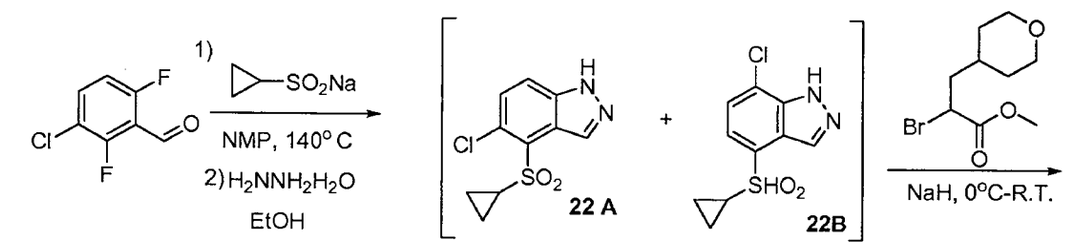
[0492] A solution of 2-(6-cyano-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide **120** (0.06g, 0.11 mmol) in EtOH (5mL) was added to a microwave vial followed by 3N NaOH (1mL) and the mixture was heated at 100°C for 40 min. The solvent was removed under vacuum and the residue was partitioned between 1N HCl and EtOAc. The organic layer was dried over Na_2SO_4 to give the crude carboxylic acid **21**. [M+H] calc'd for $C_{22}H_{24}FN_4O_6S_2$ 523.1, found 523.3.

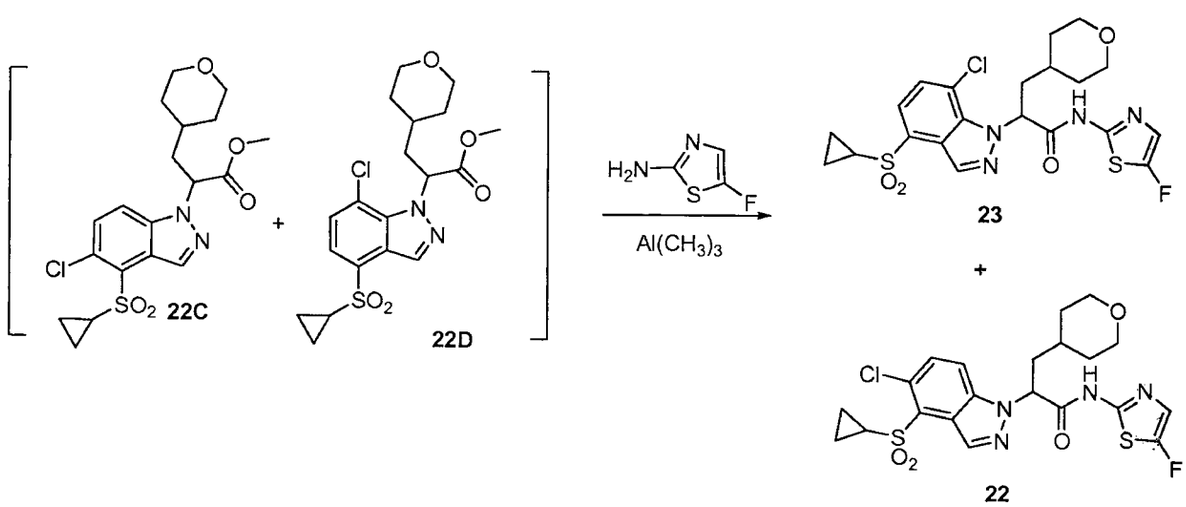
[0493] 4-(cyclopropylsulfonyl)-1-(1-(5-fluorothiazol-2-ylamino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-1H-indazole-6-carboxylic acid **21** (0.1g, 0.19 mmol), diphenyl phosphorazidate (0.05g, 0.19 mmol), triethylamine (0.03g, 0.3 mmol), and tBuOH (0.016g, 0.21 mmol) were combined in toluene (10 mL) and refluxed for 2h. The solvent was removed and the residue treated with TFA/ DCM (1/1) for 15 min. The mixture was concentrated under reduced pressure and purified using prep HPLC (Waters System: Column is Phenomenex C18, 5 μ, 150X50 mm, mobile phase A: 0.05% TFA in H_2O and

mobile phase B is 0.035% TFA in acetonitrile) to give **Compound 142** as a reddish brown solid (50 mg); [M+H] calc'd for $C_{21}H_{25}FN_5O_4S_2$ 494.1, found 494.4

Compound 22 : Methyl 2-(5-chloro-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanoate

Compound 23: methyl 2-(7-chloro-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanoate





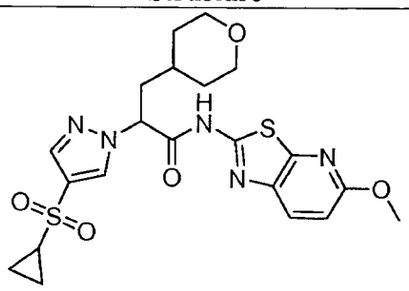
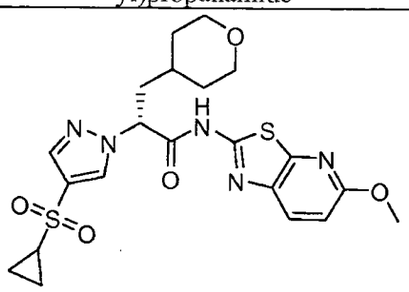
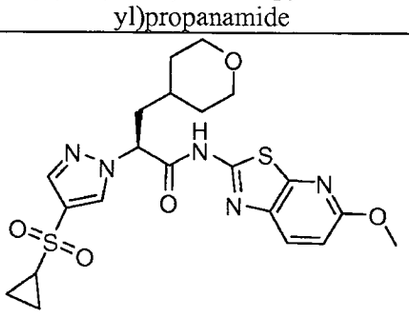
[0494] 3-chloro-2,6-difluorobenzaldehyde (0.22 g, 1.23 mmol) and sodium cyclopropanesulfinate (0.19 g, 1.35 mmol) were combined in NMP (3 mL) and heated at 140 °C for 0.5h. The reaction mixture was diluted with MeOH and purified using HPLC to give a mixture of 5-chloro-4-(cyclopropylsulfonyl)-1H-indazole **22A** and 7-chloro-4-(cyclopropylsulfonyl)-1H-indazole **22 B** as a white solid (0.14g); [M+H] calc'd for $C_{10}H_{10}ClN_2O_2S$ 257.0, found 257.1. ^{1}HNMR analysis confirmed the mixture of regioisomers in an approximate 1:1 ratio.

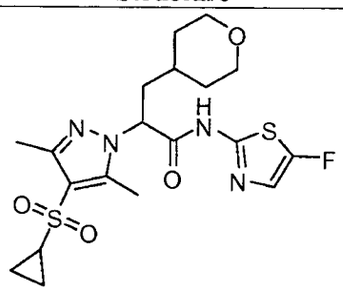
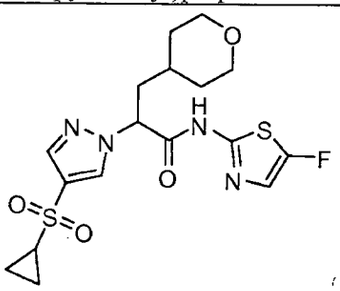
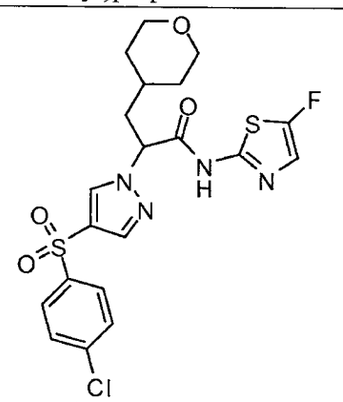
[0495] The mixture of **22A** and **22 B** (0.14g, 0.54mmol) was dissolved in DMF (4 mL) and the solution was chilled to 0 °C. NaH (0.02 g, 0.65 mmol) was added and, when the

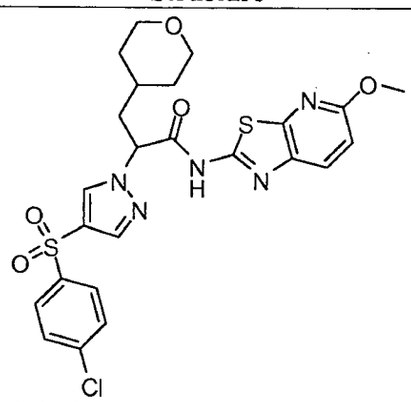
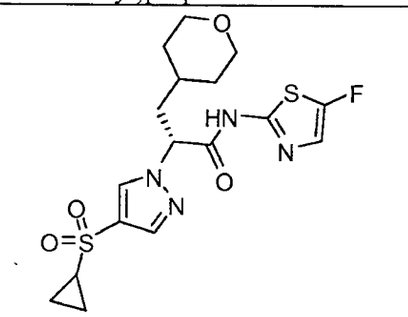
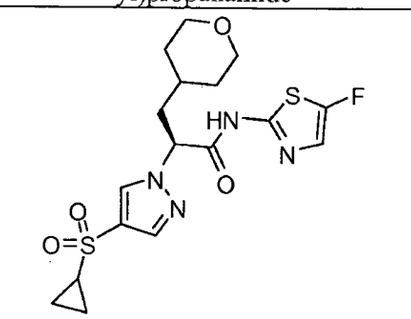
reaction subsided, methyl 2-bromo-3-(tetrahydro-2H-pyran-4-yl)propanoate (0.20, 0.81 mmol) was added to the reaction mixture. The reaction mixture was then warmed to room temperature and stirred for 1h. The reaction was quenched with a small volume of MeOH and concentrated under vacuum. The residue was portioned between EtOAc and 1N HCl. The organic layer was dried over Na_2SO_4 , filtered and purified by flash column chromatography to afford compounds **22C and 22D** as a clear oil (0.41g); [M+H] calc'd for $C_{19}H_{24}ClN_2O_5S$ 427.1, found 427.3. The mixture of isomers was used as is in the next step.

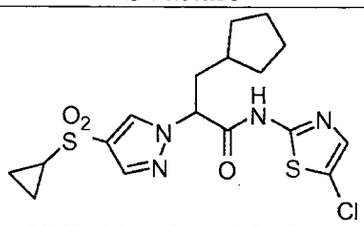
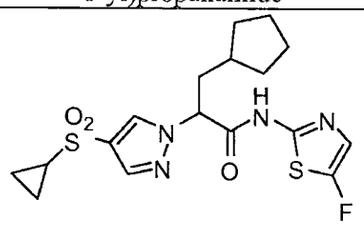
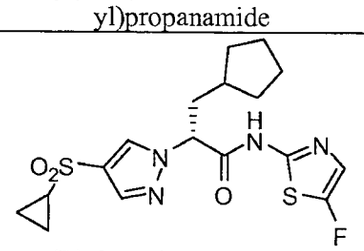
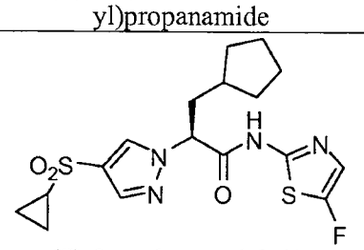
[0496] Compounds 22 and **23:** To a solution of 5-fluorothiazol-2-amine (0.29 g, 1.9 mmol) in DCE (5 ml) at 0°C under a N_2 atmosphere was added trimethyl aluminum (2M in hexanes) (1.9 mmol). After 15 min, a solution of Compounds **22C** and **22D** (0.41g, 0.96 mmole) in DCE (3 ml) was added to the reaction mixture and the solution was heated in a microwave oven at 100°C for 1h. The reaction mixture was then cooled in an ice bath, quenched with 1N HCl and extracted 2X with EtOAc. The organic layer was dried over Na_2SO_4 and the crude residue was purified by flash column chromatography using (DCM/ MeOH, 0%- 10%) to afford pure compounds **22** and **23**. Compound **22:** [M+H] calc'd for $C_{21}H_{23}ClFN_4O_4S_2$ 513.1, found 513.2; ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.96 - 1.14 (m, 2 H) 1.28 - 1.48 (m, 5 H) 1.54 (br. s., 1 H) 1.71 (d, *J*=7.58 Hz, 1 H) 2.32 - 2.60 (m, 3 H) 3.19 - 3.37 (m, 2 H) 3.78 - 4.06 (m, 2 H) 5.42 (dd, *J*=9.22, 6.19 Hz, 1 H) 7.08 (br. s., 1 H) 7.45 - 7.60 (m, 1 H) 7.68 (d, *J*=7.58 Hz, 1 H) 8.60 (s, 1 H). Compound **23** [M+H] calc'd for $C_{21}H_{23}ClFN_4O_4S_2$ 513.1, found 513.2; ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.93 - 1.20 (m, 1 H) 1.30 - 1.60 (m, 5 H) 1.67 (br. s., 3 H) 2.16 - 2.38 (m, 1 H) 2.46 - 2.74 (m, 2 H) 3.17 - 3.44 (m, 2 H) 3.79 - 4.01 (m, 2 H) 6.49 (br. s., 1 H) 7.00 (d, *J*=2.53 Hz, 1 H) 7.60 (dd, *J*=7.83, 4.04 Hz, 1 H) 7.67 - 7.80 (m, 1 H) 8.72 (s, 1 H).

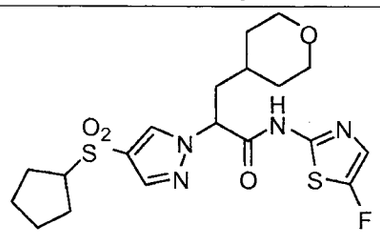
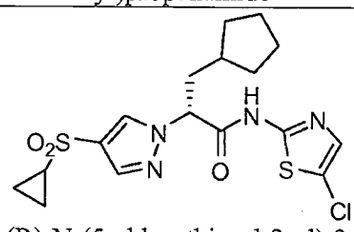
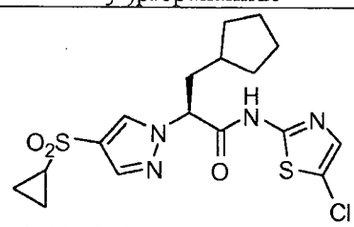
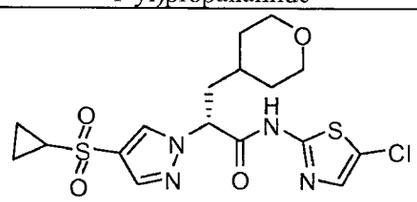
[0497] In addition to the foregoing, the above reaction schemes and variations thereof can be used to prepare the following.

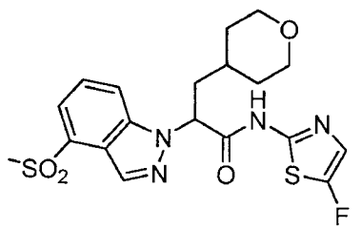
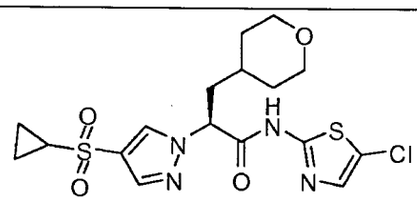
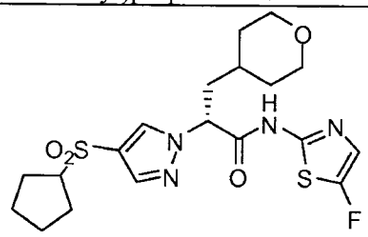
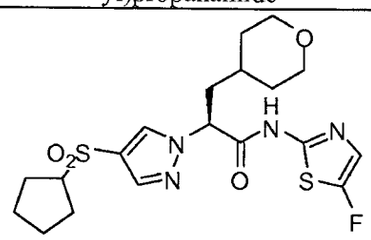
Ex.	Structure	Method	LCMS	NMR data
24	 2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 1	[M+H] calc'd for $C_{21}H_{26}N_5O_5S_2$, 492.13; found 492.0	^{1}H NMR (400 MHz, MeOD) δ ppm 1.00 - 1.14 (m, 2 H) 1.16 - 1.47 (m, 6 H) 1.66 - 1.84 (m, 2 H) 2.15 (br. s., 1 H) 2.32 (dd, *J*=14.40, 6.82 Hz, 1 H) 2.63 - 2.87 (m, 1 H) 3.77 (s, 3 H) 3.85 - 3.98 (m, 4 H) 5.47 (dd, *J*=10.23, 5.43 Hz, 1 H) 6.84 (d, *J*=8.84 Hz, 1 H) 7.90 - 7.95 (m, 1 H) 8.51 (s, 1 H).
25	 (R)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpds. 2 and 3	[M+H] calc'd for $C_{21}H_{26}N_5O_5S_2$, 492.13; found 492.0	^{1}H NMR (400 MHz, MeOD) δ ppm 1.00 - 1.14 (m, 2 H) 1.16 - 1.47 (m, 6 H) 1.66 - 1.84 (m, 2 H) 2.15 (br. s., 1 H) 2.32 (dd, *J*=14.40, 6.82 Hz, 1 H) 2.63 - 2.87 (m, 1 H) 3.77 (s, 3 H) 3.85 - 3.98 (m, 4 H) 5.47 (dd, *J*=10.23, 5.43 Hz, 1 H) 6.84 (d, *J*=8.84 Hz, 1 H) 7.90 - 7.95 (m, 1 H) 8.51 (s, 1 H).
26	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpds. 2 and 3	[M+H] calc'd for $C_{21}H_{26}N_5O_5S_2$, 492.13; found 492.0	^{1}H NMR (400 MHz, MeOD) δ ppm 1.00 - 1.14 (m, 2 H) 1.16 - 1.47 (m, 6 H) 1.66 - 1.84 (m, 2 H) 2.15 (br. s., 1 H) 2.32 (dd, *J*=14.40, 6.82 Hz, 1 H) 2.63 - 2.87 (m, 1 H) 3.77 (s, 3 H) 3.85 - 3.98 (m, 4 H) 5.47 (dd, *J*=10.23, 5.43 Hz, 1 H) 6.84 (d, *J*=8.84 Hz, 1 H) 7.90 - 7.95 (m, 1 H) 8.51 (s, 1 H).

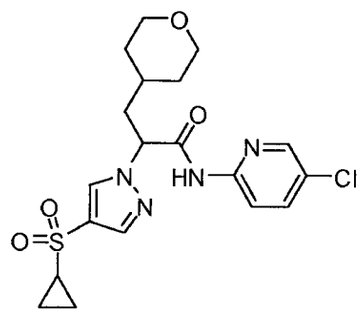
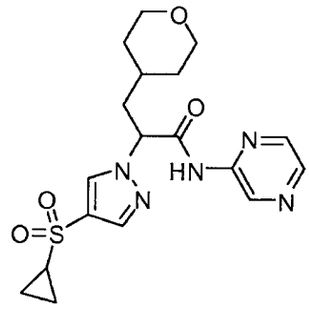
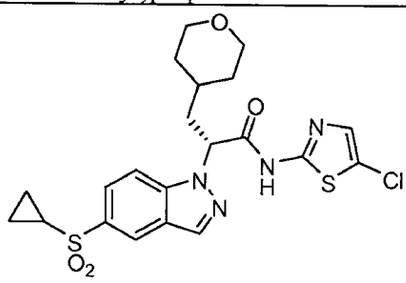
Ex.	Structure	Method	LCMS	NMR data
27	 2-(4-(cyclopropylsulfonyl)-3,5-dimethyl-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{19}H_{26}FN_4O_4S_2$, 457.13; found 457	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.03 (d, *J*=8.08 Hz, 2 H) 1.21 - 1.45 (m, 5 H) 1.50 - 1.63 (m, 2 H) 2.09 - 2.31 (m, 2 H) 2.48 (d, *J*=3.28 Hz, 1 H) 2.51 (s, 3 H) 2.54 (s, 3 H) 3.33 (d, *J*=9.60 Hz, 2 H) 3.87 - 4.01 (m, 2 H) 4.96 (dd, *J*=9.35, 5.81 Hz, 1 H) 7.06 (d, *J*=2.78 Hz, 1 H)
28	 2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{22}FN_4O_4S_2$, 429.10, found 429	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.09 (dq, *J*=7.86, 2.43 Hz, 2 H) 1.27 - 1.46 (m, 5 H) 1.53 (d, *J*=9.35 Hz, 1 H) 1.68 (d, *J*=11.87 Hz, 1 H) 2.23 (d, *J*=14.15 Hz, 1 H) 2.07 - 2.31 (m, 1 H) 2.51 - 2.62 (m, 1 H) 3.33 (dd, *J*=11.37, 2.27 Hz, 2 H) 3.95 (t, *J*=11.87 Hz, 2 H) 5.19 (dd, *J*=9.73, 5.68 Hz, 1 H) 6.40 (br.s., 1H) 7.11 (d, *J*=2.53 Hz, 1 H) 7.94 (s, 1 H) 8.09 (s, 1 H)
29	 2-(4-(4-chlorophenylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{20}H_{21}ClFN_4O_4S_2$, 499.06, found 499	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.32 (br. s., 2 H) 1.34 (d, *J*=4.29 Hz, 1 H) 1.48 (br. s., 1 H) 1.62 (br. s., 1 H) 2.16 (d, *J*=6.57 Hz, 2 H) 3.23 - 3.34 (m, 2 H) 3.93 (dd, *J*=16.42, 11.87 Hz, 2 H) 5.11 (dd, *J*=9.47, 6.19 Hz, 1 H) 5.50 (br.s., 1H) 7.08 (d, *J*=2.78 Hz, 1 H) 7.51 (d, *J*=8.59 Hz, 2 H) 7.87 - 7.93 (m, 3 H) 8.10 (s, 1 H)

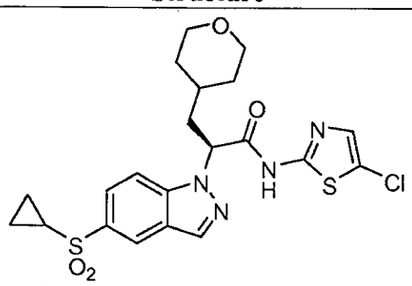
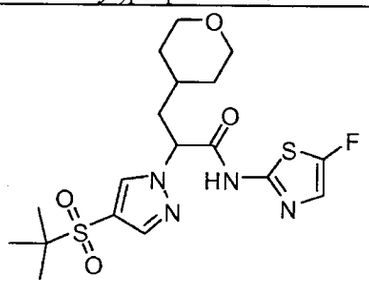
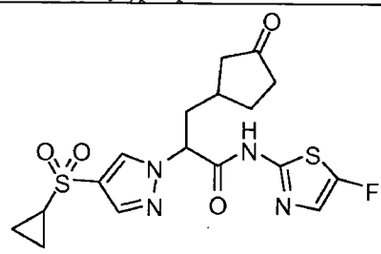
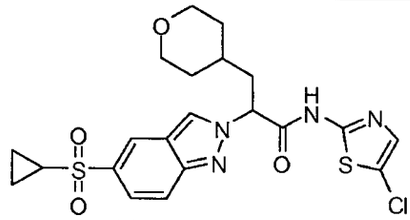
Ex.	Structure	Method	LCMS	NMR data
30	 2-(4-(4-chlorophenylsulfonyl)-1H-pyrazol-1-yl)-N-(5-methoxythiazolo[5,4-b]pyridin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{24}H_{25}ClN_5O_5S_2$, 562.09, found 562	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.34 (t, *J*=10.11 Hz, 2 H) 1.36 (br. s., 1 H) 1.50 (br. s., 1 H) 1.65 (br. s., 1 H) 2.24 (d, *J*=4.55 Hz, 1 H) 2.21 (t, *J*=6.06 Hz, 1 H) 3.27 - 3.36 (m, 2 H) 4.00 (s, 3H), 3.87 - 3.98 (m, 2H) 5.17 (dd, *J*=9.35, 6.06 Hz, 1 H) 6.87 (d, *J*=8.84 Hz, 1 H) 7.51 (d, *J*=8.34 Hz, 2 H) 7.86 - 7.93 (m, 3 H) 7.95 (s, 1 H) 8.11 (s, 1 H)
31	 (R)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpds. 2 and 3	[M+H] calc'd for $C_{17}H_{22}FN_4O_4S_2$, 429.10, found 429	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.09 (dq, *J*=7.86, 2.43 Hz, 2 H) 1.27 - 1.46 (m, 5 H) 1.53 (d, *J*=9.35 Hz, 1 H) 1.68 (d, *J*=11.87 Hz, 1 H) 2.23 (d, *J*=14.15 Hz, 1 H) 2.07 - 2.31 (m, 1 H) 2.51 - 2.62 (m, 1 H) 3.33 (dd, *J*=11.37, 2.27 Hz, 2 H) 3.95 (t, *J*=11.87 Hz, 2 H) 5.19 (dd, *J*=9.73, 5.68 Hz, 1 H) 6.40 (br.s., 1H) 7.11 (d, *J*=2.53 Hz, 1 H) 7.94 (s, 1 H) 8.09 (s, 1 H)
32	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpds. 2 and 3	[M+H] calc'd for $C_{17}H_{22}FN_4O_4S_2$, 429.10, found 429	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.09 (dq, *J*=7.86, 2.43 Hz, 2 H) 1.27 - 1.46 (m, 5 H) 1.53 (d, *J*=9.35 Hz, 1 H) 1.68 (d, *J*=11.87 Hz, 1 H) 2.23 (d, *J*=14.15 Hz, 1 H) 2.07 - 2.31 (m, 1 H) 2.51 - 2.62 (m, 1 H) 3.33 (dd, *J*=11.37, 2.27 Hz, 2 H) 3.95 (t, *J*=11.87 Hz, 2 H) 5.19 (dd, *J*=9.73, 5.68 Hz, 1 H) 6.40 (br.s., 1H) 7.11 (d, *J*=2.53 Hz, 1 H) 7.94 (s, 1 H) 8.09 (s, 1 H)

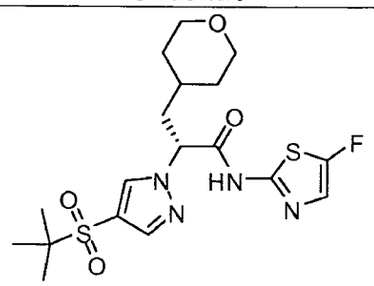
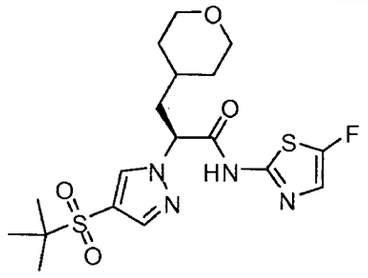
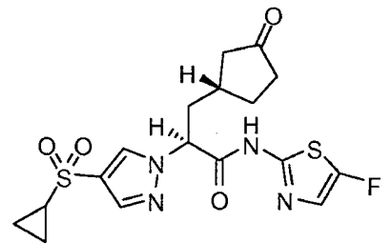
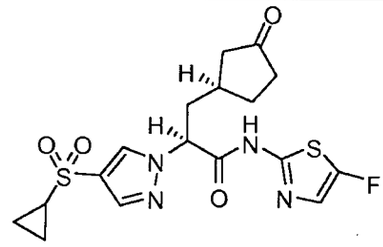
Ex.	Structure	Method	LCMS	NMR data
33	 N-(5-chlorothiazol-2-yl)-3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{22}ClN_4O_3S_2$, 429.07, found 429	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.15 (m, 4H) 1.36 (m, 2H) 1.59 (m, 6) 1.79 (m, 1H) 2.29 (m, 2H) 2.56 (m, 1H), 5.03 (m, 1H) 7.35 (s, 1H) 7.99 (s, 1H) 8.06 (m, 1H)
34	 3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{22}FN_4O_3S_2$, 413.50, found 413	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.13 (m, 4H) 1.37 (m, 2H) 1.57 (m, 6H) 1.79 (m, 1H) 2.25 (m, 2H) 2.55 (m, 1H) 5.02 (m, 1H) 7.14 (s, 1H) 7.97 (s, 1H) 8.17 (s, 1H)
35	 (R)-3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{22}FN_4O_3S_2$ 413.50; found 413.36	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.13 (m, 4H) 1.37 (m, 2H) 1.57 (m, 6H) 1.79 (m, 1H) 2.25 (m, 2H) 2.55 (m, 1H) 5.02 (m, 1H) 7.14 (s, 1H) 7.97 (s, 1H) 8.17 (s, 1H)
36	 (S)-3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{22}FN_4O_3S_2$ 413.50; found 413.36	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.13 (m, 4H) 1.37 (m, 2H) 1.57 (m, 6H) 1.79 (m, 1H) 2.25 (m, 2H) 2.55 (m, 1H) 5.02 (m, 1H) 7.14 (s, 1H) 7.97 (s, 1H) 8.17 (s, 1H)

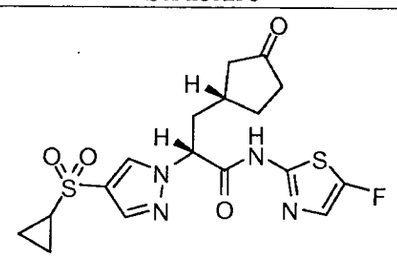
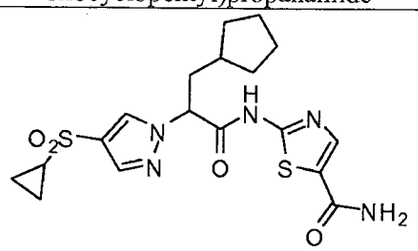
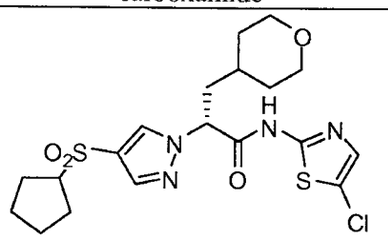
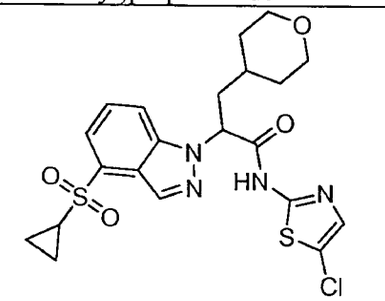
Ex.	Structure	Method	LCMS	NMR data
37	 2-(4-(cyclopentylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 5	[M+H] calc'd for $C_{19}H_{26}FN_4O_4S_2$ 457.56, found 457	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.34 (m, 3H) 1.50 (m, 1H) 1.65 (m, 3H) 1.77 (m, 2H) 2.02 (m, 4H) 2.16 (m, 1H), 2.24 (m, 1H) 3.29 (m, 2H) 3.50 (m, 1H) 3.94 (t, J = 16, 16 Hz, 2H) 5.13 (m, 1H) 7.08 (d, J = 4 Hz, 1H) 7.98 (s, 1H) 8.06 (s, 1H)
38	 (R)-N-(5-chlorothiazol-2-yl)-3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{22}ClN_4O_3S_2$ 429.96, found 429.36	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.15 (m, 4H) 1.36 (m, 2H) 1.59 (m, 6) 1.79 (m, 1H) 2.29 (m, 2H) 2.56 (m, 1H), 5.03 (m, 1H) 7.35 (s, 1H) 7.99 (s, 1H) 8.06 (m, 1H)
39	 (S)-N-(5-chlorothiazol-2-yl)-3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{22}ClN_4O_3S_2$ 429.96, Found 429.3	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.15 (m, 4H) 1.36 (m, 2H) 1.59 (m, 6) 1.79 (m, 1H) 2.29 (m, 2H) 2.56 (m, 1H), 5.03 (m, 1H) 7.35 (s, 1H) 7.99 (s, 1H) 8.06 (m, 1H)
40	 (R)-N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpds. 2 and 3	[M+H] calc'd for $C_{17}H_{22}ClN_4O_4S_2$, 445.07; found 445.2.	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.93 - 1.75 (m, 9 H) 2.19 (br. s., 2 H) 2.55 (br. s., 1 H) 3.31 (br. s., 2 H) 3.94 (br. s., 2 H) 5.10 (br. s., 1 H) 7.32 (s, 1 H) 8.01 (d, *J*=9.35 Hz, 2 H) 10.35 (bs, 1 H)

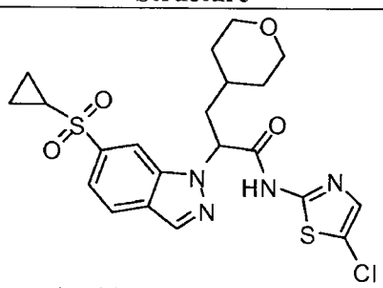
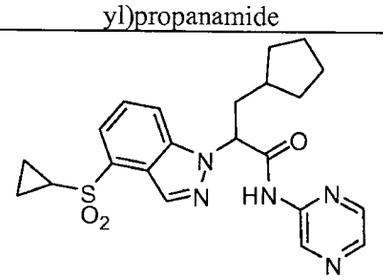
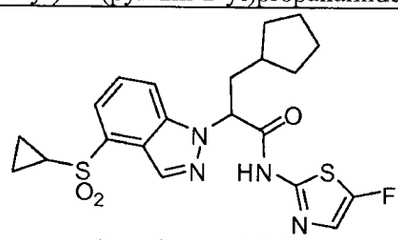
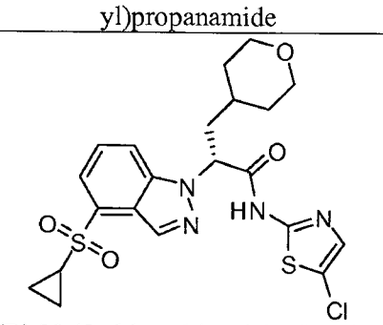
Ex.	Structure	Method	LCMS	NMR data
41	 N-(5-fluorothiazol-2-yl)-2-(4-(methylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd 10	[M+H] calc'd for $C_{19}H_{21}FN_4O_4S_2$ 454, found 454	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.21 - 1.42 (m, 3 H) 1.42 - 1.49 (m, 1 H) 1.66 - 1.74 (m, 1 H) 2.13 - 2.22 (m, 1 H) 2.49 - 2.58 (m, 1 H) 3.13 - 3.26 (m, 2 H) 3.29 (br. s., 3 H) 3.78 - 3.89 (m, 2 H) 5.65 (dd, *J*=10.61, 4.80 Hz, 1 H) 7.08 (d, *J*=2.53 Hz, 1 H) 7.30 - 7.41 (m, 2 H) 7.67 (d, *J*=8.08 Hz, 1 H) 8.11 (s, 1 H)
42	 (S)-N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpds. 2 and 3	[M+H] calc'd for $C_{17}H_{22}ClN_4O_4S_2$, 445.07; found 445.2.	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.93 - 1.75 (m, 9 H) 2.19 (br. s., 2 H) 2.55 (br. s., 1 H) 3.31 (br. s., 2 H) 3.94 (br. s., 2 H) 5.10 (br. s., 1 H) 7.32 (s, 1 H) 8.01 (d, *J*=9.35 Hz, 2 H) 10.35 (bs, 1 H)
43	 (R)-2-(4-(cyclopentylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 5	[M+H] calc'd for $C_{19}H_{26}FN_4O_4S_2$ 457.56, found 457	^{1}H NMR (400 MHz, CHLOROFORM-d). δ ppm 1.34 (m, 3H) 1.50 (m, 1H) 1.65 (m, 3H) 1.77 (m, 2H) 2.02 (m, 4H) 2.16 (m, 1H), 2.24 (m, 1H) 3.29 (m, 2H) 3.50 (m, 1H) 3.94 (t, J = 16, 16 Hz, 2H) 5.13 (m, 1H) 7.08 (d, J = 4 Hz, 1H) 7.98 (s, 1H) 8.06 (s, 1H)
44	 (S)-2-(4-(cyclopentylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 5	[M+H] calc'd for $C_{19}H_{26}FN_4O_4S_2$ 457.56, found 457	^{1}H NMR (400 MHz, CHLOROFORM-d). δ ppm 1.34 (m, 3H) 1.50 (m, 1H) 1.65 (m, 3H) 1.77 (m, 2H) 2.02 (m, 4H) 2.16 (m, 1H), 2.24 (m, 1H) 3.29 (m, 2H) 3.50 (m, 1H) 3.94 (t, J = 16, 16 Hz, 2H) 5.13 (m, 1H) 7.08 (d, J = 4 Hz, 1H) 7.98 (s, 1H) 8.06 (s, 1H)

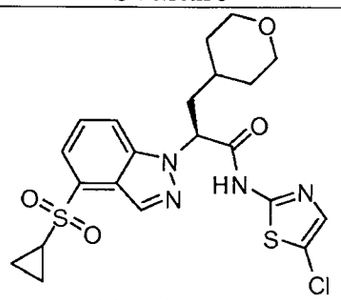
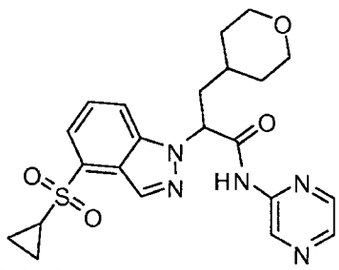
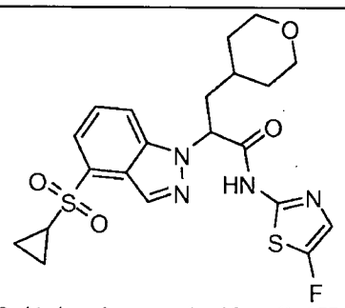
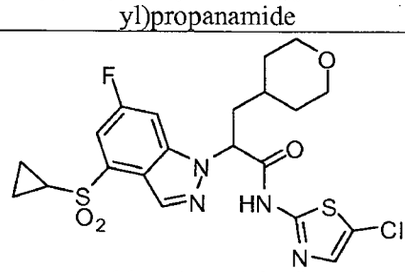
Ex.	Structure	Method	LCMS	NMR data
45	 N-(5-chloropyridin-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{19}H_{24}ClN_4O_4S$, 439.11, found 439	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.08 (dd, *J*=8.08, 2.02 Hz, 2 H) 1.30 - 1.44 (m, 1 H) 1.36 (dd, *J*=4.42, 2.15 Hz, 4 H) 1.53 (d, *J*=9.09 Hz, 1 H) 1.68 (d, *J*=9.85 Hz, 1 H) 2.19 (t, *J*=6.32 Hz, 1 H) 2.25 (dd, *J*=9.85, 4.04 Hz, 1 H) 2.57 (ddd, *J*=7.96, 4.80, 3.16 Hz, 1 H) 3.31 (td, *J*=11.24, 8.08 Hz, 1 H) 3.25 - 3.37 (m, 1 H) 3.88 - 4.00 (m, 2 H) 5.12 (dd, *J*=9.73, 5.68 Hz, 1 H) 7.74 (dd, *J*=8.84, 2.53 Hz, 1 H) 7.98 (s, 1 H) 8.11 (s, 1 H) 8.20 (d, *J*=8.84 Hz, 1 H) 8.24 (d, *J*=2.27 Hz, 1 H) 9.66 (br. s., 1 H)
46	 2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{18}H_{24}N_5O_4S$, 406.15, found 406	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.09 (dd, *J*=7.71, 1.64 Hz, 2 H) 1.29 - 1.47 (m, 5 H) 1.54 (br. s., 1 H) 1.66 (br. s., 1 H) 2.14 - 2.38 (m, 2 H) 2.51 - 2.63 (m, 1 H) 3.23 - 3.42 (m, 2 H) 3.87 - 4.03 (m, 2 H) 5.07 (dd, *J*=9.60, 5.56 Hz, 1 H) 8.03 (d, *J*=6.57 Hz, 2 H) 8.32 (s, 1 H) 8.42 (d, *J*=2.27 Hz, 1 H) 9.27 (br. s., 1 H) 9.50 (s, 1 H)
47	 (R)-N-(5-chlorothiazol-2-yl)-2-(5-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}ClN_4O_4S_2$ 496.01, found 496.1	

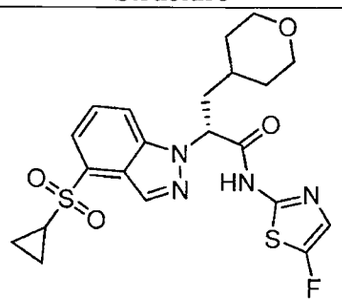
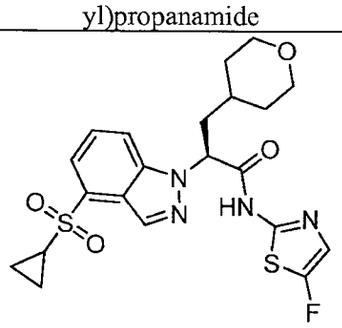
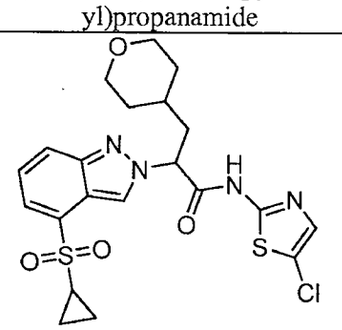
Ex.	Structure	Method	LCMS	NMR data
48	 (S)-N-(5-chlorothiazol-2-yl)-2-(5-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}ClN_4O_4S_2$ 496.01, found 496.1	
49	 2-(4-(tert-butylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{18}H_{26}FN_4O_4S_2$, 445.13, found 445.3	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 - 1.45 (m, 3 H) 1.38 (s, 9 H) 1.51 (d, *J*=2.27 Hz, 1 H) 1.64 (d, *J*=11.62 Hz, 1 H) 2.04 - 2.29 (m, 2 H) 3.14 - 3.35 (m, 2 H) 3.80 - 4.02 (m, 2 H) 5.12 (dd, *J*=9.85, 5.81 Hz, 1 H) 7.12 (d, *J*=2.78 Hz, 1 H) 7.95 (s, 1 H) 8.03 (s, 1 H)
50	 2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(3-oxocyclopentyl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{20}FN_4O_4S_2$ 427.08, found 427.1	
51	 N-(5-chlorothiazol-2-yl)-2-(5-(cyclopropylsulfonyl)-2H-indazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}ClN_4O_4S_2$ 496.01, found 496.1	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.00 - 1.13 (m, 2 H) 1.20 - 1.64 (m, 7 H) 1.76 (d, *J*=12.38 Hz, 1 H) 2.27 - 2.42 (m, 1 H) 2.43 - 2.60 (m, 2 H) 3.30 (t, *J*=10.86 Hz, 2 H) 3.87 - 4.08 (m, 2 H) 5.57 (dd, *J*=9.73, 5.18 Hz, 1 H) 7.32 (br. s., 1 H) 7.70 - 7.82 (m, 1 H) 7.87 (d, *J*=9.09 Hz, 1 H) 8.42 (d, *J*=5.56 Hz, 2 H)

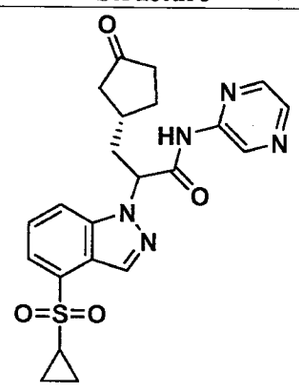
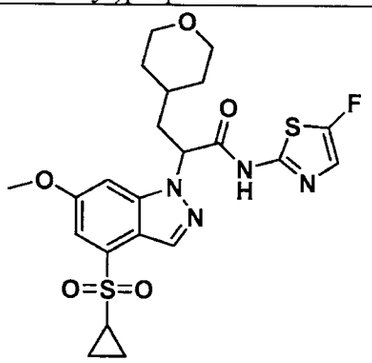
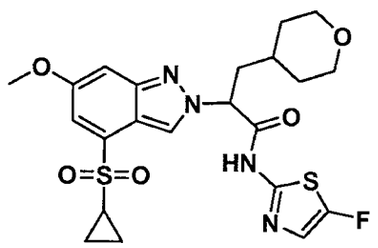
Ex.	Structure	Method	LCMS	NMR data
52	 (R)-2-(4-(tert-butylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpds. 2 and 3	[M+H] calc'd for $C_{18}H_{26}FN_4O_4S_2$, 445.13, found 445.3	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 - 1.45 (m, 3 H) 1.38 (s, 9 H) 1.51 (d, *J*=2.27 Hz, 1 H) 1.64 (d, *J*=11.62 Hz, 1 H) 2.04 - 2.29 (m, 2 H) 3.14 - 3.35 (m, 2 H) 3.80 - 4.02 (m, 2 H) 5.12 (dd, *J*=9.85, 5.81 Hz, 1 H) 7.12 (d, *J*=2.78 Hz, 1 H) 7.95 (s, 1 H) 8.03 (s, 1 H)
53	 (S)-2-(4-(tert-butylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpds. 2 and 3	[M+H] calc'd for $C_{18}H_{26}FN_4O_4S_2$, 445.13, found 445.3	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 - 1.45 (m, 3 H) 1.38 (s, 9 H) 1.51 (d, *J*=2.27 Hz, 1 H) 1.64 (d, *J*=11.62 Hz, 1 H) 2.04 - 2.29 (m, 2 H) 3.14 - 3.35 (m, 2 H) 3.80 - 4.02 (m, 2 H) 5.12 (dd, *J*=9.85, 5.81 Hz, 1 H) 7.12 (d, *J*=2.78 Hz, 1 H) 7.95 (s, 1 H) 8.03 (s, 1 H)
54	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-((R)-3-oxocyclopentyl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{20}FN_4O_4S_2$ 427.08, found 427.1	
55	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-((S)-3-oxocyclopentyl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{20}FN_4O_4S_2$ 427.08, found 427.1	

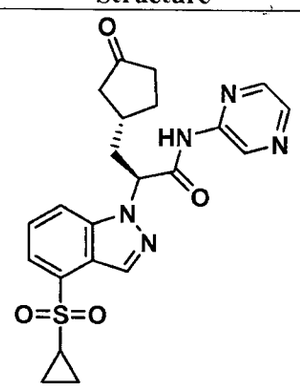
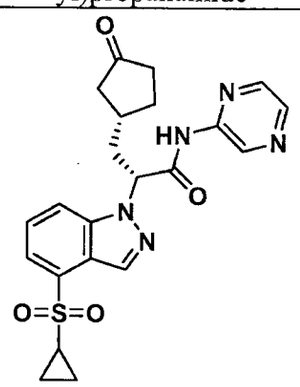
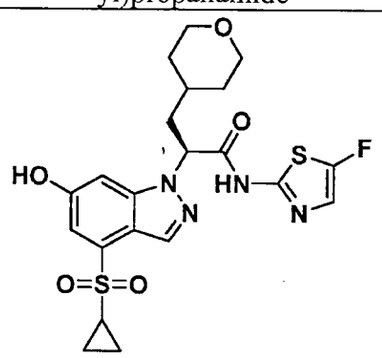
Ex.	Structure	Method	LCMS	NMR data
56	 (R)-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-((R)-3-oxocyclopentyl)propanamide	*See* Cmpd. 4	[M+H] calc'd for $C_{17}H_{20}FN_4O_4S_2$ 427.08, found 427.1	
57	 2-(3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-pyrazol-1-yl)propanamido)thiazole-5-carboxamide	*See* Cmpds. 6 and 7	[M+H] calc'd for $C_{18}H_{24}N_5O_4S_2$ 438.54, found 438	^{1}H NMR (400 MHz, DMSO-d6). δ ppm 1.06 (m, 4H) 1.27 (m, 1H) 1.56 (m, 6H) 2.11 (m, 1H) 2.33 (m, 1H) 2.84 (m, 1H), 3.75 (s, 2H) 5.36 (m, 1H) 7.95 (s, 1H) 8.08 (s, 1H) 8.63 (s, 1H)
58	 (R)-N-(5-chlorothiazol-2-yl)-2-(4-(cyclopentylsulfonyl)-1H-pyrazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 5	[M+H] calc'd for $C_{19}H_{26}ClN_4O_4S_2$ 474.01, found 474	^{1}H NMR (400 MHz, CHLOROFORM-d). δ ppm 1.34 (m, 3H) 1.50 (m, 1H) 1.65 (m, 3H) 1.77 (m, 2H) 2.02 (m, 4H) 2.19 (m, 2H), 3.29 (m, 2H) 3.52 (m, 1H) 3.95 (t, J = 12, 12 Hz, 2H) 5.16 (m, 1H) 7.32 (d, J = 4 Hz, 1H) 7.98 (s, 1H) 8.06 (s, 1H)
59	 N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}ClN_4O_4S_2$ 496.01, found 496.1	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.12 (m, 2 H) 1.14 - 1.38 (m, 5 H) 1.45 (br. s., 1 H) 1.60 (br. s., 1 H) 2.26 (d, *J*=6.57 Hz, 1 H) 2.46 (br. s., 1 H) 2.91 - 3.21 (m, 3 H) 3.68 - 3.84 (m, 2 H) 5.87 (dd, *J*=9.98, 4.93 Hz, 1 H) 7.56 (s, 1 H) 7.63 - 7.76 (m, 2 H) 8.18 (d, *J*=8.34 Hz, 1 H) 8.45 (s, 1 H)

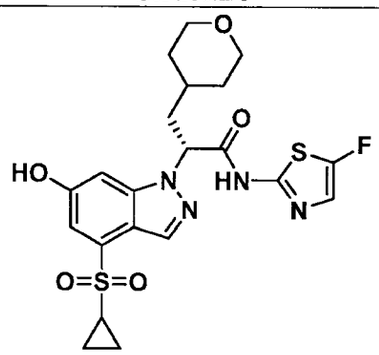
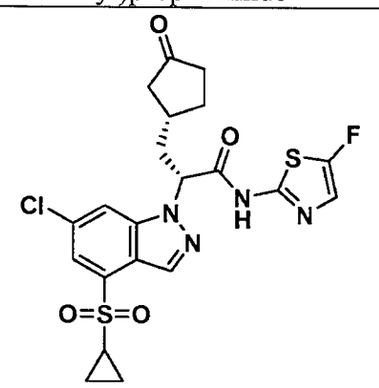
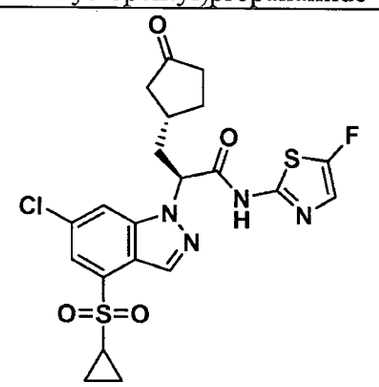
Ex.	Structure	Method	LCMS	NMR data
60	 N-(5-chlorothiazol-2-yl)-2-(6-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}ClN_4O_4S_2$ 496.01, found 496.1	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.09 (m, 2 H) 1.12 - 1.37 (m, 5 H) 1.45 (d, *J*=8.08 Hz, 1 H) 1.60 (d, *J*=12.13 Hz, 1 H) 2.21 - 2.33 (m, 1 H) 2.35 - 2.47 (m, 1 H) 2.83 - 2.94 (m, 1 H) 3.00 - 3.17 (m, 2 H) 3.70 - 3.85 (m, 2 H) 5.93 (dd, *J*=9.60, 5.31 Hz, 1 H) 7.56 (s, 1 H) 7.64 - 7.72 (m, 1 H) 8.08 (d, *J*=8.59 Hz, 1 H) 8.41 (d, *J*=10.86 Hz, 2 H)
61	 3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(pyrazin-2-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{26}N_5O_3S$ 440.53; found 440	^{1}H NMR (400 MHz, MeOD). δ ppm 1.06 (m, 3H) 1.29 (m, 3H) 1.43 (m, 2H) 1.60 (m, 4H) 1.74 (m, 1H) 2.31 (m, 1H) 2.64 (m, 1H) 2.81 (m, 1H) 5.64 (m, 1H) 7.74 (d, J = 4 Hz, 1H) 8.11 (d, J = 8 Hz, 1H) 8.30 (s, 1H) 8.34 (s, 1H) 8.50 (s, 1H)
62	 3-cyclopentyl-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}FN_4O_3S_2$ 463.56; found 463	^{1}H NMR (400 MHz, MeOD). δ ppm 1.07 (m, 3H) 1.29 (m, 3H) 1.45 (m, 3H) 1.60 (m, 3H) 1.74 (m, 1H) 2.29 (m, 1H) 2.60 (m, 1H) 2.80 (m, 1H) 5.64 (m, 1H) 7.09 (d, J = 4 Hz, 1H) 7.64 (t, J = 8, 8 Hz, 1H) 7.74 (d, J = 8 Hz, 1H) 8.09 (d, J = 12 Hz, 1H) 8.47 (s, 1H)
63	 (R)-N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}ClN_4O_4S_2$ 496.01, found 496.1	

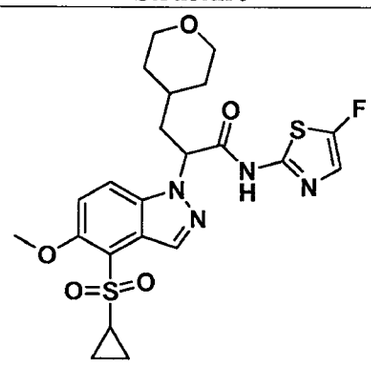
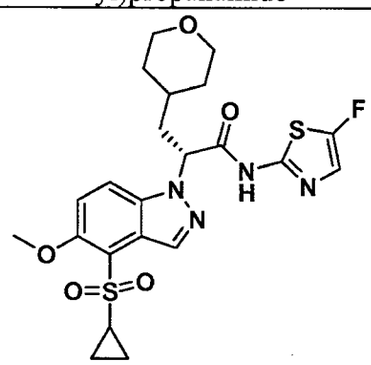
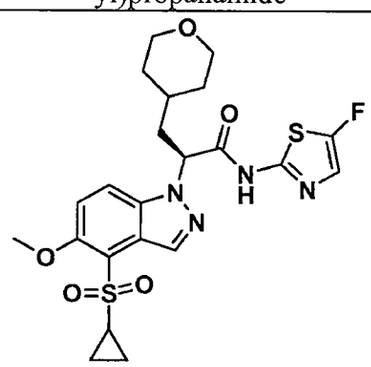
Ex.	Structure	Method	LCMS	NMR data
64	 (S)-N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}ClN_4O_4S_2$ 496.01, found 496.1	
65	 2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{26}N_5O_4S$ 456.53, found 456.5	^{1}H NMR (400 MHz, MeOD) δ ppm 0.91 - 1.03 (m, 2 H) 1.16 - 1.35 (m, 5 H) 1.38 - 1.47 (m, 1 H) 1.59 - 1.70 (m, 1 H) 2.10 - 2.21 (m, 1 H) 2.47 - 2.59 (m, 1 H) 2.72 (tt, *J*=7.89, 4.74 Hz, 1 H) 3.05 - 3.18 (m, 2 H) 3.68 - 3.83 (m, 2 H) 5.71 (dd, *J*=10.61, 4.80 Hz, 1 H) 7.51 - 7.59 (m, 1 H) 7.63 - 7.69 (m, 1 H) 8.02 (d, *J*=8.59 Hz, 1 H) 8.24 (d, *J*=15.92 Hz, 2 H) 8.40 (s, 1 H) 9.23 (br. s., 1 H)
66	 2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}FN_4O_4S_2$ 479.56, found 479.5	^{1}H NMR (400 MHz, MeOD) δ ppm 0.94 - 1.00 (m, 2 H) 1.17 - 1.32 (m, 5 H) 1.35 - 1.43 (m, 1 H) 1.58 - 1.67 (m, 1 H) 2.08 - 2.18 (m, 1 H) 2.48 (ddd, *J*=14.46, 10.42, 4.42 Hz, 1 H) 2.72 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.04 - 3.17 (m, 2 H) 3.69 - 3.82 (m, 2 H) 5.66 (dd, *J*=10.61, 5.05 Hz, 1 H) 6.99 (d, *J*=2.53 Hz, 1 H) 7.55 (dd, *J*=8.34, 7.33 Hz, 1 H) 7.66 (d, *J*=6.57 Hz, 1 H) 7.97 (d, *J*=8.59 Hz, 1 H) 8.38 (s, 1 H)
67	 N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-6-fluoro-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{23}ClFN_4O_4S_2$ 514.01, found 514	^{1}H NMR (400 MHz, MeOD) δ ppm 1.09 (m, 2 H) 1.32 (m, 5 H) 1.47 (m, 1 H) 1.70 (m, 1 H) 2.23 (m, 1 H) 2.56 (m, 1 H) 2.86 (m, 1 H) 3.20 (m, 2 H) 3.85 (m, 2 H) 5.71 (m, 1 H) 7.56 (m, 1 H) 7.87 (m, 1 H) 8.47 (s, 1 H)

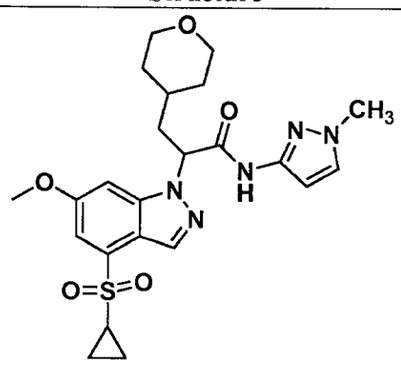
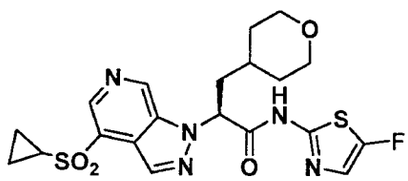
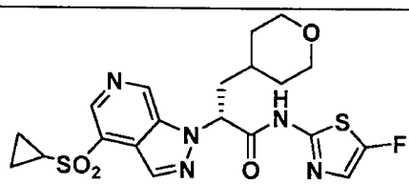
Ex.	Structure	Method	LCMS	NMR data
68	 (R)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}FN_4O_4S_2$ 479.56, found 479.5	
69	 (S)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}FN_4O_4S_2$ 479.56, found 479.5	
70	 N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-2H-indazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}ClN_4O_4S_2$ 496.01, found 496.1	^{1}H NMR (400 MHz, MeOD) δ ppm 0.93 - 1.00 (m, 2 H) 1.16 - 1.36 (m, 5 H) 1.39 - 1.47 (m, 1 H) 1.64 - 1.74 (m, 1 H) 2.09 - 2.21 (m, 1 H) 2.40 (ddd, *J*=14.46, 10.17, 4.67 Hz, 1 H) 2.71 - 2.75 (m, 1 H) 3.11 - 3.20 (m, 2 H) 3.70 - 3.84 (m, 2 H) 5.63 (dd, *J*=10.36, 5.31 Hz, 1 H) 7.24 (s, 1 H) 7.41 (dd, *J*=8.59, 7.07 Hz, 1 H) 7.62 (d, *J*=6.32 Hz, 1 H) 7.89 (d, *J*=8.84 Hz, 1 H) 8.67 (d, *J*=1.01 Hz, 1 H)

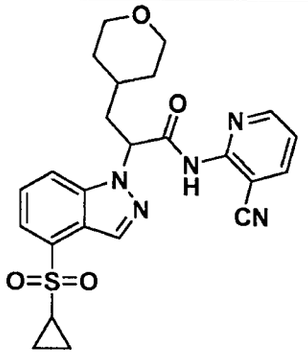
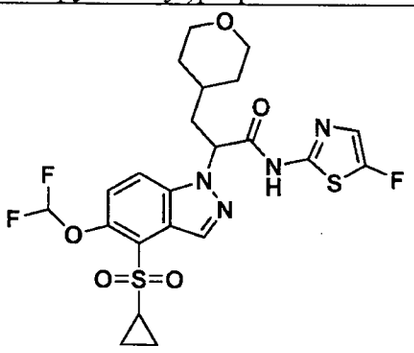
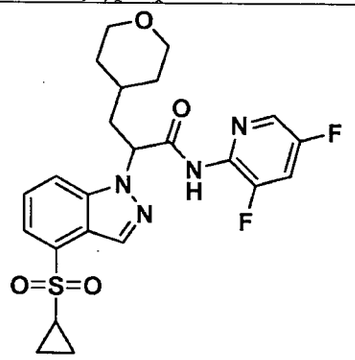
Ex.	Structure	Method	LCMS	NMR data
71	 2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-((R)-3-oxocyclopentyl)-N-(pyrazin-2-yl)propanamide	*See* Cmpd. 11	[M+H] calc'd for $C_{22}H_{24}N_5O_4S$ 454.2, found 454.0	see separated diastereomers for ^{1}H NMR
72	 2-(4-(cyclopropylsulfonyl)-6-methoxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{26}FN_4O_5S_2$ 509, found 509	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.52 (s, 1 H), 7.45 (d, *J*=1.8 Hz, 1 H), 7.00 (br. s., 1 H), 6.96 (s, 1 H), 5.30 (s, 1 H), 3.95 (s, 3 H), 3.78 - 3.93 (m, 2 H), 3.13 - 3.30 (m, 2 H), 2.57 - 2.73 (m, 1 H), 2.50 (br. s., 1 H), 2.25 (d, *J*=5.6 Hz, 1 H), 1.59 (d, *J*=12.4 Hz, 1 H), 1.44 - 1.55 (m, 2 H), 1.28 - 1.44 (m, 4 H), 1.01 - 1.16 ppm (m, 2 H)
73	 2-(4-(cyclopropylsulfonyl)-6-methoxy-2H-indazol-2-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{26}FN_4O_5S_2$ 509, found 509	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.37 (s, 1 H), 7.45 (d, *J*=2.0 Hz, 1 H), 7.27 (d, *J*=2.0 Hz, 1 H), 7.02 (d, *J*=2.8 Hz, 1 H), 5.25 (dd, *J*=10.0, 5.4 Hz, 1 H), 3.95 (s, 3 H), 3.73 - 3.91 (m, 2 H), 3.20 - 3.33 (m, 2 H), 2.49 - 2.58 (m, 1 H), 2.37 - 2.48 (m, 1 H), 2.21 - 2.32 (m, 1 H), 1.69 (d, *J*=12.1 Hz, 1 H), 1.51 (dd, *J*=9.3, 2.0 Hz, 1 H), 1.28 - 1.45 (m, 5 H), 0.99 - 1.08 ppm (m, 2 H)

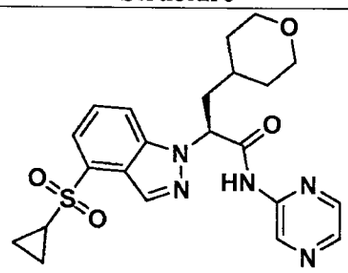
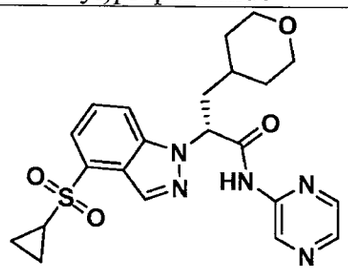
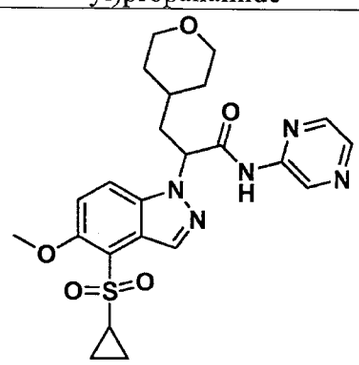
Ex.	Structure	Method	LCMS	NMR data
74	 (S)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-((R)-3-oxocyclopentyl)-N-(pyrazin-2-yl)propanamide	*See* Cmpd. 11	[M+H] calc'd for $C_{22}H_{24}N_5O_4S$ 454.2, found 454.0	^{1}H NMR (400 MHz, MeOD) δ ppm 1.01 - 1.14 (m, 2 H) 1.16 - 1.32 (m, 2 H) 1.62 - 1.85 (m, 2 H) 2.00 - 2.13 (m, 3 H) 2.15 - 2.29 (m, 2 H) 2.52 (ddd, *J*=14.08, 7.14, 5.05 Hz, 1 H) 2.65 - 2.86 (m, 2 H) 5.79 (dd, *J*=10.11, 5.05 Hz, 1 H) 7.55 - 7.72 (m, 1 H) 7.76 (d, *J*=6.57 Hz, 1 H) 8.14 (d, *J*=8.59 Hz, 1 H) 8.24 - 8.44 (m, 2 H) 8.51 (s, 1 H) 9.29 - 9.37 (m, 1 H)
75	 (R)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-((R)-3-oxocyclopentyl)-N-(pyrazin-2-yl)propanamide	*See* Cmpd. 11	[M+H] calc'd for $C_{22}H_{24}N_5O_4S$ 454.2, found 454.0	^{1}H NMR (400 MHz, MeOD) δ ppm 0.92 - 1.13 (m, 2 H) 1.18 - 1.37 (m, 2 H) 1.50 - 1.68 (m, 1 H) 1.89 - 2.13 (m, 4 H) 2.14 - 2.39 (m, 2 H) 2.44 (ddd, *J*=13.96, 8.91, 4.93 Hz, 1 H) 2.70 - 2.92 (m, 2 H) 5.73 (dd, *J*=10.61, 4.80 Hz, 1 H) 7.52 - 7.73 (m, 1 H) 7.75 (d, *J*=6.82 Hz, 1 H) 8.13 (d, *J*=8.59 Hz, 1 H) 8.35 (br. s., 2 H) 8.51 (s, 1 H) 9.33 (br. s., 1 H)
76	 (S)-2-(4-(cyclopropylsulfonyl)-6-hydroxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}FN_4O_5S_2$ 495, found 495	^{1}H NMR (DMSO-d_6 ,400MHz): δ = 12.70 (s, 1 H), 10.48 (s, 1 H), 8.23 (s, 1 H), 7.33 - 7.36 (m, 2 H), 7.23 (d, *J*=1.8 Hz, 1 H), 5.62 (d, *J*=4.3 Hz, 1 H), 3.71 - 3.85 (m, 3 H), 3.06 - 3.21 (m, 2 H), 2.24 - 2.41 (m, 1 H), 2.09 - 2.24 (m, 1 H), 1.54 - 1.63 (m, 1 H), 1.48 (br. s., 1 H), 1.28 (br. s., 3 H), 1.16 (br. s., 2 H), 1.06 ppm (dd, *J*=7.8, 2.0 Hz, 2 H)

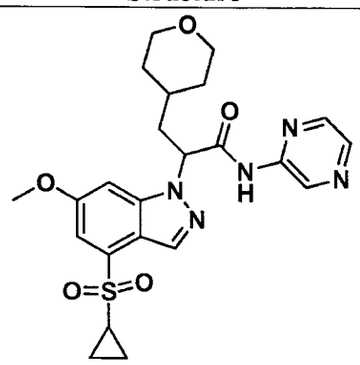
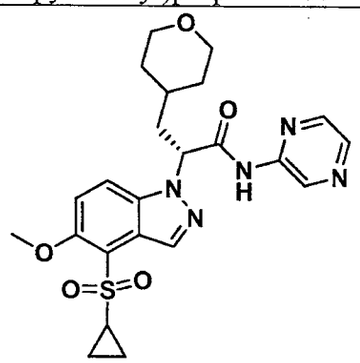
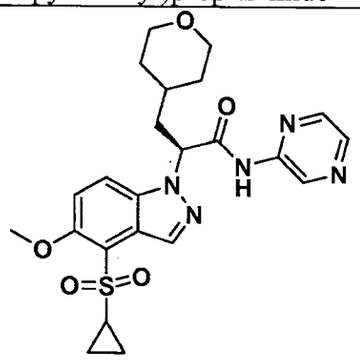
Ex.	Structure	Method	LCMS	NMR data
77	 (R)-2-(4-(cyclopropylsulfonyl)-6-hydroxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}FN_4O_5S_2$ 495, found 495	^{1}H NMR (DMSO-d_6 ,400MHz): δ = 12.70 (s, 1 H), 10.48 (s, 1 H), 8.23 (s, 1 H), 7.33 - 7.36 (m, 2 H), 7.23 (d, *J*=1.8 Hz, 1 H), 5.62 (d, *J*=4.3 Hz, 1 H), 3.71 - 3.85 (m, 3 H), 3.06 - 3.21 (m, 2 H), 2.24 - 2.41 (m, 1 H), 2.09 - 2.24 (m, 1 H), 1.54 - 1.63 (m, 1 H), 1.48 (br. s., 1 H), 1.28 (br. s., 3 H), 1.16 (br. s., 2 H), 1.06 ppm (dd, *J*=7.8, 2.0 Hz, 2 H)
78	 (R)-2-(6-chloro-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-((R)-3-oxocyclopentyl)propanamide	*See* Cmpd. 11	[M+H] calc'd for $C_{21}H_{21}ClFN_4O_4S_2$ 511.1, found 511.3	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.07 - 1.31 (m, 2 H) 1.34 - 1.57 (m, 2 H) 1.57 - 1.84 (m, 3 H) 1.93 - 2.21 (m, 3 H) 2.32 (dd, *J*=18.32, 8.21 Hz, 1 H) 2.47 - 2.70 (m, 2 H) 2.97 - 3.20 (m, 1 H) 5.33 (dd, *J*=9.98, 5.18 Hz, 1 H) 6.93 - 7.13 (m, 1 H) 7.71 - 7.91 (m, 2 H) 8.49 - 8.69 (m, 1 H)
79	 (S)-2-(6-chloro-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-((R)-3-oxocyclopentyl)propanamide	*See* Cmpd. 11	[M+H] calc'd for $C_{21}H_{21}ClFN_4O_4S_2$ 511.1, found 511.3	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.07 - 1.31 (m, 2 H) 1.39 - 1.69 (m, 4 H) 1.81 - 1.92 (m, 1 H) 1.93 - 2.14 (m, 2 H) 2.18 - 2.38 (m, 2 H) 2.46 (ddd, *J*=14.02, 8.84, 5.18 Hz, 1 H) 2.53 - 2.79 (m, 2 H) 5.27 (dd, *J*=10.48, 4.93 Hz, 1 H) 7.03 (d, *J*=3.03 Hz, 1 H) 7.71 - 7.93 (m, 2 H) 8.63 (s, 1 H)

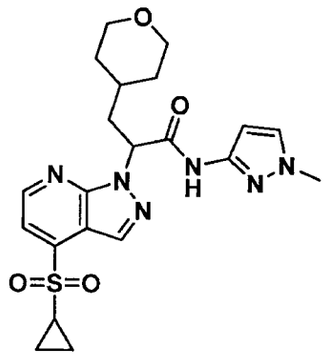
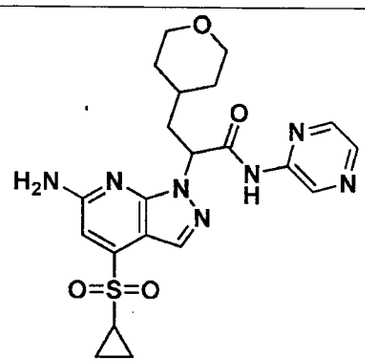
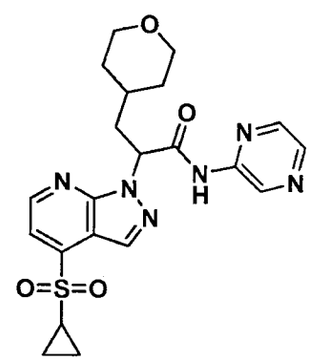
Ex.	Structure	Method	LCMS	NMR data
80	 2-(4-(cyclopropylsulfonyl)-5-methoxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 15	[M+H] calc'd for $C_{22}H_{26}FN_4O_5S_2$ 509, found 509	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.74 (s, 1 H), 7.67 (d, *J*=9.1 Hz, 1 H), 7.33 (d, *J*=9.3 Hz, 1 H), 7.02 (d, *J*=2.8 Hz, 1 H), 5.37 (dd, *J*=10.6, 4.8 Hz, 1 H), 4.08 (s, 3 H), 3.82 - 3.95 (m, 2 H), 3.05 - 3.29 (m, 3 H), 2.49 (ddd, *J*=14.2, 10.5, 5.1 Hz, 1 H), 2.23 (ddd, *J*=14.0, 8.8, 4.8 Hz, 1 H), 1.53 - 1.66 (m, 1 H), 1.42 - 1.49 (m, 2 H), 1.27 - 1.42 (m, 3 H), 1.21 (dd, *J*=7.5, 3.9 Hz, 1 H), 1.02 ppm (dddd, *J*=16.8, 8.1, 6.5, 4.9 Hz, 2 H)
81	 (R)-2-(4-(cyclopropylsulfonyl)-5-methoxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 15	[M+H] calc'd for $C_{22}H_{26}FN_4O_5S_2$ 509, found 509	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.74 (s, 1 H), 7.67 (d, *J*=9.1 Hz, 1 H), 7.33 (d, *J*=9.3 Hz, 1 H), 7.02 (d, *J*=2.8 Hz, 1 H), 5.37 (dd, *J*=10.6, 4.8 Hz, 1 H), 4.08 (s, 3 H), 3.82 - 3.95 (m, 2 H), 3.05 - 3.29 (m, 3 H), 2.49 (ddd, *J*=14.2, 10.5, 5.1 Hz, 1 H), 2.23 (ddd, *J*=14.0, 8.8, 4.8 Hz, 1 H), 1.53 - 1.66 (m, 1 H), 1.42 - 1.49 (m, 2 H), 1.27 - 1.42 (m, 3 H), 1.21 (dd, *J*=7.5, 3.9 Hz, 1 H), 1.02 ppm (dddd, *J*=16.8, 8.1, 6.5, 4.9 Hz, 2 H)
82	 (S)-2-(4-(cyclopropylsulfonyl)-5-methoxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 15	[M+H] calc'd for $C_{22}H_{26}FN_4O_5S_2$ 509, found 509	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.74 (s, 1 H), 7.67 (d, *J*=9.1 Hz, 1 H), 7.33 (d, *J*=9.3 Hz, 1 H), 7.02 (d, *J*=2.8 Hz, 1 H), 5.37 (dd, *J*=10.6, 4.8 Hz, 1 H), 4.08 (s, 3 H), 3.82 - 3.95 (m, 2 H), 3.05 - 3.29 (m, 3 H), 2.49 (ddd, *J*=14.2, 10.5, 5.1 Hz, 1 H), 2.23 (ddd, *J*=14.0, 8.8, 4.8 Hz, 1 H), 1.53 - 1.66 (m, 1 H), 1.42 - 1.49 (m, 2 H), 1.27 - 1.42 (m, 3 H), 1.21 (dd, *J*=7.5, 3.9 Hz, 1 H), 1.02 ppm (dddd, *J*=16.8, 8.1, 6.5, 4.9 Hz, 2 H)

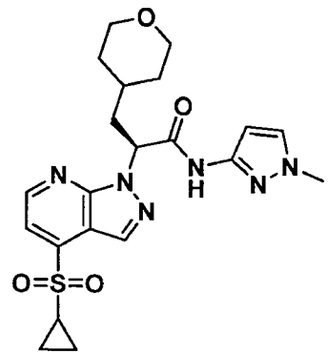
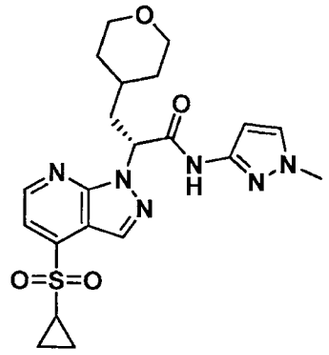
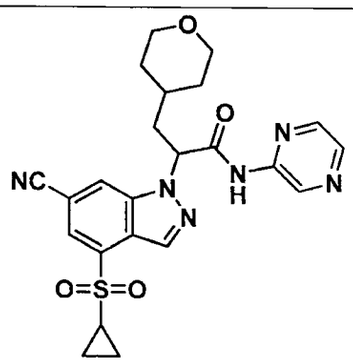
Ex.	Structure	Method	LCMS	NMR data
83	 2-(4-(cyclopropylsulfonyl)-6-methoxy-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{23}H_{30}N_5O_5S$ 488, found 488	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 10.28 (s, 1 H), 8.45 (s, 1 H), 7.42 (d, *J*=1.8 Hz, 1 H), 7.33 (d, *J*=2.3 Hz, 1 H), 7.12 - 7.18 (m, 1 H), 6.77 (d, *J*=2.5 Hz, 1 H), 5.40 (dd, *J*=10.1, 5.1 Hz, 1 H), 3.93 (s, 3 H), 3.90 - 4.04 (m, 2 H), 3.85 (s, 3 H), 3.21 - 3.40 (m, 2 H), 2.48 - 2.66 (m, 2 H), 2.22 - 2.34 (m, 1 H), 1.68 (d, *J*=12.4 Hz, 1 H), 1.51 - 1.61 (m, 1 H), 1.28 - 1.50 (m, 5 H), 0.97 - 1.12 ppm (m, 2 H)
84	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 13	[M+H] calc'd for $C_{20}H_{23}FN_5O_4S_2$ 480, found 480	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.09 - 1.19 (m, 2 H) 1.21 - 1.29 (m, 1 H) 1.31 - 1.55 (m, 5 H) 1.59 - 1.72 (m, 1 H) 2.33 (ddd, *J*=14.15, 8.34, 5.31 Hz, 1 H) 2.42 - 2.56 (m, 1 H) 2.64 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.22 (m, *J*=17.91, 11.64, 11.64, 2.27 Hz, 2 H) 3.90 (ddd, *J*=13.45, 11.43, 2.65 Hz, 2 H) 5.61 (dd, *J*=10.23, 5.43 Hz, 1 H) 7.09 (d, *J*=2.78 Hz, 1 H) 8.65 (s, 1 H) 8.87 (s, 1 H) 9.34 (s, 1 H) 9.99 (br. s., 1 H)
85	 (R)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 13	[M+H] calc'd for $C_{20}H_{23}FN_5O_4S_2$ 480, found 480	

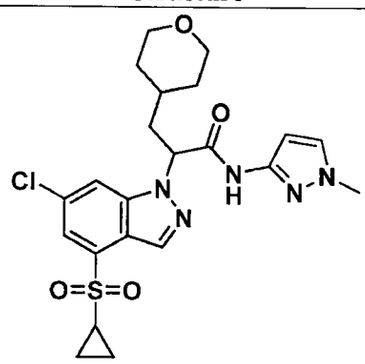
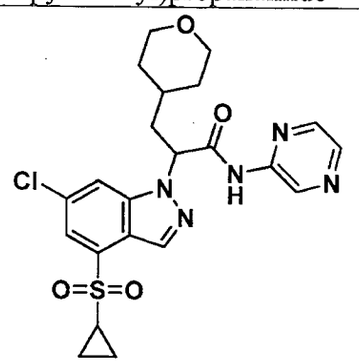
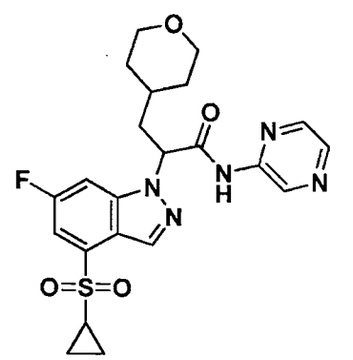
Ex.	Structure	Method	LCMS	NMR data
86	 N-(3-cyanopyridin-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{24}H_{26}N_5O_4S$ 480.3, found 480.5	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.89 - 1.05 (m, 2 H) 1.18 - 1.45 (m, 5 H) 1.49 (d, *J*=9.60 Hz, 1 H) 1.53 - 1.65 (m, 1 H) 2.15 - 2.36 (m, 3 H) 2.36 - 2.63 (m, 2 H) 3.07 - 3.28 (m, 2 H) 3.83 (t, *J*=10.74 Hz, 2 H) 5.44 (dd, *J*=9.98, 5.18 Hz, 1 H) 7.55 (dd, *J*=8.72, 7.20 Hz, 1 H) 7.73 (d, *J*=7.58 Hz, 2 H) 7.91 (d, *J*=7.83 Hz, 1 H) 8.62 (s, 1 H), 9.50 (s, 1H)
87	 2-(4-(cyclopropylsulfonyl)-5-(difluoromethoxy)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 12	[M+H] calc'd for $C_{22}H_{24}F_3N_4O_5S_2$ 545, found 545	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.02 - 1.13 (m, 2 H) 1.34 - 1.49 (m, 4 H) 1.50 - 1.61 (m, 1 H) 1.65 - 1.76 (m, 1 H) 2.24 - 2.35 (m, 1 H) 2.47 - 2.60 (m, 1 H) 2.66 - 2.77 (m, 2 H) 3.20 - 3.36 (m, 2 H) 3.89 - 3.99 (m, 2 H) 5.46 (dd, *J*=10.86, 4.80 Hz, 1 H) 6.93 (s, 1 H) 7.07 - 7.13 (m, 1 H) 7.29 - 7.60 (m, 1 H) 7.58 - 7.67 (m, 1 H) 8.27 (s, 1 H)
88	 2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(3,5-difluoropyridin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{23}H_{25}F2N_4O_4S$ 491.5, found 491.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.94 - 1.13 (m, 2 H) 1.13 - 1.37 (m, 4 H) 1.47 - 1.59 (m, 1 H) 1.66 (d, *J*=10.11 Hz, 1 H) 2.25 (d, *J*=7.83 Hz, 1 H) 2.34 - 2.47 (m, 1 H) 2.92 - 3.22 (m, 4 H) 3.71 - 3.86 (m, 2 H) 5.82 (dd, *J*=9.73, 5.43 Hz, 1 H) 7.59 - 7.79 (m, 2 H) 8.02 (ddd, *J*=9.79, 8.40, 2.53 Hz, 1 H) 8.21 (d, *J*=8.34 Hz, 1 H) 8.35 (d, *J*=2.53 Hz, 1 H) 8.39 - 8.51 (m, 1 H) 10.73 (s, 1 H)

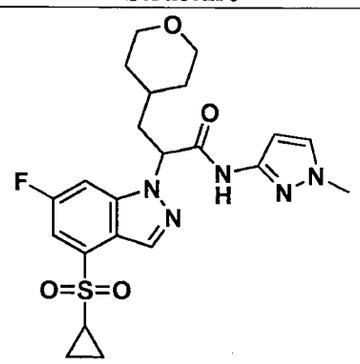
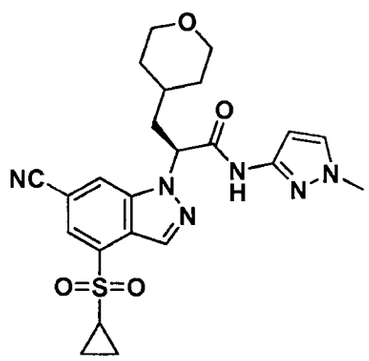
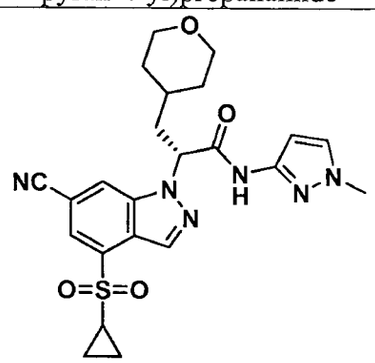
Ex.	Structure	Method	LCMS	NMR data
89	 (S)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{26}N_5O_4S$ 456.53, found 456.5	
90	 (R)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{26}N_5O_4S$ 456.53, found 456.5	
91	 2-(4-(cyclopropylsulfonyl)-5-methoxy-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 15	[M+H] calc'd for $C_{23}H_{28}N_5O_5S$ 486, found 486	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.49 (s, 1 H), 9.20 (s, 1 H), 8.79 (s, 1 H), 8.32 (d, *J*=1.5 Hz, 1 H), 8.36 (d, *J*=2.5 Hz, 1 H), 7.71 (d, *J*=9.3 Hz, 1 H), 7.35 (d, *J*=9.3 Hz, 1 H), 5.34 (dd, *J*=10.5, 4.9 Hz, 1 H), 4.08 (s, 3 H), 3.85 - 3.99 (m, 2 H), 3.07 - 3.32 (m, 3 H), 2.54 (d, *J*=3.5 Hz, 1 H), 2.28 (d, *J*=5.3 Hz, 1 H), 1.60 (br. s., 1 H), 1.26 - 1.48 (m, 6 H), 0.92 - 1.12 ppm (m, 2 H)

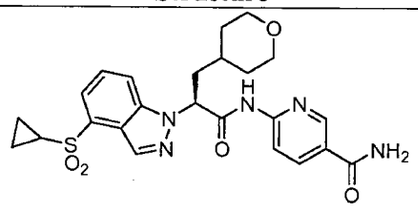
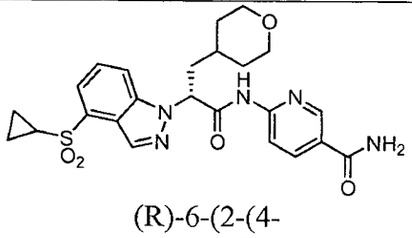
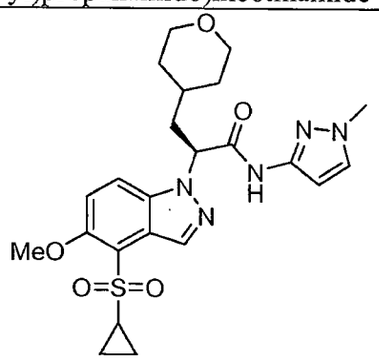
Ex.	Structure	Method	LCMS	NMR data
92	 2-(4-(cyclopropylsulfonyl)-6-methoxy-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{23}H_{28}N_5O_5S$ 486, found 486	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.50 (s, 1 H), 9.22 (s, 1 H), 8.55 (s, 1 H), 8.33 - 8.41 (m, 1 H), 8.28 (s, 1 H), 7.44 (d, *J*=2.0 Hz, 1 H), 7.03 (d, *J*=1.3 Hz, 1 H), 5.31 (dd, *J*=10.5, 4.9 Hz, 1 H), 3.95 (s, 4 H), 3.87 - 3.97 (m, 1 H), 3.25 - 3.32 (m, 1 H), 3.21 (td, *J*=11.7, 2.5 Hz, 1 H), 2.51 - 2.65 (m, 2 H), 2.25 - 2.35 (m, 1 H), 1.52 - 1.66 (m, 2 H), 1.31 - 1.50 (m, 5 H), 1.02 - 1.13 ppm (m, 2 H)
93	 (R)-2-(4-(cyclopropylsulfonyl)-5-methoxy-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 15	[M+H] calc'd for $C_{23}H_{28}N_5O_5S$ 486, found 486	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.49 (s, 1 H), 9.20 (s, 1 H), 8.79 (s, 1 H), 8.32 (d, *J*=1.5 Hz, 1 H), 8.36 (d, *J*=2.5 Hz, 1 H), 7.71 (d, *J*=9.3 Hz, 1 H), 7.35 (d, *J*=9.3 Hz, 1 H), 5.34 (dd, *J*=10.5, 4.9 Hz, 1 H), 4.08 (s, 3 H), 3.85 - 3.99 (m, 2 H), 3.07 - 3.32 (m, 3 H), 2.54 (d, *J*=3.5 Hz, 1 H), 2.28 (d, *J*=5.3 Hz, 1 H), 1.60 (br. s., 1 H), 1.26 - 1.48 (m, 6 H), 0.92 - 1.12 ppm (m, 2 H)
94	 (S)-2-(4-(cyclopropylsulfonyl)-5-methoxy-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 15	[M+H] calc'd for $C_{23}H_{28}N_5O_5S$ 486, found 486	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.49 (s, 1 H), 9.20 (s, 1 H), 8.79 (s, 1 H), 8.32 (d, *J*=1.5 Hz, 1 H), 8.36 (d, *J*=2.5 Hz, 1 H), 7.71 (d, *J*=9.3 Hz, 1 H), 7.35 (d, *J*=9.3 Hz, 1 H), 5.34 (dd, *J*=10.5, 4.9 Hz, 1 H), 4.08 (s, 3 H), 3.85 - 3.99 (m, 2 H), 3.07 - 3.32 (m, 3 H), 2.54 (d, *J*=3.5 Hz, 1 H), 2.28 (d, *J*=5.3 Hz, 1 H), 1.60 (br. s., 1 H), 1.26 - 1.48 (m, 6 H), 0.92 - 1.12 ppm (m, 2 H)

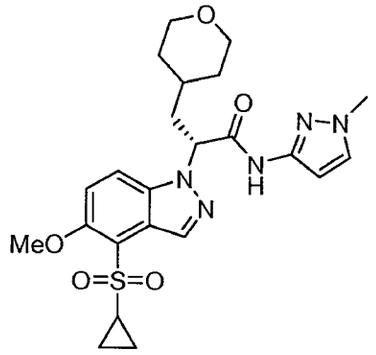
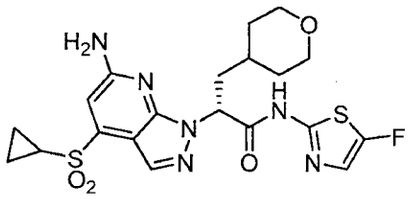
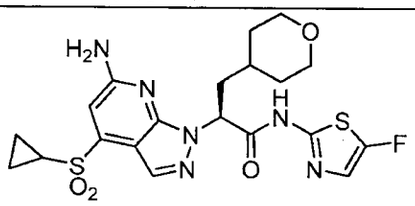
Ex.	Structure	Method	LCMS	NMR data
95	 2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16	[M+H] calc'd for $C_{21}H_{27}N_6O_4S$ 459, found 459	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.08 - 1.18 (m, 2 H) 1.28 - 1.44 (m, 5 H) 1.54 (d, *J*=9.35 Hz, 1 H) 1.74 (dd, *J*=10.11, 1.77 Hz, 1 H) 2.17 - 2.27 (m, 1 H) 2.67 (ddd, *J*=14.21, 10.93, 3.66 Hz, 1 H) 2.89 (tt, *J*=7.86, 4.77 Hz, 1 H) 3.10 - 3.28 (m, 2 H) 3.76 (s, 3 H) 3.85 (dd, *J*=10.74, 4.93 Hz, 2 H) 5.99 (dd, *J*=10.99, 4.67 Hz, 1 H) 6.42 (d, *J*=2.53 Hz, 1 H) 7.42 (d, *J*=2.27 Hz, 1 H) 7.69 (d, *J*=4.80 Hz, 1 H) 8.51 (s, 1 H) 8.81 (d, 1 H)
96	 2-(6-amino-4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16	[M+H] calc'd for $C_{21}H_{26}N_7O_4S$ 472, found 472	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.99 - - 1.06 (m, 2 H) 1.29 - 1.44 (m, 5 H) 1.52 (d, *J*=9.35 Hz, 1 H) 1.71 - 1.79 (m, 1 H) 2.13 - 2.22 (m, 1 H) 2.56 - 2.66 (m, 1 H) 2.90 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.12 - 3.29 (m, 2 H) 3.86 (t, *J*=10.74 Hz, 2 H) 5.90 (dd, *J*=10.99, 4.42 Hz, 1 H) 8.17 (s, 1 H) 8.27 - 8.37 (m, 3 H) 9.31 (s, 1 H)
97	 2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16 & 95	[M+H] calc'd for $C_{21}H_{25}N_6O_4S$ 457, found 457	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.09 - 1.20 (m, 2 H) 1.32 - 1.47 (m, 5 H) 1.56 (dd, *J*=9.47, 1.89 Hz, 1 H) 1.76 (dd, *J*=9.73, 1.89 Hz, 1 H) 2.20 - 2.29 (m, 1 H) 2.73 (ddd, *J*=14.15, 11.12, 3.54 Hz, 1 H) 2.91 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.12 - 3.29 (m, 2 H) 3.81 - 3.91 (m, 2 H) 6.10 (dd, *J*=11.12, 4.29 Hz, 1 H) 7.71 (d, *J*=4.55 Hz, 1 H) 8.31 (d, *J*=2.53 Hz, 1 H) 8.36 (dd, *J*=2.53, 1.52 Hz, 1 H) 8.53 (s, 1 H) 8.83 (d, *J*=4.80 Hz, 1 H) 9.29 (s, 1 H)

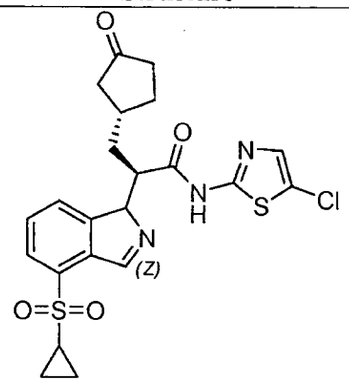
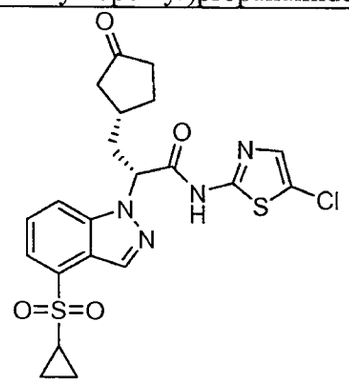
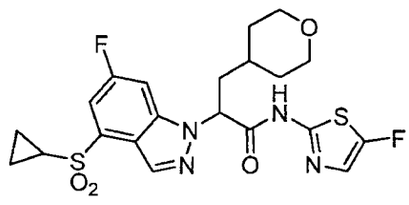
Ex.	Structure	Method	LCMS	NMR data
98	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16 & 95	[M+H] calc'd for $C_{21}H_{27}N_6O_4S$ 459, found 459	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.08 - 1.18 (m, 2 H) 1.28 - 1.44 (m, 5 H) 1.54 (d, *J*=9.35 Hz, 1 H) 1.74 (dd, *J*=10.11, 1.77 Hz, 1 H) 2.17 - 2.27 (m, 1 H) 2.67 (ddd, *J*=14.21, 10.93, 3.66 Hz, 1 H) 2.89 (tt, *J*=7.86, 4.77 Hz, 1 H) 3.10 - 3.28 (m, 2 H) 3.76 (s, 3 H) 3.85 (dd, *J*=10.74, 4.93 Hz, 2 H) 5.99 (dd, *J*=10.99, 4.67 Hz, 1 H) 6.42 (d, *J*=2.53 Hz, 1 H) 7.42 (d, *J*=2.27 Hz, 1 H) 7.69 (d, *J*=4.80 Hz, 1 H) 8.51 (s, 1 H) 8.81 (d, 1 H)
99	 (R)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16 & 95	[M+H] calc'd for $C_{21}H_{27}N_6O_4S$ 459, found 459	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.08 - 1.18 (m, 2 H) 1.28 - 1.44 (m, 5 H) 1.54 (d, *J*=9.35 Hz, 1 H) 1.74 (dd, *J*=10.11, 1.77 Hz, 1 H) 2.17 - 2.27 (m, 1 H) 2.67 (ddd, *J*=14.21, 10.93, 3.66 Hz, 1 H) 2.89 (tt, *J*=7.86, 4.77 Hz, 1 H) 3.10 - 3.28 (m, 2 H) 3.76 (s, 3 H) 3.85 (dd, *J*=10.74, 4.93 Hz, 2 H) 5.99 (dd, *J*=10.99, 4.67 Hz, 1 H) 6.42 (d, *J*=2.53 Hz, 1 H) 7.42 (d, *J*=2.27 Hz, 1 H) 7.69 (d, *J*=4.80 Hz, 1 H) 8.51 (s, 1 H) 8.81 (d, 1 H)
100	 2-(6-cyano-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 19	[M+H] calc'd for $C_{23}H_{25}N_6O_4S$ 481, found 481	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.55 (br. s., 1 H), 9.40 (br. s., 1 H), 8.74 (s, 1 H), 8.45 (br. s., 1 H), 8.37 (br. s., 1 H), 8.22 (s, 1 H), 7.99 (s, 1 H), 5.52 (dd, *J*=9.9, 5.8 Hz, 1 H), 3.90 - 4.09 (m, 2 H), 3.19 - 3.41 (m, 2 H), 2.48 - 2.68 (m, 2 H), 2.39 (dd, *J*=13.8, 7.7 Hz, 1 H), 1.68 (d, *J*=12.1 Hz, 1 H), 1.57 - 1.64 (m, 1 H), 1.34 - 1.54 (m, 5 H), 1.09 - 1.19 ppm (m, 2 H)

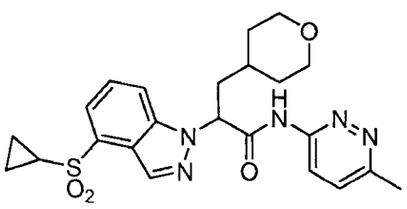
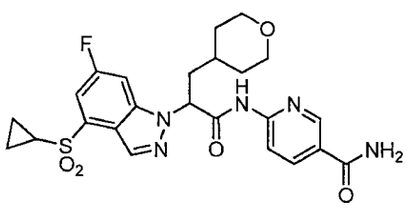
Ex.	Structure	Method	LCMS	NMR data
101	 2-(6-chloro-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{27}ClN_5O_4S$ 492, found 492	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.57 (s, 2H), 7.67 - 7.82 (m, 2H), 7.23 (d, *J* = 2.53 Hz, 1H), 6.62 (s, 1H), 5.28 (dd, *J* = 5.18, 10.23 Hz, 1H), 3.84 - 3.98 (m, 2H), 3.76 (s, 3H), 3.10 - 3.32 (m, 2H), 2.56 - 2.67 (m, 1H), 2.43 - 2.56 (m, 1H), 2.23 - 2.36 (m, 1H), 1.57 - 1.63 (m, 2H), 1.30 - 1.56 (m, 5H), 1.02 - 1.16 (m, 2H)
102	 2-(6-chloro-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{25}ClN_5O_4S$ 490, found 490	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.47 - 9.50 (m, 1H), 8.93 (s, 1H), 8.64 (s, 1H), 8.36 (d, *J* = 2.53 Hz, 1H), 8.23 (dd, *J* = 1.52, 2.53 Hz, 1H), 7.70 - 7.83 (m, 2H), 5.34 (dd, *J* = 5.31, 10.36 Hz, 1H), 3.80 - 3.97 (m, 2H), 3.14 - 3.35 (m, 2H), 2.47 - 2.67 (m, 2H), 2.27 - 2.38 (m, 1H), 1.53 - 1.65 (m, 2H), 1.31 - 1.52 (m, 5H), 1.04 - 1.16 (m, 2H)
103	 2-(4-(cyclopropylsulfonyl)-6-fluoro-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{25}FN_5O_4S$ 474, found 474	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.05 - 1.13 (m, 2 H) 1.28 - 1.44 (m, 5 H) 1.52 (dd, *J*=9.47, 1.89 Hz, 1 H) 1.68 - 1.77 (m, 1 H) 2.19 - 2.28 (m, 1 H) 2.55 - 2.65 (m, 1 H) 2.81 - 2.90 (m, 1 H) 3.16 - 3.29 (m, 2 H) 3.80 - 3.92 (m, 2 H) 5.73 (dd, *J*=10.61, 5.05 Hz, 1 H) 7.57 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.89 - 7.94 (m, 1 H) 8.32 (d, *J*=2.53 Hz, 1 H) 8.34 - 8.39 (m, 1 H) 8.48 (s, 1 H) 9.32 (d, 1 H)

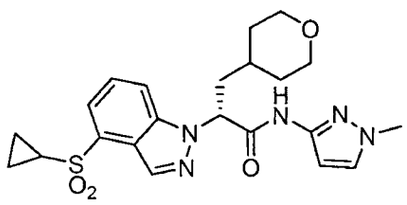
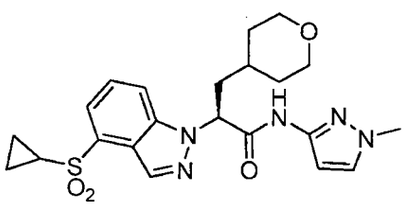
Ex.	Structure	Method	LCMS	NMR data
104	 2-(4-(cyclopropylsulfonyl)-6-fluoro-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{27}FN_5O_4S$ 476, found 476	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.05 - 1.13 (m, 2 H) 1.27 - 1.43 (m, 5 H) 1.49 - 1.57 (m, 1 H) 1.72 (dd, *J*=10.23, 1.89 Hz, 1 H) 2.18 - 2.27 (m, 1 H) 2.50 - 2.59 (m, 1 H) 2.81 - 2.89 (m, 1 H) 3.16 - 3.29 (m, 2 H) 3.77 (s, 3 H) 3.81 - 3.91 (m, 2 H) 5.60 (dd, *J*=10.36, 5.31 Hz, 1 H) 6.45 (d, *J*=2.27 Hz, 1 H) 7.43 (d, *J*=2.27 Hz, 1 H) 7.56 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.90 (dd, *J*=9.09, 1.01 Hz, 1 H) 8.46 (s, 1 H)
105	 (S)-2-(6-cyano-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See Ex* Cmpd. 19	[M+H] calc'd for $C_{23}H_{27}N_6O_4S$ 483, found 483	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.68 (s, 1 H), 8.45 (s, 1 H), 8.17 (s, 1 H), 7.95 (d, *J*=1.0 Hz, 1 H), 7.24 (d, *J*=2.3 Hz, 1 H), 6.62 (d, *J*=2.3 Hz, 1 H), 5.39 (dd, *J*=9.9, 5.8 Hz, 1 H), 3.91 (t, *J*=11.7 Hz, 2 H), 3.77 (s, 3 H), 3.15 - 3.32 (m, 2 H), 2.56 - 2.66 (m, 1 H), 2.49 (s, 1 H), 2.36 (d, *J*=5.8 Hz, 1 H), 1.62 (m, 1 H), 1.31 - 1.50 (m, 6 H), 1.08 - 1.19 ppm (m, 2 H)
106	 (R)-2-(6-cyano-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 19	[M+H] calc'd for $C_{23}H_{27}N_6O_4S$ 483, found 483	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.68 (s, 1 H), 8.45 (s, 1 H), 8.17 (s, 1 H), 7.95 (d, *J*=1.0 Hz, 1 H), 7.24 (d, *J*=2.3 Hz, 1 H), 6.62 (d, *J*=2.3 Hz, 1 H), 5.39 (dd, *J*=9.9, 5.8 Hz, 1 H), 3.91 (t, *J*=11.7 Hz, 2 H), 3.77 (s, 3 H), 3.15 - 3.32 (m, 2 H), 2.56 - 2.66 (m, 1 H), 2.49 (s, 1 H), 2.36 (d, *J*=5.8 Hz, 1 H), 1.62 (m, 1 H), 1.31 - 1.50 (m, 6 H), 1.08 - 1.19 ppm (m, 2 H)

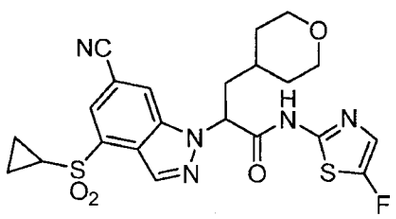
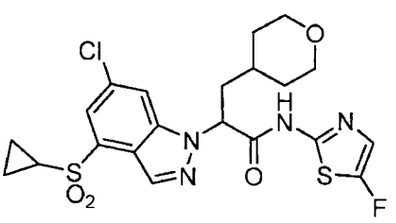
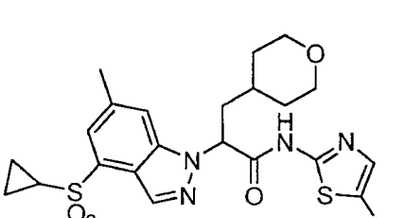
Ex.	Structure	Method	LCMS	NMR data
107	 (S)-6-(2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamido)nicotinamide	*See* Cmpd. 14	[M+H] calc'd for $C_{24}H_{28}N_5O_5S$ 498.5, found 498.5	
108	 (R)-6-(2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamido)nicotinamide	*See* Cmpd. 14	[M+H] calc'd for $C_{24}H_{28}N_5O_5S$ 498.5, found 498.5	
109	 (S)-2-(4-(cyclopropylsulfonyl)-5-methoxy-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 15	[M+H] calc'd for $C_{23}H_{29}N_5O_5S$ 488, found 488	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.72 (s, 1 H), 8.64 (s, 1 H), 7.67 (d, *J*=9.3 Hz, 1 H), 7.30 (d, *J*=9.1 Hz, 1 H), 7.22 (d, *J*=2.5 Hz, 1 H), 6.61 (d, *J*=2.3 Hz, 1 H), 5.27 (dd, *J*=10.6, 4.8 Hz, 1 H), 4.07 (s, 3 H), 3.82 - 3.92 (m, 2 H), 3.75 (s, 3 H), 3.09 - 3.29 (m, 3 H), 2.44 - 2.56 (m, 1 H), 2.28 (d, *J*=5.1 Hz, 1 H), 1.42 - 1.52 (m, 2 H), 1.29 - 1.40 (m, 3 H), 1.21 (d, *J*=6.1 Hz, 2 H), 0.95 - 1.09 ppm (m, 2 H)

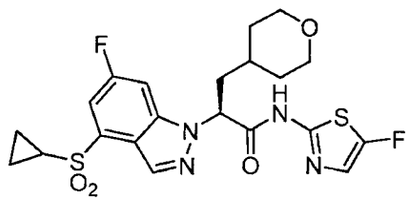
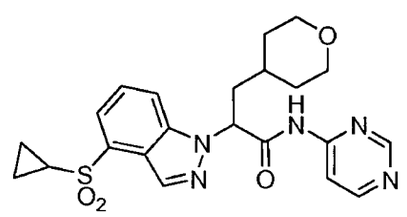
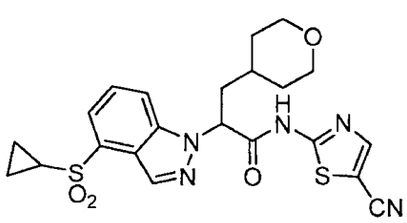
Ex.	Structure	Method	LCMS	NMR data
110	 (R)-2-(4-(cyclopropylsulfonyl)-5-methoxy-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 15	[M+H] calc'd for $C_{23}H_{29}N_5O_5S$ 488, found 488	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.72 (s, 1 H), 8.64 (s, 1 H), 7.67 (d, *J*=9.3 Hz, 1 H), 7.30 (d, *J*=9.1 Hz, 1 H), 7.22 (d, *J*=2.5 Hz, 1 H), 6.61 (d, *J*=2.3 Hz, 1 H), 5.27 (dd, *J*=10.6, 4.8 Hz, 1 H), 4.07 (s, 3 H), 3.82 - 3.92 (m, 2 H), 3.75 (s, 3 H), 3.09 - 3.29 (m, 3 H), 2.44 - 2.56 (m, 1 H), 2.28 (d, *J*=5.1 Hz, 1 H), 1.42 - 1.52 (m, 2 H), 1.29 - 1.40 (m, 3 H), 1.21 (d, *J*=6.1 Hz, 2 H), 0.95 - 1.09 ppm (m, 2 H)
111	 (R)-2-(6-amino-4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16	[M+H] calc'd for $C_{20}H_{24}FN_6O_4S_2$ 495.5, found 495.5	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.99 - 1.07 (m, 9 H) 1.29 - 1.42 (m, 22 H) 1.47 - 1.54 (m, 4 H) 1.71 - 1.78 (m, 4 H) 2.09 - 2.19 (m, 4 H) 2.52 - 2.63 (m, 5 H) 2.90 (tt, *J*=8.08, 4.80 Hz, 5 H) 3.12 - 3.28 (m, 9 H) 3.80 - 3.90 (m, 9 H) 5.86 (dd, *J*=10.99, 4.42 Hz, 5 H) 7.08 (d, *J*=2.53 Hz, 4 H) 8.15 (s, 4 H) 8.32 (s, 4 H).
112	 (S)-2-(6-amino-4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16	[M+H] calc'd for $C_{20}H_{24}FN_6O_4S_2$ 495.5, found 495.5	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.99 - 1.07 (m, 9 H) 1.29 - 1.42 (m, 22 H) 1.47 - 1.54 (m, 4 H) 1.71 - 1.78 (m, 4 H) 2.09 - 2.19 (m, 4 H) 2.52 - 2.63 (m, 5 H) 2.90 (tt, *J*=8.08, 4.80 Hz, 5 H) 3.12 - 3.28 (m, 9 H) 3.80 - 3.90 (m, 9 H) 5.86 (dd, *J*=10.99, 4.42 Hz, 5 H) 7.08 (d, *J*=2.53 Hz, 4 H) 8.15 (s, 4 H) 8.32 (s, 4 H).

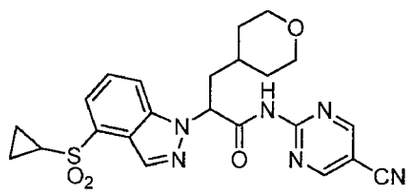
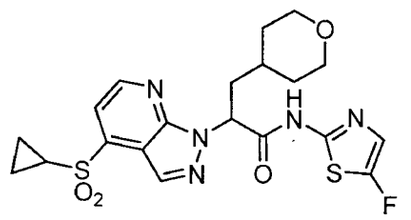
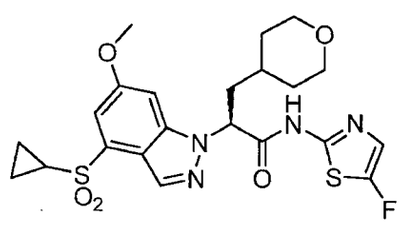
Ex.	Structure	Method	LCMS	NMR data
113	 (S)-N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-((R)-3-oxocyclopentyl)propanamide	*See* Cmpd. 11	[M+H] calc'd for $C_{21}H_{22}ClN_4O_4S_2$ 493.1, found 493.2	
114	 (R)-N-(5-chlorothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-((R)-3-oxocyclopentyl)propanamide	*See* Cmpd. 11	[M+H] calc'd for $C_{21}H_{22}ClN_4O_4S_2$ 493.1, found 493.2	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.94 - 1.13 (m, 2 H) 1.18 - 1.38 (m, 3 H) 1.55 - 1.74 (m, 3 H) 1.75 - 2.04 (m, 3 H) 2.21 - 2.41 (m, 1 H) 2.49 - 2.72 (m, 1 H) 2.73 - 2.89 (m, 1 H) 5.56 - 5.80 (m, 1 H) 7.30 (s, 1 H) 7.64 (dd, *J*=8.59, 7.33 Hz, 1 H) 7.75 (d, *J*=7.07 Hz, 1 H) 8.07 (dd, *J*=8.59, 3.03 Hz, 1 H) 8.48 (s, 1 H)
115	 2-(4-(cyclopropylsulfonyl)-6-fluoro-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{22}F_2N_4O_4S_3$ 498, found 498	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.05 - 1.13 (m, 2 H) 1.25 - 1.37 (m, 5 H) 1.45 - 1.53 (m, 1 H) 1.67 - 1.75 (m, 1 H) 2.17 - 2.27 (m, 1 H) 2.55 (ddd, *J*=14.46, 10.42, 4.42 Hz, 1 H) 2.85 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.15 - 3.28 (m, 2 H) 3.79 - 3.91 (m, 2 H) 5.69 (dd, *J*=10.61, 5.05 Hz, 1 H) 7.09 (d, *J*=2.78 Hz, 1 H) 7.57 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.87 (dd, *J*=9.09, 1.01 Hz, 1 H) 8.46 (s, 1 H)

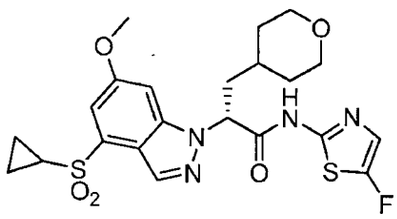
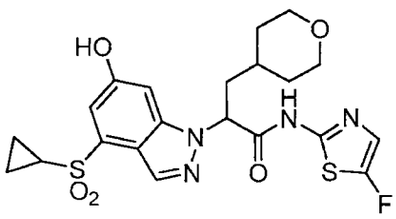
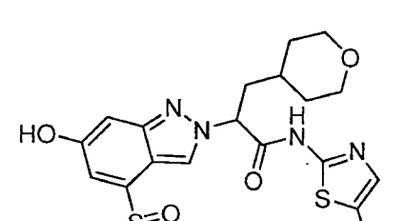
Ex.	Structure	Method	LCMS	NMR data
116	 2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(6-methylpyridazin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{23}H_{27}N_5O_4S$ 471, found 471	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.02 - 1.09 (m, 2 H) 1.25 - 1.44 (m, 5 H) 1.49 (dd, *J*=9.35, 1.77 Hz, 1 H) 1.72 (d, *J*=12.13 Hz, 1 H) 2.21 - 2.30 (m, 1 H) 2.62 (ddd, *J*=14.15, 10.61, 3.79 Hz, 1 H) 2.72 (s, 3 H) 2.80 (tt, *J*=7.89, 4.74 Hz, 1 H) 3.13 - 3.27 (m, 2 H) 3.79 - 3.91 (m, 2 H) 5.84 (dd, *J*=10.61, 4.80 Hz, 1 H) 7.64 (dd, *J*=8.46, 7.20 Hz, 1 H) 7.75 (d, *J*=6.57 Hz, 1 H) 7.99 (d, *J*=9.35 Hz, 1 H) 8.10 (d, *J*=8.59 Hz, 1 H) 8.48 (s, 1 H) 8.71 (d, 1 H)
117	 6-(2-(4-(cyclopropylsulfonyl)-6-fluoro-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamido)nicotinamide	*See* Cmpd. 10	[M+H] calc'd for $C_{24}H_{26}FN_5O_5S$ 517, found 517	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.13 (m, 2 H) 1.17 - 1.38 (m, 5 H) 1.48 - 1.66 (m, 2 H) 2.19 - 2.29 (m, 1 H) 2.40 - 2.48 (m, 1 H) 3.03 - 3.19 (m, 3 H) 3.72 - 3.84 (m, 2 H) 5.81 (dd, *J*=9.73, 5.43 Hz, 1 H) 7.48 (s, 1 H) 7.60 (dd, *J*=8.34, 2.02 Hz, 1 H) 8.05 (s, 1 H) 8.18 - 8.22 (m, 1 H) 8.45 (s, 1 H) 8.83 (d, *J*=1.77 Hz, 1 H) 11.26 (br. s., 1 H)

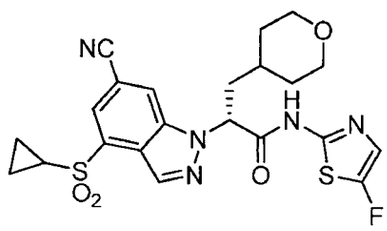
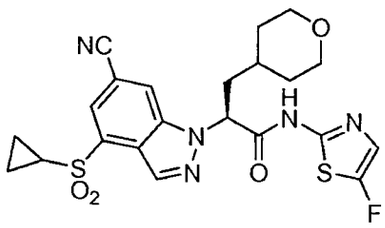
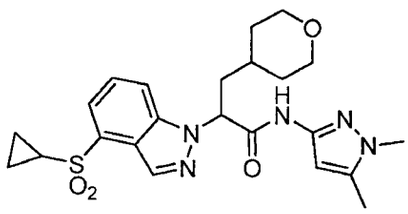
Ex.	Structure	Method	LCMS	NMR data
118	 (R)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{27}N_5O_4S$ 459, found 459	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.02 - 1.09 (m, 2 H) 1.25 - 1.42 (m, 5 H) 1.53 (dd, *J*=9.60, 1.77 Hz, 1 H) 1.72 (dd, *J*=9.98, 1.89 Hz, 1 H) 2.18 - 2.28 (m, 1 H) 2.54 - 2.63 (m, 1 H) 2.81 (s, 1 H) 3.15 - 3.28 (m, 2 H) 3.76 (s, 3 H) 3.81 - 3.90 (m, 2 H) 5.67 (dd, *J*=10.36, 5.31 Hz, 1 H) 6.45 (d, *J*=2.27 Hz, 1 H) 7.43 (d, *J*=2.27 Hz, 1 H) 7.63 (dd, *J*=8.34, 7.33 Hz, 1 H) 7.75 (d, *J*=6.57 Hz, 1 H) 8.09 (d, *J*=8.34 Hz, 1 H) 8.48 (s, 1 H)
119	 (S)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{27}N_5O_4S$ 459, found 459	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.02 - 1.09 (m, 2 H) 1.25 - 1.42 (m, 5 H) 1.53 (dd, *J*=9.60, 1.77 Hz, 1 H) 1.72 (dd, *J*=9.98, 1.89 Hz, 1 H) 2.18 - 2.28 (m, 1 H) 2.54 - 2.63 (m, 1 H) 2.81 (s, 1 H) 3.15 - 3.28 (m, 2 H) 3.76 (s, 3 H) 3.81 - 3.90 (m, 2 H) 5.67 (dd, *J*=10.36, 5.31 Hz, 1 H) 6.45 (d, *J*=2.27 Hz, 1 H) 7.43 (d, *J*=2.27 Hz, 1 H) 7.63 (dd, *J*=8.34, 7.33 Hz, 1 H) 7.75 (d, *J*=6.57 Hz, 1 H) 8.09 (d, *J*=8.34 Hz, 1 H) 8.48 (s, 1 H)

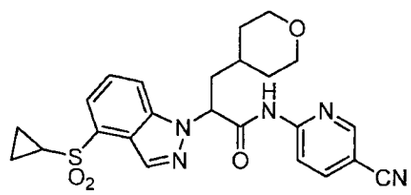
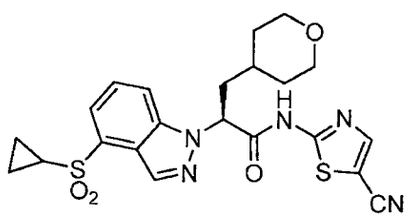
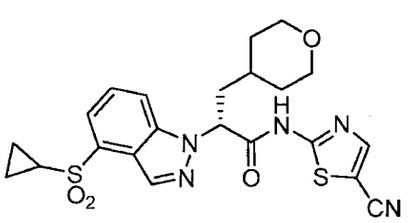
Ex.	Structure	Method	LCMS	NMR data
120	 2-(6-cyano-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{22}FN_5O_4S_2$ 505, found 505	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.07 - 1.14 (m, 2 H) 1.27 - 1.45 (m, 5 H) 1.46 - 1.53 (m, 1 H) 1.68 - 1.76 (m, 1 H) 2.23 - 2.32 (m, 1 H) 2.60 (ddd, *J*=14.46, 10.42, 4.42 Hz, 1 H) 2.89 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.16 - 3.28 (m, 2 H) 3.80 - 3.91 (m, 2 H) 5.83 (dd, *J*=10.61, 5.05 Hz, 1 H) 7.10 (d, *J*=2.78 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.59 (s, 1 H) 8.64 (s, 1 H)
121	 2-(6-chloro-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{23}ClFN_4O_4S_2$ 514.0, found 514.0	^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.55 (s, 1H), 8.34 (s, 1H), 7.92 (s, 1H), 7.00 (d, *J* = 2.78 Hz, 1H), 5.69 (dd, *J* = 5.43, 10.23 Hz, 1H), 3.82 - 3.92 (m, 2H), 3.16 - 3.29 (m, 2H), 2.53 - 2.71 (m, 2H), 2.16 - 2.28 (m, 1H), 1.67 (d, *J* = 12.13 Hz, 1H), 1.48 - 1.58 (m, 1H), 1.28 - 1.46 (m, 5H), 1.04 - 1.16 (m, 2H)
122	 2-(4-(cyclopropylsulfonyl)-6-methyl-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{26}FN_4O_4S_2$ 493.5, found 493.5	^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.45 (s, 1H), 8.27 (s, 1H), 7.71 (s, 1H), 7.09 (d, *J* = 2.53 Hz, 1H), 5.68 (dd, *J* = 5.05, 10.61 Hz, 1H), 3.79 - 3.91 (m, 2H), 3.66 (s, 1H), 3.14 - 3.27 (m, 2H), 2.84 - 2.92 (m, 4H), 2.57 (ddd, *J* = 4.29, 10.55, 14.46 Hz, 1H), 2.15 - 2.25 (m, 1H), 1.68 - 1.76 (m, 1H), 1.44 - 1.52 (m, 1H), 1.28 - 1.44 (m, 3H), 1.18 - 1.26 (m, 2H), 1.05 - 1.11 (m, 2H)

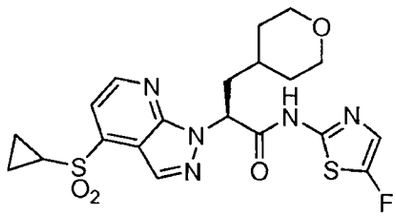
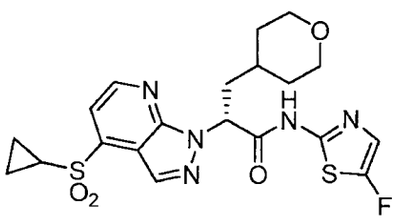
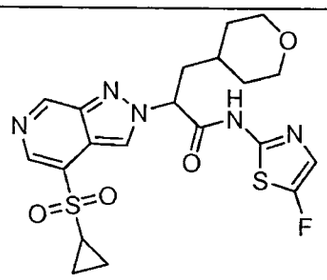
Ex.	Structure	Method	LCMS	NMR data
123	 (S)-2-(4-(cyclopropylsulfonyl)-6-fluoro-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{22}F_2N_4O_4S_2$ 498, found 498	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.05 - 1.13 (m, 2 H) 1.26 - 1.37 (m, 5 H) 1.45 - 1.52 (m, 1 H) 1.67 - 1.75 (m, 1 H) 2.17 - 2.27 (m, 1 H) 2.55 (ddd, *J*=14.46, 10.42, 4.42 Hz, 1 H) 2.85 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.15 - 3.28 (m, 2 H) 3.79 - 3.91 (m, 2 H) 5.69 (dd, *J*=10.61, 5.05 Hz, 1 H) 7.09 (d, *J*=2.78 Hz, 1 H) 7.57 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.87 (dd, *J*=9.09, 1.01 Hz, 1 H) 8.46 (s, 1 H)
124	 2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(pyrimidin-4-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{25}N_5O_4S$ 457, found 457	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.02 - 1.12 (m, 2 H) 1.25 - 1.41 (m, 5 H) 1.41 - 1.53 (m, 1 H) 1.68 - 1.76 (m, 1 H) 2.18 - 2.30 (m, 1 H) 2.59 (m, *J*=14.31, 10.59, 10.59, 3.92 Hz, 1 H) 2.77 - 2.87 (m, 1 H) 3.12 - 3.27 (m, 2 H) 3.78 - 3.91 (m, 2 H) 5.62 - 5.86 (m, 1 H) 7.58 - 7.68 (m, 1 H) 7.70 - 7.79 (m, 1 H) 8.05 - 8.12 (m, 1 H) 8.24 (dd, *J*=6.06, 1.26 Hz, 1 H) 8.49 (s, 1 H) 8.66 (d, *J*=6.06 Hz, 1 H) 8.92 (s, 1 H)
125	 N-(5-cyanothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{23}N_5O_4S_2$ 487, found 487	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.01 - 1.10 (m, 2 H) 1.26 - 1.42 (m, 5 H) 1.50 (dd, *J*=9.35, 2.02 Hz, 1 H) 1.70 - 1.77 (m, 1 H) 2.23 - 2.32 (m, 1 H) 2.58 (ddd, *J*=14.27, 10.61, 3.92 Hz, 1 H) 2.81 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.15 - 3.27 (m, 2 H) 3.79 - 3.90 (m, 2 H) 5.77 (dd, *J*=10.61, 4.80 Hz, 1 H) 7.62 (dd, *J*=8.46, 7.20 Hz, 1 H) 7.74 (d, *J*=6.57 Hz, 1 H) 8.03 - 8.07 (m, 2 H) 8.46 (s, 1 H)

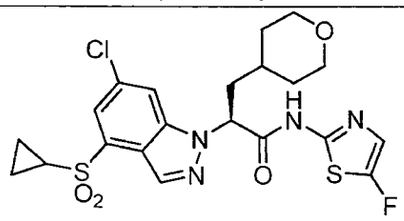
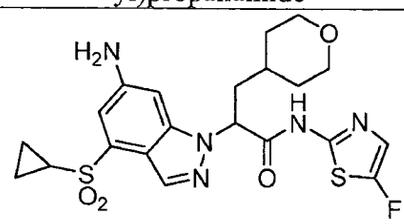
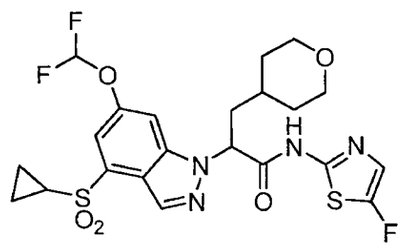
Ex.	Structure	Method	LCMS	NMR data
126	 N-(5-cyanopyrimidin-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{23}H_{24}N_6O_4S$ 482, found 482	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.02 - 1.11 (m, 2 H) 1.26 - 1.41 (m, 5 H) 1.42 - 1.52 (m, 1 H) 1.70 - 1.79 (m, 1 H) 2.18 - 2.30 (m, 1 H) 2.53 - 2.65 (m, 1 H) 2.77 - 2.87 (m, 1 H) 3.12 - 3.27 (m, 2 H) 3.79 - 3.91 (m, 2 H) 5.65 (dd, *J*=11.37, 4.29 Hz, 1 H) 7.63 (dt, *J*=8.59, 6.95 Hz, 1 H) 7.74 (dd, *J*=6.57, 5.05 Hz, 1 H) 7.99 - 8.10 (m, 1 H) 8.45 (d, *J*=12.88 Hz, 1 H) 8.54 (s, 1 H) 8.95 (s, 1 H)
127	 2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16 & 95	[M+H] calc'd for $C_{20}H_{22}FN_5O_4S_2$ 481, found 481	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.10 - 1.20 (m, 2 H) 1.30 - 1.43 (m, 5 H) 1.50 - 1.57 (m, 1 H) 1.76 (dd, *J*=10.23, 1.89 Hz, 1 H) 2.16 - 2.26 (m, 1 H) 2.67 (ddd, *J*=14.27, 10.99, 3.79 Hz, 1 H) 2.90 (tt, *J*=7.93, 4.71 Hz, 1 H) 3.11 - 3.28 (m, 2 H) 3.81 - 3.90 (m, 2 H) 6.05 (dd, *J*=11.12, 4.29 Hz, 1 H) 7.08 (d, *J*=2.53 Hz, 1 H) 7.71 (d, *J*=4.80 Hz, 1 H) 8.51 (s, 1 H) 8.82 (d, 1 H)
128	 (S)-2-(4-(cyclopropylsulfonyl)-6-methoxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{26}FN_4O_5S_2$ 509, found 509	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.52 (s, 1 H), 7.45 (d, *J*=1.8 Hz, 1 H), 7.00 (br. s., 1 H), 6.96 (s, 1 H), 5.30 (s, 1 H), 3.95 (s, 3 H), 3.78 - 3.93 (m, 2 H), 3.13 - 3.30 (m, 2 H), 2.57 - 2.73 (m, 1 H), 2.50 (br. s., 1 H), 2.25 (d, *J*=5.6 Hz, 1 H), 1.59 (d, *J*=12.4 Hz, 1 H), 1.44 - 1.55 (m, 2 H), 1.28 - 1.44 (m, 4 H), 1.01 - 1.16 ppm (m, 2 H)

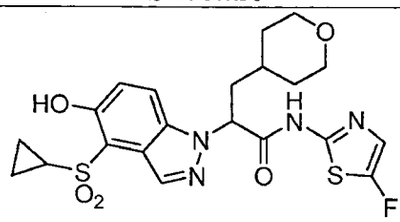
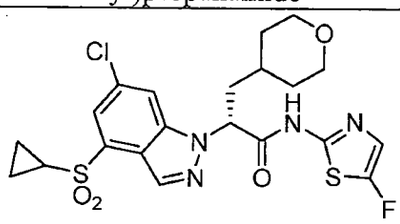
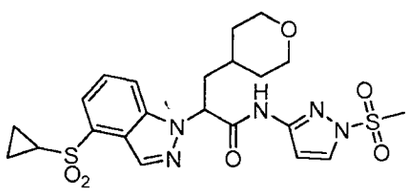
Ex.	Structure	Method	LCMS	NMR data
129	 (R)-2-(4-(cyclopropylsulfonyl)-6-methoxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{26}FN_4O_5S_2$ 509, found 509	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.52 (s, 1 H), 7.45 (d, *J*=1.8 Hz, 1 H), 7.00 (br. s., 1 H), 6.96 (s, 1 H), 5.30 (s, 1 H), 3.95 (s, 3 H), 3.78 - 3.93 (m, 2 H), 3.13 - 3.30 (m, 2 H), 2.57 - 2.73 (m, 1 H), 2.50 (br. s., 1 H), 2.25 (d, *J*=5.6 Hz, 1 H), 1.59 (d, *J*=12.4 Hz, 1 H), 1.44 - 1.55 (m, 2 H), 1.28 - 1.44 (m, 4 H), 1.01 - 1.16 ppm (m, 2 H)
130	 2-(4-(cyclopropylsulfonyl)-6-hydroxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 12	[M+H] calc'd for $C_{21}H_{24}FN_4O_5S_2$ 495, found 495	^{1}H NMR (DMSO-d_6 ,400MHz): δ = 12.70 (s, 1 H), 10.48 (s, 1 H), 8.23 (s, 1 H), 7.33 - 7.36 (m, 2 H), 7.23 (d, *J*=1.8 Hz, 1 H), 5.62 (d, *J*=4.3 Hz, 1 H), 3.71 - 3.85 (m, 3 H), 3.06 - 3.21 (m, 2 H), 2.24 - 2.41 (m, 1 H), 2.09 - 2.24 (m, 1 H), 1.54 - 1.63 (m, 1 H), 1.48 (br. s., 1 H), 1.28 (br. s., 3 H), 1.16 (br. s., 2 H), 1.06 ppm (dd, *J*=7.8, 2.0 Hz, 2 H)
131	 2-(4-(cyclopropylsulfonyl)-6-hydroxy-2H-indazol-2-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 12	[M+H] calc'd for $C_{21}H_{24}FN_4O_5S_2$ 495, found 495	^{1}H NMR (DMSO-d_6 ,400MHz): δ = 13.41 (br.s., 1H), 12.74 (s, 1 H), 8.21 (s, 1 H), 7.35 (d, *J*=2.5 Hz, 1 H), 7.30 (d, *J*=2.0 Hz, 1 H), 7.21 (d, *J*=1.0 Hz, 1 H), 5.18 (d, *J*=9.3 Hz, 1 H), 3.79 - 3.87 (m, 2 H), 3.21 - 3.35 (m, 2 H), 2.93 - 3.02 (m, 1 H), 1.92 - 2.00 (m, 1 H), 1.84 (d, *J*=3.5 Hz, 1 H), 1.82 (br. s., 1 H), 1.64 (br. s., 2 H), 1.28 (br. s., 2 H), 1.14 - 1.19 (m, 2 H), 1.00 - 1.06 ppm (m, 2 H)

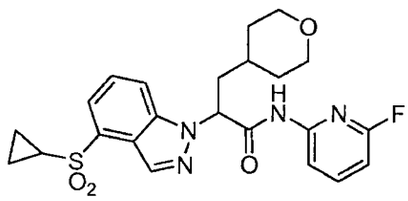
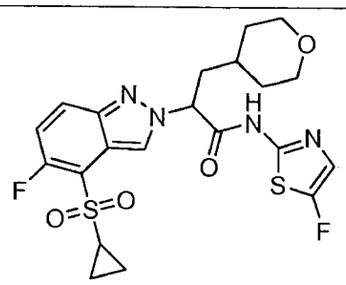
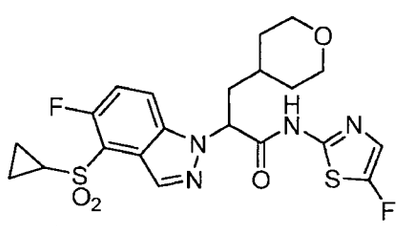
Ex.	Structure	Method	LCMS	NMR data
132	 (R)-2-(6-cyano-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{22}FN_5O_4S_2$ 505, found 505	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.07 - 1.14 (m, 2 H) 1.27 - 1.45 (m, 5 H) 1.46 - 1.53 (m, 1 H) 1.68 - 1.76 (m, 1 H) 2.23 - 2.32 (m, 1 H) 2.60 (ddd, *J*=14.46, 10.42, 4.42 Hz, 1 H) 2.89 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.16 - 3.28 (m, 2 H) 3.80 - 3.91 (m, 2 H) 5.83 (dd, *J*=10.61, 5.05 Hz, 1 H) 7.10 (d, *J*=2.78 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.59 (s, 1 H) 8.64 (s, 1 H)
133	 (S)-2-(6-cyano-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{22}FN_5O_4S_2$ 505, found 505	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.07 - 1.14 (m, 2 H) 1.27 - 1.45 (m, 5 H) 1.46 - 1.53 (m, 1 H) 1.68 - 1.76 (m, 1 H) 2.23 - 2.32 (m, 1 H) 2.60 (ddd, *J*=14.46, 10.42, 4.42 Hz, 1 H) 2.89 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.16 - 3.28 (m, 2 H) 3.80 - 3.91 (m, 2 H) 5.83 (dd, *J*=10.61, 5.05 Hz, 1 H) 7.10 (d, *J*=2.78 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.59 (s, 1 H) 8.64 (s, 1 H)
134	 2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(1,5-dimethyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{23}H_{29}N_5O_4S$ 473, found 473	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.01 - 1.09 (m, 2 H) 1.25 - 1.43 (m, 5 H) 1.51 (d, *J*=9.35 Hz, 1 H) 1.71 (d, *J*=11.87 Hz, 1 H) 2.17 - 2.28 (m, 4 H) 2.57 (ddd, *J*=14.15, 10.36, 4.04 Hz, 1 H) 2.81 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.14 - 3.28 (m, 2 H) 3.63 - 3.69 (m, 3 H) 3.80 - 3.90 (m, 2 H) 5.66 (dd, *J*=10.36, 5.05 Hz, 1 H) 6.24 (s, 1 H) 7.61 - 7.66 (m, 1 H) 7.74 (d, *J*=6.57 Hz, 1 H) 8.08 (d, *J*=8.34 Hz, 1 H) 8.48 (s, 1 H)

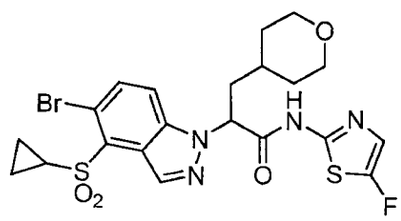
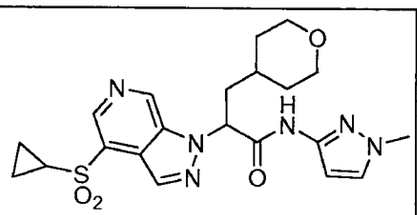
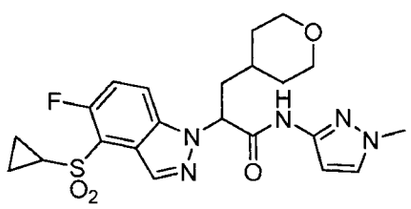
Ex.	Structure	Method	LCMS	NMR data
135	 N-(5-cyanopyridin-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{24}H_{25}N_5O_4S$ 481, found 481	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.01 - 1.09 (m, 2 H) 1.25 - 1.43 (m, 5 H) 1.50 (dd, *J*=9.47, 1.89 Hz, 1 H) 1.72 (d, *J*=12.13 Hz, 1 H) 2.18 - 2.27 (m, 1 H) 2.60 (ddd, *J*=14.15, 10.48, 3.92 Hz, 1 H) 2.81 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.13 - 3.27 (m, 2 H) 3.79 - 3.90 (m, 2 H) 5.79 (dd, *J*=10.48, 4.93 Hz, 1 H) 7.63 (dd, *J*=8.59, 7.33 Hz, 1 H) 7.74 (d, *J*=6.57 Hz, 1 H) 8.04 - 8.12 (m, 2 H) 8.24 (d, *J*=8.84 Hz, 1 H) 8.49 (s, 1 H) 8.60 - 8.64 (m, 1 H)
136	 (S)-N-(5-cyanothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{23}N_5O_4S_2$ 487, found 487	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.01 - 1.10 (m, 2 H) 1.26 - 1.42 (m, 5 H) 1.50 (dd, *J*=9.35, 2.02 Hz, 1 H) 1.70 - 1.77 (m, 1 H) 2.23 - 2.32 (m, 1 H) 2.58 (ddd, *J*=14.27, 10.61, 3.92 Hz, 1 H) 2.81 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.15 - 3.27 (m, 2 H) 3.79 - 3.90 (m, 2 H) 5.77 (dd, *J*=10.61, 4.80 Hz, 1 H) 7.62 (dd, *J*=8.46, 7.20 Hz, 1 H) 7.74 (d, *J*=6.57 Hz, 1 H) 8.03 - 8.07 (m, 2 H) 8.46 (s, 1 H)
137	 (R)-N-(5-cyanothiazol-2-yl)-2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{23}N_5O_4S_2$ 487, found 487	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.01 - 1.10 (m, 2 H) 1.26 - 1.42 (m, 5 H) 1.50 (dd, *J*=9.35, 2.02 Hz, 1 H) 1.70 - 1.77 (m, 1 H) 2.23 - 2.32 (m, 1 H) 2.58 (ddd, *J*=14.27, 10.61, 3.92 Hz, 1 H) 2.81 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.15 - 3.27 (m, 2 H) 3.79 - 3.90 (m, 2 H) 5.77 (dd, *J*=10.61, 4.80 Hz, 1 H) 7.62 (dd, *J*=8.46, 7.20 Hz, 1 H) 7.74 (d, *J*=6.57 Hz, 1 H) 8.03 - 8.07 (m, 2 H) 8.46 (s, 1 H)

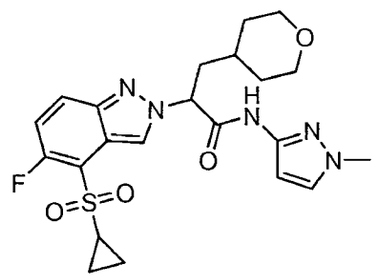
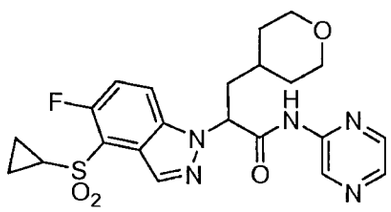
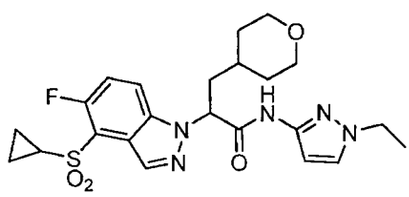
Ex.	Structure	Method	LCMS	NMR data
138	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16 & 95	[M+H] calc'd for $C_{20}H_{22}FN_5O_4S_2$ 481, found 481	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.10 - 1.20 (m, 2 H) 1.30 - 1.43 (m, 5 H) 1.50 - 1.57 (m, 1 H) 1.76 (dd, *J*=10.23, 1.89 Hz, 1 H) 2.16 - 2.26 (m, 1 H) 2.67 (ddd, *J*=14.27, 10.99, 3.79 Hz, 1 H) 2.90 (tt, *J*=7.93, 4.71 Hz, 1 H) 3.11 - 3.28 (m, 2 H) 3.81 - 3.90 (m, 2 H) 6.05 (dd, *J*=11.12, 4.29 Hz, 1 H) 7.08 (d, *J*=2.53 Hz, 1 H) 7.71 (d, *J*=4.80 Hz, 1 H) 8.51 (s, 1 H) 8.82 (d, 1 H)
139	 (R)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16 & 95	[M+H] calc'd for $C_{20}H_{22}FN_5O_4S_2$ 481, found 481	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.10 - 1.20 (m, 2 H) 1.30 - 1.43 (m, 5 H) 1.50 - 1.57 (m, 1 H) 1.76 (dd, *J*=10.23, 1.89 Hz, 1 H) 2.16 - 2.26 (m, 1 H) 2.67 (ddd, *J*=14.27, 10.99, 3.79 Hz, 1 H) 2.90 (tt, *J*=7.93, 4.71 Hz, 1 H) 3.11 - 3.28 (m, 2 H) 3.81 - 3.90 (m, 2 H) 6.05 (dd, *J*=11.12, 4.29 Hz, 1 H) 7.08 (d, *J*=2.53 Hz, 1 H) 7.71 (d, *J*=4.80 Hz, 1 H) 8.51 (s, 1 H) 8.82 (d, 1 H)
140	 2-(4-(cyclopropylsulfonyl)-2H-pyrazolo[3,4-c]pyridin-2-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 13	[M+H] calc'd for $C_{20}H_{23}FN_5O_4S_2$ 480, found 480	

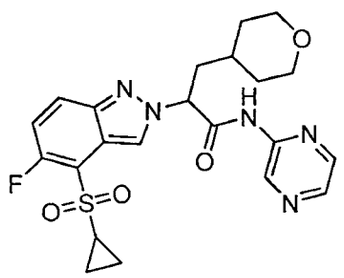
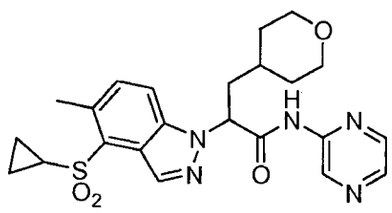
Ex.	Structure	Method	LCMS	NMR data
141	 (S)-2-(6-chloro-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{23}ClFN_4O_4S_2$ 514.0, found 514.0	
142	 2-(6-amino-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 21	[M+H] calc'd for $C_{21}H_{25}FN_5O_4S_2$ 494.1, found 494.4	
143	 2-(4-(cyclopropylsulfonyl)-6-(difluoromethoxy)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 12	[M+H] calc'd for $C_{22}H_{24}F_3N_4O_5S_2$ 545.1, found 545.3	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.03 - 1.14 (m, 2 H) 1.23 - 1.45 (m, 5 H) 1.45 - 1.55 (m, 1 H) 1.72 (dd, *J*=12.51, 2.40 Hz, 1 H) 2.16 - 2.31 (m, 1 H) 2.55 (ddd, *J*=14.46, 10.42, 4.42 Hz, 1 H) 2.86 (tt, *J*=7.83, 4.80 Hz, 1 H) 3.22 (m, *J*=17.15, 11.57, 11.57, 2.15 Hz, 2 H) 3.76 - 3.96 (m, 2 H) 7.01 (d, *J*=73.01 Hz, 1 H) 7.10 (d, *J*=2.53 Hz, 1 H) 7.56 (d, *J*=1.77 Hz, 1 H) 7.87 (s, 1 H) 8.47 (s, 1 H)

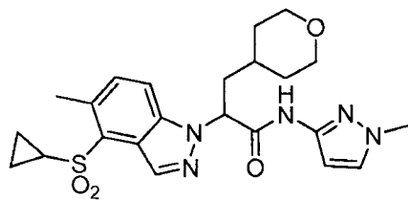
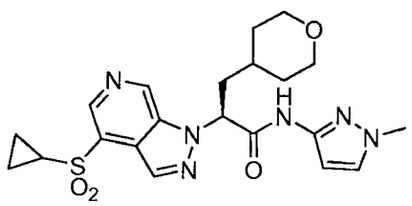
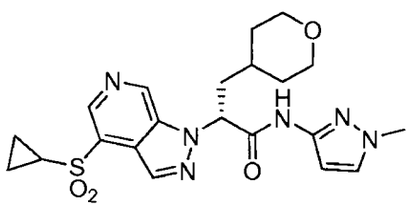
Ex.	Structure	Method	LCMS	NMR data
144	 2-(4-(cyclopropylsulfonyl)-5-hydroxy-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{24}FN_4O_5S_2$ 495.1, found 495.3	
145	 (R)-2-(6-chloro-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{21}H_{23}ClFN_4O_4S_2$ 514.0, found 514.0	
146	 2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(1-(methylsulfonyl)-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{28}N_5O_6S_2$ 522.1, found 522.1	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.00 (s, 1H), 8.66 (s, 1H), 7.92 (d, *J* = 3.03 Hz, 1H), 7.81 (d, *J* = 6.57 Hz, 1H), 7.74 (d, *J* = 8.84 Hz, 1H), 7.61 (dd, *J* = 7.33, 8.59 Hz, 1H), 7.02 (d, *J* = 2.78 Hz, 1H), 5.38 (dd, *J* = 5.05, 10.61 Hz, 1H), 3.89 (br. s., 2H), 3.09 - 3.30 (m, 5H), 2.60 - 2.71 (m, 1H), 2.46 - 2.59 (m, 1H), 2.29 (ddd, *J* = 5.05, 8.65, 14.08 Hz, 1H), 1.28 - 1.55 (m, 6H), 1.25 (br. s., 1H), 1.01 - 1.20 (m, 2H)

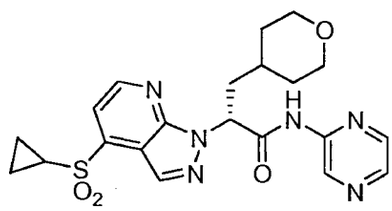
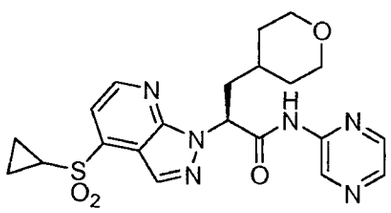
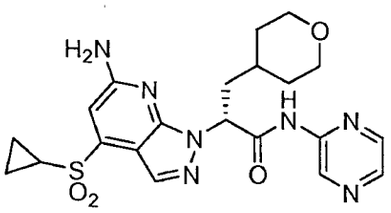
Ex.	Structure	Method	LCMS	NMR data
147	 2-(4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(6-fluoropyridin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{23}H_{26}FN_4O_4S$ 473.2, found 473.2	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.92 (s, 1H), 8.67 (s, 1H), 8.04 (dd, *J* = 1.64, 7.96 Hz, 1H), 7.73 - 7.86 (m, 3H), 7.60 (dd, *J* = 7.33, 8.59 Hz, 1H), 6.68 (dd, *J* = 2.27, 8.08 Hz, 1H), 5.39 (dd, *J* = 4.93, 10.48 Hz, 1H), 3.81 - 3.97 (m, 2H), 3.11 - 3.34 (m, 3H), 2.46 - 2.70 (m, 2H), 2.29 (ddd, *J* = 4.93, 8.59, 14.02 Hz, 1H), 1.62 (d, *J* = 12.88 Hz, 1H), 1.31 - 1.55 (m, 4H), 1.26 (qd, *J* = 4.29, 7.66 Hz, 1H), 0.96 - 1.15 (m, 2H)
148	 2-(4-(cyclopropylsulfonyl)-5-fluoro-2H-indazol-2-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 19	[M+H] calc'd for $C_{21}H_{23}F_2N_4O_4S_2$ 497.1, found 497.1	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.61 (s, 1H), 8.04 (dd, *J* = 4.17, 9.22 Hz, 1H), 7.24 - 7.35 (m, 2H), 7.03 (br. s., 1H), 5.34 (dd, *J* = 5.43, 9.98 Hz, 1H), 3.91 (br. s., 2H), 3.18 - 3.34 (m, 2H), 2.80 - 2.97 (m, 1H), 2.37 - 2.53 (m, 1H), 2.20 - 2.37 (m, 1H), 1.68 (br. s., 1H), 1.45 - 1.55 (m, 2H), 1.26 - 1.45 (m, 4H), 1.00 - 1.15 (m, 2H)
149	 2-(4-(cyclopropylsulfonyl)-5-fluoro-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 19	[M+H] calc'd for $C_{21}H_{23}F_2N_4O_4S_2$ 497.1, found 497.1	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.72 (s, 1H), 7.73 (dd, *J* = 2.91, 9.22 Hz, 1H), 7.37 (t, *J* = 9.35 Hz, 1H), 7.07 (d, *J* = 2.27 Hz, 1H), 5.46 (dd, *J* = 4.93, 10.48 Hz, 1H), 3.92 (ddd, *J* = 2.53, 11.37, 13.39 Hz, 2H), 3.14 - 3.31 (m, 2H), 2.83 - 2.94 (m, 1H), 2.45 - 2.61 (m, 1H), 2.28 (ddd, *J* = 4.93, 8.78, 14.08 Hz, 1H), 1.58 - 1.69 (m, 1H), 1.32 - 1.58 (m, 5H), 1.21 (d, *J* = 3.79 Hz, 1H), 1.04 - 1.17 (m, 2H)

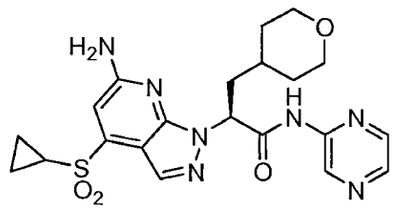
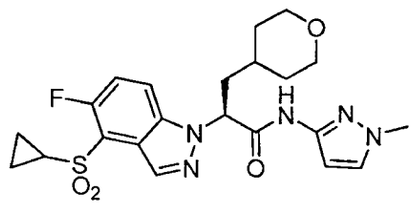
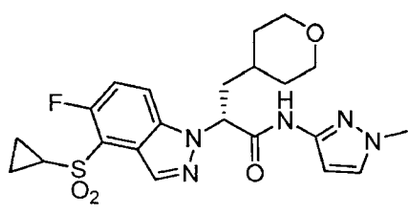
Ex.	Structure	Method	LCMS	NMR data
150	 2-(5-bromo-4-(cyclopropylsulfonyl)-1H-indazol-1-yl)-N-(5-fluorothiazol-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 19	[M+H] calc'd for $C_{21}H_{23}BrFN_4O_4S_2$ 558, found 558	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 7.82 (d, *J* = 7.58 Hz, 1H), 7.56 (d, *J* = 7.58 Hz, 1H), 7.38 (d, *J* = 2.53 Hz, 1H), 5.82 (dd, *J* = 5.68, 9.73 Hz, 1H), 3.73 - 3.86 (m, 2H), 3.09 - 3.20 (m, 2H), 2.89 - 3.04 (m, 1H), 2.45 - 2.61 (m, 1H) 2.20 - 2.36 (m, 1H), 1.64 (d, *J* = 7.83 Hz, 1H), 1.51 (d, *J* = 13.14 Hz, 1H), 1.20 - 1.37 (m, 5H), 0.97 - 1.09 (m, 2H)
151	 2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 13	[M+H] calc'd for $C_{21}H_{26}N_6O_4S$ 460, found 460	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 - 1.13 (m, 2 H) 1.17 - 1.36 (m, 5 H) 1.48 - 1.70 (m, 2 H) 2.28 (d, *J*=6.82 Hz, 1 H) 2.44 (br. s., 1 H) 3.03 - 3.23 (m, 3 H) 3.69 - 3.84 (m, 5 H) 5.87 (d, *J*=3.54 Hz, 1 H) 6.37 (d, *J*=2.02 Hz, 1 H) 7.55 (d, *J*=2.02 Hz, 1 H) 8.51 (s, 1 H) 8.68 (s, 1 H) 9.67 (s, 1 H) 11.08 (s, 1 H)
152	 2-(4-(cyclopropylsulfonyl)-5-fluoro-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 22	[M+H] calc'd for $C_{22}H_{27}FN_5O_4S$ 476, found 476	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.58 - 8.83 (m, 2 H), 7.74 (dd, *J*=9.1, 3.0 Hz, 1 H), 7.34 (t, *J*=9.3 Hz, 1 H), 7.23 (d, *J*=2.0 Hz, 1 H), 6.61 (d, *J*=2.3 Hz, 1 H), 5.33 (dd, *J*=10.4, 5.1 Hz, 1 H), 3.81 - 3.94 (m, 2 H), 3.76 (s, 3 H), 3.08 - 3.32 (m, 2 H), 2.90 (dd, *J*=4.8, 3.3 Hz, 1 H), 2.49 (d, *J*=3.8 Hz, 1 H), 2.22 - 2.37 (m, 1 H), 1.59 (d, *J*=12.4 Hz, 1 H), 1.19 - 1.55 (m, 5 H), 1.04 - 1.19 (m, 2 H), 0.78 - 0.93 ppm (m, 1 H)

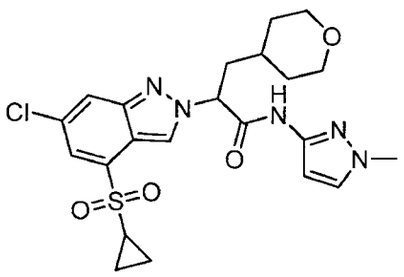
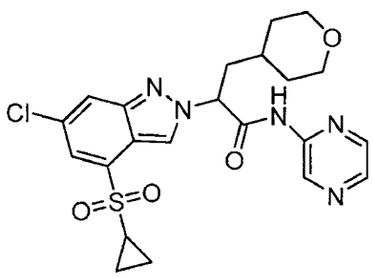
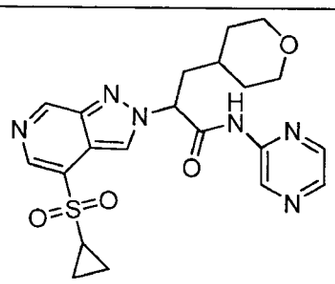
Ex.	Structure	Method	LCMS	NMR data
153	 2-(4-(cyclopropylsulfonyl)-5-fluoro-2H-indazol-2-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 22	[M+H] calc'd for $C_{22}H_{27}FN_5O_4S$ 476, found 476	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.16 (s, 1 H), 8.59 (s, 1 H), 8.04 (dd, *J*=9.3, 3.5 Hz, 1 H), 7.28 (d, 1 H), 7.24 (d, *J*=2.5 Hz, 1 H), 6.63 (d, *J*=2.3 Hz, 1 H), 5.27 (dd, *J*=9.9, 5.6 Hz, 1 H), 3.93 (dd, *J*=11.4, 2.3 Hz, 1 H), 3.87 (d, *J*=10.9 Hz, 1 H), 3.77 (s, 3 H), 3.23 - 3.37 (m, 2 H), 2.78 - 2.94 (m, 1 H), 2.42 (dd, *J*=9.6, 4.5 Hz, 1 H), 2.27 - 2.37 (m, 1 H), 1.59 - 1.84 (m, 2 H), 1.28 - 1.52 (m, 5 H), 0.95 - 1.18 ppm (m, 2 H)
154	 2-(4-(cyclopropylsulfonyl)-5-fluoro-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 22	[M+H] calc'd for $C_{22}H_{25}FN_5O_4S$ 474, found 474	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.39 - 9.52 (m, 1 H), 9.05 (s, 1 H), 8.80 (s, 1 H), 8.31 - 8.40 (m, 1 H), 8.18 - 8.29 (m, 1 H), 7.77 (dd, *J*=9.2, 2.9 Hz, 1 H), 7.39 (t, *J*=9.5 Hz, 1 H), 5.39 (dd, *J*=10.4, 5.1 Hz, 1 H), 3.76 - 4.00 (m, 2 H), 3.09 - 3.34 (m, 2 H), 2.74 - 2.96 (m, 1 H), 2.43 - 2.62 (m, 1 H), 2.19 - 2.43 (m, 1 H), 1.57 - 1.66 (m, 1 H), 1.24 - 1.55 (m, 6 H), 1.03 - 1.19 ppm (m, 2 H)
155	 2-(4-(cyclopropylsulfonyl)-5-fluoro-1H-indazol-1-yl)-N-(1-ethyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 22	[M+H] calc'd for $C_{23}H_{29}FN_5O_4S$ 490, found 490	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.38 (s, 1H), 8.71 (s, 1H), 7.75-7.78 (m, 1H), 7.23 - 7.36 (m, 2 H), 6.67 - 6.72 (m, 1 H), 5.25 - 5.46 (m, 1 H), 4.00 - 4.12 (m, 2 H), 3.83 - 3.95 (m, 2 H), 3.12 - 3.34 (m, 2 H), 2.81 - 2.94 (m, 1 H), 2.39 - 2.59 (m, 1 H), 2.23 - 2.39 (m, 1 H), 1.32 - 1.54 (m, 10 H), 0.96 - 1.19 ppm (m, 2 H)

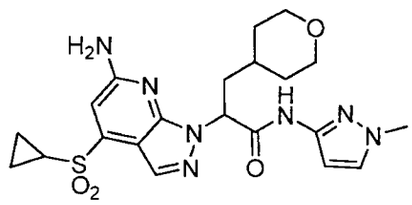
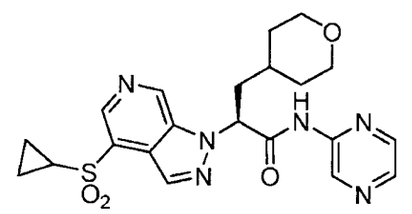
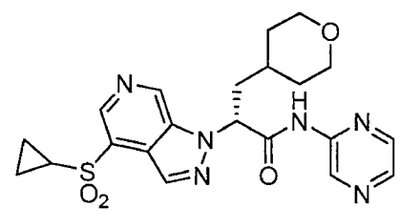
Ex.	Structure	Method	LCMS	NMR data
156	 2-(4-(cyclopropylsulfonyl)-5-fluoro-2H-indazol-2-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 22	[M+H] calc'd for $C_{22}H_{25}FN_5O_4S$ 474, found 474	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.53 (s, 2 H), 8.81 (s, 1 H), 8.42 (d, *J*=3.0 Hz, 2 H), 7.78 (dd, *J*=9.0, 3.4 Hz, 1 H), 7.41 (t, *J*=9.5 Hz, 1 H), 5.43 (dd, *J*=10.1, 5.3 Hz, 1 H), 3.89 - 4.13 (m, 2 H), 3.18 - 3.42 (m, 2 H), 2.78 - 2.96 (m, 1 H), 2.52 (dd, *J*=9.9, 4.5 Hz, 1 H), 2.21 - 2.41 (m, 1 H), 1.65 (d, *J*=12.6 Hz, 1 H), 1.38 - 1.56 (m, 5 H), 1.31 - 1.37 (m, 1 H), 1.11 - 1.24 ppm (m, 2 H)
157	 2-(4-(cyclopropylsulfonyl)-5-methyl-1H-indazol-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 22	[M+H] calc'd for $C_{23}H_{28}N_5O_4S$ 470, found 470	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.53 (br. s., 1H), 9.31 (br. s., 1 H), 8.77 (s, 1 H), 8.27 - 8.50 (m, 2 H), 7.64 (d, *J*=8.6 Hz, 1 H), 7.43 (d, *J*=8.8 Hz, 1 H), 5.38 (dd, *J*=10.4, 5.1 Hz, 1 H), 3.80 - 4.00 (m, 2 H), 3.11 - 3.34 (m, 2 H), 2.86 (s, 3 H), 2.69 (tt, *J*=8.0, 4.8 Hz, 1 H), 2.44 - 2.60 (m, 1 H), 2.29 (ddd, *J*=13.9, 8.3, 5.1 Hz, 1 H), 1.62 (d, *J*=12.6 Hz, 1 H), 1.34 - 1.55 (m, 5 H), 1.25 - 1.33 (m, 1 H), 0.96 - 1.14 ppm (m, 2 H

Ex.	Structure	Method	LCMS	NMR data
158	 2-(4-(cyclopropylsulfonyl)-5-methyl-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 22	[M+H] calc'd for $C_{23}H_{30}N_5O_4S$ 472, found 472	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 9.26 (s, 1 H), 8.67 (s, 1 H), 7.64 (d, *J*=8.8 Hz, 1 H), 7.38 (d, *J*=8.6 Hz, 1 H), 7.15 - 7.32 (m, 1 H), 6.67 (d, *J*=2.5 Hz, 1 H), 5.34 (dd, *J*=10.5, 4.9 Hz, 1 H), 3.88 (td, *J*=11.2, 2.7 Hz, 2 H), 3.78 (s, 3 H), 3.08 - 3.31 (m, 2 H), 2.85 (s, 3 H), 2.60 - 2.80 (m, 1 H), 2.39 - 2.60 (m, 1 H), 2.27 (ddd, *J*=14.0, 8.5, 5.1 Hz, 1 H), 1.62 (d, *J*=12.6 Hz, 1 H), 1.30 - 1.51 (m, 5 H), 1.21 - 1.29 (m, 1 H), 1.03 (d, *J*=7.3 Hz, 1 H), 1.02 ppm (s, 1 H)
159	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 13	[M+H] calc'd for $C_{21}H_{26}N_6O_4S$ 460, found 460	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 - 1.13 (m, 2 H) 1.17 - 1.36 (m, 5 H) 1.48 - 1.70 (m, 2 H) 2.28 (d, *J*=6.82 Hz, 1 H) 2.44 (br. s., 1 H) 3.03 - 3.23 (m, 3 H) 3.69 - 3.84 (m, 5 H) 5.87 (d, *J*=3.54 Hz, 1 H) 6.37 (d, *J*=2.02 Hz, 1 H) 7.55 (d, *J*=2.02 Hz, 1 H) 8.51 (s, 1 H) 8.68 (s, 1 H) 9.67 (s, 1 H) 11.08 (s, 1 H)
160	 (R)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 13	[M+H] calc'd for $C_{21}H_{26}N_6O_4S$ 460, found 460	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 - 1.13 (m, 2 H) 1.17 - 1.36 (m, 5 H) 1.48 - 1.70 (m, 2 H) 2.28 (d, *J*=6.82 Hz, 1 H) 2.44 (br. s., 1 H) 3.03 - 3.23 (m, 3 H) 3.69 - 3.84 (m, 5 H) 5.87 (d, *J*=3.54 Hz, 1 H) 6.37 (d, *J*=2.02 Hz, 1 H) 7.55 (d, *J*=2.02 Hz, 1 H) 8.51 (s, 1 H) 8.68 (s, 1 H) 9.67 (s, 1 H) 11.08 (s, 1 H)

Ex.	Structure	Method	LCMS	NMR data
161	 (R)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16 & 92	[M+H] calc'd for $C_{21}H_{24}N_6O_4S$ 458, found 458	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.09 - 1.19 (m, 2 H) 1.33 - 1.46 (m, 5 H) 1.56 (dd, *J*=9.47, 1.89 Hz, 1 H) 1.76 (dd, *J*=9.73, 1.89 Hz, 1 H) 2.20 - 2.30 (m, 1 H) 2.73 (ddd, *J*=14.15, 11.12, 3.54 Hz, 1 H) 2.91 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.11 - 3.28 (m, 2 H) 3.81 - 3.90 (m, 2 H) 6.10 (dd, *J*=11.12, 4.29 Hz, 1 H) 7.71 (d, *J*=4.55 Hz, 1 H) 8.31 (d, *J*=2.53 Hz, 1 H) 8.36 (dd, *J*=2.53, 1.52 Hz, 1 H) 8.53 (s, 1 H) 8.83 (d, *J*=4.80 Hz, 1 H) 9.29 (s, 1 H)
162	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16 & 92	[M+H] calc'd for $C_{21}H_{24}N_6O_4S$ 458, found 458	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.09 - 1.19 (m, 2 H) 1.33 - 1.46 (m, 5 H) 1.56 (dd, *J*=9.47, 1.89 Hz, 1 H) 1.76 (dd, *J*=9.73, 1.89 Hz, 1 H) 2.20 - 2.30 (m, 1 H) 2.73 (ddd, *J*=14.15, 11.12, 3.54 Hz, 1 H) 2.91 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.11 - 3.28 (m, 2 H) 3.81 - 3.90 (m, 2 H) 6.10 (dd, *J*=11.12, 4.29 Hz, 1 H) 7.71 (d, *J*=4.55 Hz, 1 H) 8.31 (d, *J*=2.53 Hz, 1 H) 8.36 (dd, *J*=2.53, 1.52 Hz, 1 H) 8.53 (s, 1 H) 8.83 (d, *J*=4.80 Hz, 1 H) 9.29 (s, 1 H)
163	 (R)-2-(6-amino-4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16	[M+H] calc'd for $C_{21}H_{25}N_7O_4S$ 473, found 473	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.99 - 1.06 (m, 2 H) 1.29 - 1.42 (m, 5 H) 1.52 (d, *J*=9.35 Hz, 1 H) 1.71 - 1.79 (m, 1 H) 2.13 - 2.23 (m, 1 H) 2.57 - 2.66 (m, 1 H) 2.90 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.13 - 3.27 (m, 2 H) 3.86 (t, *J*=10.74 Hz, 2 H) 5.90 (dd, *J*=10.99, 4.42 Hz, 1 H) 8.17 (s, 1 H) 8.27 - 8.38 (m, 3 H) 9.31 (s, 1 H)

Ex.	Structure	Method	LCMS	NMR data
164	 (S)-2-(6-amino-4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16	[M+H] calc'd for $C_{21}H_{25}N_7O_4S$ 473, found 473	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.99 - 1.06 (m, 2 H) 1.29 - 1.42 (m, 5 H) 1.52 (d, *J*=9.35 Hz, 1 H) 1.71 - 1.79 (m, 1 H) 2.13 - 2.23 (m, 1 H) 2.57 - 2.66 (m, 1 H) 2.90 (tt, *J*=7.96, 4.80 Hz, 1 H) 3.13 - 3.27 (m, 2 H) 3.86 (t, *J*=10.74 Hz, 2 H) 5.90 (dd, *J*=10.99, 4.42 Hz, 1 H) 8.17 (s, 1 H) 8.27 - 8.38 (m, 3 H) 9.31 (s, 1 H)
165	 (S)-2-(4-(cyclopropylsulfonyl)-5-fluoro-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 22	[M+H] calc'd for $C_{22}H_{27}FN_5O_4S$ 476, found 476	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.58 - 8.83 (m, 2 H), 7.74 (dd, *J*=9.1, 3.0 Hz, 1 H), 7.34 (t, *J*=9.3 Hz, 1 H), 7.23 (d, *J*=2.0 Hz, 1 H), 6.61 (d, *J*=2.3 Hz, 1 H), 5.33 (dd, *J*=10.4, 5.1 Hz, 1 H), 3.81 - 3.94 (m, 2 H), 3.76 (s, 3 H), 3.08 - 3.32 (m, 2 H), 2.90 (dd, *J*=4.8, 3.3 Hz, 1 H), 2.49 (d, *J*=3.8 Hz, 1 H), 2.22 - 2.37 (m, 1 H), 1.59 (d, *J*=12.4 Hz, 1 H), 1.19 - 1.55 (m, 5 H), 1.04 - 1.19 (m, 2 H), 0.78 - 0.93 ppm (m, 1 H)
166	 (R)-2-(4-(cyclopropylsulfonyl)-5-fluoro-1H-indazol-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 22	[M+H] calc'd for $C_{22}H_{27}FN_5O_4S$ 476, found 476	^{1}H NMR (CHLOROFORM-d ,400MHz): δ = 8.58 - 8.83 (m, 2 H), 7.74 (dd, *J*=9.1, 3.0 Hz, 1 H), 7.34 (t, *J*=9.3 Hz, 1 H), 7.23 (d, *J*=2.0 Hz, 1 H), 6.61 (d, *J*=2.3 Hz, 1 H), 5.33 (dd, *J*=10.4, 5.1 Hz, 1 H), 3.81 - 3.94 (m, 2 H), 3.76 (s, 3 H), 3.08 - 3.32 (m, 2 H), 2.90 (dd, *J*=4.8, 3.3 Hz, 1 H), 2.49 (d, *J*=3.8 Hz, 1 H), 2.22 - 2.37 (m, 1 H), 1.59 (d, *J*=12.4 Hz, 1 H), 1.19 - 1.55 (m, 5 H), 1.04 - 1.19 (m, 2 H), 0.78 - 0.93 ppm (m, 1 H)

Ex.	Structure	Method	LCMS	NMR data
167	 2-(6-chloro-4-(cyclopropylsulfonyl)-2H-indazol-2-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{27}ClN_5O_4S$ 492, found 492	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.17 (s, 1H), 8.47 (d, *J* = 1.01 Hz, 1H), 8.04 (d, *J* = 1.01 Hz, 1H), 7.69 (d, *J* = 1.77 Hz, 1H), 7.18 - 7.31 (m, 1H), 6.62 (d, *J* = 2.27 Hz, 1H), 5.26 (dd, *J* = 5.81, 9.85 Hz, 1H), 3.82 - 4.00 (m, 2H), 3.72 - 3.81 (m, 3H), 3.26 (td, *J* = 1.89, 11.43 Hz, 2H), 2.48 - 2.62 (m, 1H), 2.25 - 2.48 (m, 2H), 1.61 - 1.76 (m, 1H), 1.47 - 1.55 (m, 1H), 1.26 - 1.47 (m, 5H), 0.97 - 1.11 (m, 2H)
168	 2-(6-chloro-4-(cyclopropylsulfonyl)-2H-indazol-2-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 10	[M+H] calc'd for $C_{22}H_{25}ClN_5O_4S$ 490.1, found 490.1	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.59 (s, 1H), 9.49 (br. s., 1H), 8.52 (s, 1H), 8.38 (br. s., 1H), 8.26 (s, 1H), 8.08 (s, 1H), 7.71 (d, *J* = 1.52 Hz, 1H), 5.33 (dd, *J* = 5.81, 9.85 Hz, 1H), 3.81 - 4.02 (m, 2H), 3.18 - 3.32 (m, 2H), 2.42 - 2.66 (m, 2H), 2.26 - 2.42 (m, 1H), 1.70 (d, *J* = 12.13 Hz, 1H), 1.62 (br. s., 1H), 1.49 - 1.58 (m, 1H), 1.29 - 1.49 (m, 4H), 1.00 - 1.14 (m, 2H)
169	 2-(4-(cyclopropylsulfonyl)-2H-pyrazolo[3,4-c]pyridin-2-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 13 & 140	[M+H] calc'd for $C_{21}H_{24}N_6O_4S$ 458, found 458	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.14 (m, 2 H) 1.17 - 1.40 (m, 5 H) 1.48 - 1.71 (m, 2 H) 2.23 - 2.35 (m, 1 H) 2.53 - 2.60 (m, 1 H) 3.02 - 3.21 (m, 3 H) 3.70 - 3.88 (m, 2 H) 5.97 (dd, *J*=9.85, 5.56 Hz, 1 H) 8.38 - 8.49 (m, 2 H) 8.57 (s, 1 H) 9.00 (s, 1 H) 9.27 (d, *J*=1.26 Hz, 1 H) 9.56 (s, 1 H) 11.56 (s, 1 H)

Ex.	Structure	Method	LCMS	NMR data
170	 2-(6-amino-4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 16	[M+H] calc'd for $C_{21}H_{27}N_7O_4S$ 475, found 475	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.11 - 1.19 (m, 2 H) 1.28 - 1.44 (m, 5 H) 1.49 - 1.56 (m, 1 H) 1.73 - 1.81 (m, 1 H) 2.24 (ddd, *J*=13.77, 8.97, 4.55 Hz, 1 H) 2.67 - 2.77 (m, 1 H) 2.85 - 2.95 (m, 1 H) 3.10 - 3.28 (m, 2 H) 3.79 - 3.90 (m, 5 H) 6.08 (dd, *J*=11.37, 4.29 Hz, 1 H) 7.72 (d, *J*=4.80 Hz, 1 H) 7.75 (s, 1 H) 8.53 (s, 1 H) 8.84 (d, 1 H)
171	 (S)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 20	[M+H] calc'd for $C_{21}H_{25}N_6O_4S$ 458, found 458	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.12 (m, 2 H) 1.20 - 1.37 (m, 5 H) 1.50 (d, *J*=11.62 Hz, 1 H) 1.66 (d, *J*=11.12 Hz, 1 H) 2.25 - 2.35 (m, 1 H) 2.52 - 2.58 (m, 1 H) 3.04 - 3.17 (m, 3 H) 3.71 - 3.83 (m, 2 H) 6.06 (dd, *J*=10.11, 5.31 Hz, 1 H) 8.40 (d, *J*=2.53 Hz, 1 H) 8.42 - 8.46 (m, 1 H) 8.55 (s, 1 H) 8.70 (s, 1 H) 9.24 (d, *J*=1.26 Hz, 1 H) 9.68 (s, 1 H).
172	 (R)-2-(4-(cyclopropylsulfonyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide	*See* Cmpd. 20	[M+H] calc'd for $C_{21}H_{25}N_6O_4S$ 458, found 458	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.12 (m, 2 H) 1.20 - 1.37 (m, 5 H) 1.50 (d, *J*=11.62 Hz, 1 H) 1.66 (d, *J*=11.12 Hz, 1 H) 2.25 - 2.35 (m, 1 H) 2.52 - 2.58 (m, 1 H) 3.04 - 3.17 (m, 3 H) 3.71 - 3.83 (m, 2 H) 6.06 (dd, *J*=10.11, 5.31 Hz, 1 H) 8.40 (d, *J*=2.53 Hz, 1 H) 8.42 - 8.46 (m, 1 H) 8.55 (s, 1 H) 8.70 (s, 1 H) 9.24 (d, *J*=1.26 Hz, 1 H) 9.68 (s, 1 H).

Biological Testing

[0498] The activity of compounds as glucokinase activators may be assayed *in vitro*, *in vivo* or in a cell line. Provided below is an enzymatic glucokinase activity assay.

[0499] Purified glucokinase may be obtained as follows. DNA encoding residues 12-465 of the full-length sequence of the human enzyme may be amplified by PCR and cloned into the HindIII and EcoRI sites of pFLAG-CTC (Sigma). SEQ. I.D. No. 1 corresponds to residues 12-465 of glucokinase.

[0500] The expression of recombinant glucokinase protein may be carried out by transformation and growth of DH10b-T1r E.coli cells incorporating the (pFLAG-CTC) plasmid in LB media. Protein expression can be induced in this system by the addition of IPTG to the culture medium.

[0501] Recombinant protein may be isolated from cellular extracts by passage over Sepharose Q Fast Flow resin (Pharmacia). This partially purified GK extract may then be further purified by a second passage over Poros HQ10 (Applied Biosystems). The purity of GK may be determined on denaturing SDS-PAGE gel. Purified GK may then be concentrated to a final concentration of 20.0 mg/ml. After flash freezing in liquid nitrogen, the proteins can be stored at -78°C in a buffer containing 25mM TRIS-HCl pH 7.6, 50mM NaCl, and 0.5 mM TCEP.

[0502] It should be noted that a variety of other expression systems and hosts are also suitable for the expression of glucokinase, as would be readily appreciated by one of skill in the art.

[0503] The activation properties of compounds for GK may be determined using a black 384-well-plate format under the following reaction conditions: 25 mM Hepes pH 7.2, 25 mM NaCl, 10 mM $MgCl_2$, 0.01% Brij35, 1 mM DTT, 5 μM ATP, 5 mM Glucose 2% DMSO. The amount of ATP consumed may be determined quantitatively by addition of equal volume of luciferase reagent (luciferase + beetle luciferin ---KinaseGlo Luminescent Kinase Assay kit from Promega). The luminescence intensity may be measured by using the Analyst HT from LJL Biosystems.

[0504] The assay reaction may be initiated as follows: 4 μl of substrate mixture (12.5 μM ATP and 12.5 mM Glucose) was added to each well of the plate, followed by the addition of 2 μl of activator (2 fold serial dilutions for 11 data points for each activator) containing 10% DMSO. 4 μL of 1.25 nM GK solution may be added to initiate the reaction. The reaction mixture may then be incubated at room temperature for 60 min, and quenched and developed by addition of 10 μL of luciferase reagent. Luminescence intensities of the resulting reaction mixtures may be measured after a 10 min incubation at room

temperature. The luminescence intensity may be measured by using the Analyst HT from LJL Biosystems.

[0505] pK_{act} and $\%ACT_{max}$ values may be calculated by non-linear curve fitting of the compound concentrations and luminescence intensities to a standard inhibition/activation equation. K_{act} is the concentration that displays 50% of the maximal increase in GK activity observed using a saturating activator concentration. $\%Act_{max}$ represents the calculated maximal gain in GK enzyme activity at a saturating concentration of the compound. pK_{act} and $\%ACT_{max}$ values for select compounds of the present invention are given in Table 1.

TABLE 1: pK_{act} and $\%ACT_{max}$ **of Exemplified Compounds Against GK**

Compound	pK_{act}	$\%ACT_{max}$
1	≤4.8	≤ 90
2	≤4.8	≤ 90
3	≤4.8	≤ 90
4	4.9 – 5.4	101 - 105
5	5.9 – 6.4	≥ 111
6	4.9 – 5.4	≥ 111
7	4.9 – 5.4	≤ 90
8	4.9 – 5.4	≤ 90
9	4.9 – 5.4	≤ 90
10	5.5 – 5.8	≥ 111
11	≥6.5	101 - 105
12	5.5 – 5.8	≤ 90
13	≥6.5	106 - 110
14	≥6.5	≥ 111
15	5.9 – 6.4	90 - 100
16	≥6.5	106 - 110
19	≥6.5	≤ 90
20 (Free Base)	5.9 – 6.4	101 - 105
20 (TFA Salt)	5.5 – 5.8	106 - 110
22	≥6.5	≥ 111
23	≥6.5	≥ 111
24	≤4.8	≤ 90
25	≤4.8	≤ 90
26	≤4.8	≤ 90
27	5.5 – 5.8	≤ 90
28	4.9 – 5.4	≥ 111
29	5.9 – 6.4	≥ 111
30	4.9 – 5.4	≤ 90
31	≤4.8	≤ 90
32	4.9 – 5.4	101 - 105
33	5.5 – 5.8	≥ 111
34	5.5 – 5.8	≥ 111

Compound	pK_{act}	$\%ACT_{max}$
35	≤4.8	≤ 90
36	5.5 – 5.8	≥ 111
37	5.5 – 5.8	≥ 111
38	≤4.8	≥ 111
39	5.5 – 5.8	≥ 111
40	≤4.8	≤ 90
41	5.5 – 5.8	≤ 90
42	5.5 – 5.8	≥ 111
43	≤4.8	≤ 90
44	5.9 – 6.4	≥ 111
45	4.9 – 5.4	≥ 111
46	≤4.8	101 - 105
47	4.9 – 5.4	≥ 111
48	5.9 – 6.4	≥ 111
49	4.9 – 5.4	90 - 100
50	≤4.8	≤ 90
51	5.9 – 6.4	≥ 111
52	≤4.8	90 - 100
53	≤4.8	≤ 90
54	4.9 – 5.4	≤ 90
55	4.9 – 5.4	≤ 90
56	≤4.8	≤ 90
57	4.9 – 5.4	101 - 105
58	≤4.8	101 - 105
59	≥6.5	106 - 110
60	≤4.8	≤ 90
61	5.9 – 6.4	90 - 100
62	5.9 – 6.4	90 - 100
63	4.9 – 5.4	≥ 111
64	≥6.5	≥ 111
65	5.9 – 6.4	90 - 100
66	≥6.5	101 - 105

Compound	pK_{act}	$\%ACT_{max}$
67	≥6.5	106 - 110
68	4.9 – 5.4	101 - 105
69	≥6.5	106 - 110
70	5.5 – 5.8	101 - 105
71	5.5 – 5.8	≤ 90
72	≥6.5	≤ 90
73	≤4.8	90 - 100
74	5.5 – 5.8	90 - 100
75	5.9 – 6.4	90 - 100
76	≥6.5	106 - 110
77	≤4.8	101 - 105
78	5.5 – 5.8	90 - 100
79	≥6.5	90 - 100
80	≥6.5	101 - 105
81	4.9 – 5.4	101 - 105
82	≥6.5	106 - 110
83	4.9 – 5.4	≤ 90
84	≥6.5	106 - 110
85	5.5 – 5.8	90 - 100
86	≤4.8	≤ 90
87	5.5 – 5.8	90 - 100
88	≤4.8	≤ 90
89	5.5 – 5.8	101 - 105
90	≤4.8	90 - 100
91	5.9 – 6.4	101 - 105
92	4.9 – 5.4	≤ 90
93	≤4.8	≤ 90
94	≥6.5	90 - 100
95	5.5 – 5.8	101 - 105
96	5.9 – 6.4	101 - 105
97	5.9 – 6.4	106 - 110
98	5.9 – 6.4	90 - 100
99	4.9 – 5.4	90 - 100
100	5.9 – 6.4	≤ 90
101	5.9 – 6.4	90 - 100
102	5.9 – 6.4	90 - 100
103	5.5 – 5.8	101 - 105
104	5.5 – 5.8	90 - 100
105 (TFA Salt)	5.9 – 6.4	≤ 90
105 (Free Base)	≥6.5	≤ 90
106	≤4.8	90 - 100
107	≥6.5	≥ 111
108	4.9 – 5.4	≥ 111
109	≥6.5	101 - 105
110	≤4.8	106 - 110
111	5.9 – 6.4	106 - 110
112	≥6.5	106 - 110
113	5.9 – 6.4	101 - 105
114	≥6.5	101 - 105
115	≥6.5	106 - 110
116	4.9 – 5.4	≤ 90
117	≥6.5	106 - 110

Compound	pK_{act}	$\%ACT_{max}$
118	≤4.8	≤ 90
119	5.9 – 6.4	90 - 100
120	≥6.5	90 - 100
121	≥6.5	90 - 100
122	4.9 – 5.4	≥ 111
123	≥6.5	≥ 111
124	4.9 – 5.4	≥ 111
125	5.5 – 5.8	≥ 111
126	≤4.8	≤ 90
127	≥6.5	101 - 105
128	≥6.5	90 - 100
129	4.9 – 5.4	≤ 90
130	≥6.5	101 - 105
131	≤4.8	≤ 90
132	5.5 – 5.8	90 - 100
133	≥6.5	101 - 105
134	5.5 – 5.8	≥ 111
135	5.9 – 6.4	106 - 110
136	5.9 – 6.4	≥ 111
137	4.9 – 5.4	≤ 90
138	5.9 – 6.4	90 - 100
139	≤4.8	106 - 110
140	≤4.8	≤ 90
141	≥6.5	90 - 100
142	≥6.5	101 - 105
143	≥6.5	≤ 90
144	≥6.5	106 - 110
145	4.9 – 5.4	≤ 90
146	4.9 – 5.4	≤ 90
147	5.5 – 5.8	≥ 111
148	4.9 – 5.4	≤ 90
149	≥6.5	≥ 111
150	5.9 – 6.4	≥ 111
151	5.5 – 5.8	90 - 100
152	≥6.5	106 - 110
153	≤4.8	106 - 110
154	≥6.5	106 - 110
155	≥6.5	106 - 110
156	≥6.5	101 - 105
157	5.9 – 6.4	≥ 111
158	5.9 – 6.4	≥ 111
159	5.5 – 5.8	101 - 105
160	4.9 – 5.4	90 - 100
161	≤4.8	≤ 90
162	5.5 – 5.8	106 - 110
163	5.5 – 5.8	≤ 90
164	5.9 – 6.4	106 - 110
165	≥6.5	90 - 100
166	4.9 – 5.4	90 - 100
167	4.9 – 5.4	≤ 90
168	≤4.8	≤ 90
169	≤4.8	≤ 90

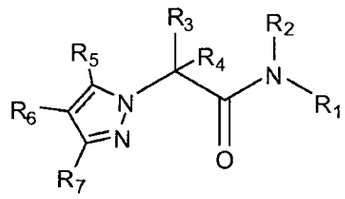
Compound	pK_{act}	$\%ACT_{max}$
170	≤4.8	≤ 90

Compound	pK_{act}	$\%ACT_{max}$
171	5.5 – 5.8	106 - 110

[0506] It will be apparent to those skilled in the art that various modifications and variations can be made in the compounds, compositions, kits, and methods of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

What is claimed is:

1. A compound having the formula:



or a polymorph, solvate, ester, tautomer, enantiomer, pharmaceutically acceptable salt or prodrug thereof, wherein

R_1 is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, heteroaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is selected from the group consisting of hydrogen and a substituent convertible to hydrogen *in vivo*;

R_3 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is –L-R_{18};

R_4 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or

unsubstituted, or R_3 and R_4 are taken together to form a substituted or unsubstituted ring;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_6 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_6 is $-L_1$-R_{22};

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl,

sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_7 is $-L_1$-R_{22};

or any two R_5, R_6 and R_7 are taken together to form a substituted or unsubstituted ring;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

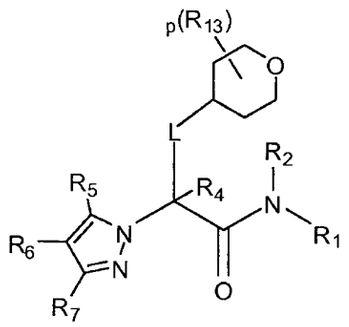
R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino,

sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring,

with the provisos that (a) R_1 is not 5-(3-acetamidocyclobutyl)-1H-pyrazol-3-yl when R_5 and R_6, together with the ring to which they are attached, form an unsubstituted indazol-1-yl; and (b) R_1 is not 5-(2-chlorobenzyl)thiazol-2-yl when R_3 is phenyl and R_2, R_4, R_5, R_6 and R_7 are all hydrogen.

2. The compound of claim 1 comprising:

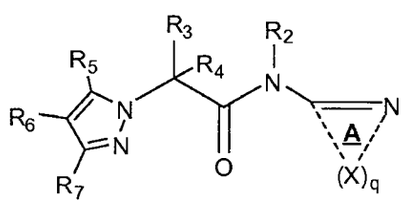


wherein

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9; and

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring.

3. The compound of claim 1 comprising:



wherein

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

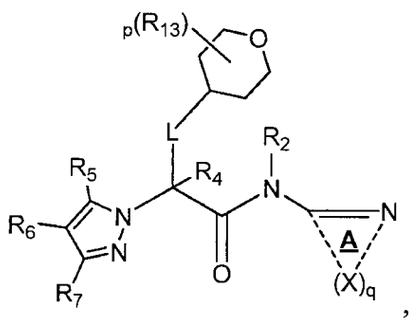
R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and

hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring,

with the provisos that (a) ring A is not 5-(3-acetamidocyclobutyl)-1H-pyrazol-3-yl when R_5 and R_6, together with the ring to which they are attached, form an unsubstituted indazol-1-yl; and (b) ring A is not 5-(2-chlorobenzyl)thiazol-2-yl when R_3 is phenyl and R_2, R_4, R_5, R_6 and R_7 are all hydrogen.

4. The compound of claim 1 comprising:



,

wherein

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or

unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

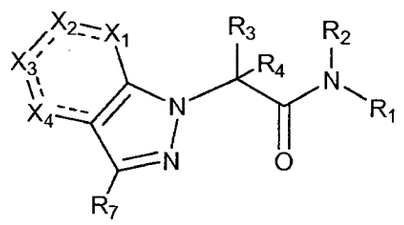
R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl,

(C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring.

5. The compound of claim 1 comprising:



wherein

X_1, X_2, X_3 and X_4 are each independently selected from the group consisting of CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S and O;

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

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl,

carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_9 and R_{10} are taken together to form oxo, with the proviso that R_{10} is absent when the atom to which it is bound forms part of a double bond;

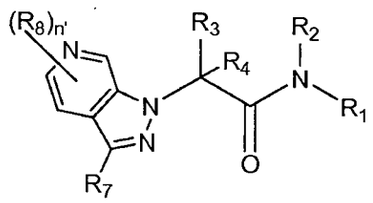
R_{11} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl,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

R_{12} is selected from the group consisting of hydrogen, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl,

each substituted or unsubstituted, with the proviso that R_{12} is absent when the atom to which it is bound forms part of a double bond,

or any two R_7, R_9, R_{10}, R_{11} and R_{12} are taken together to form a substituted or unsubstituted ring.

6. The compound of claim 1 comprising:

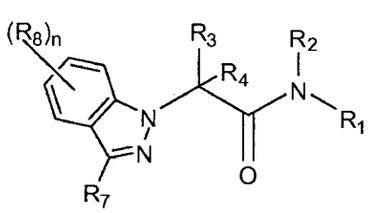


wherein

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

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring.

7. The compound of claim 1 comprising:

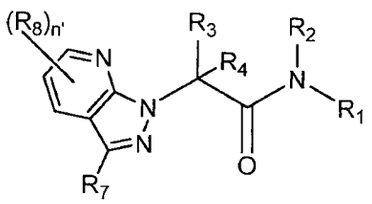


wherein

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

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring.

8. The compound of claim 1 comprising:

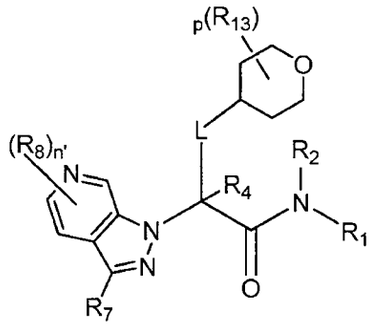


wherein

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

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring.

9. The compound of claim 1 comprising:



wherein

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

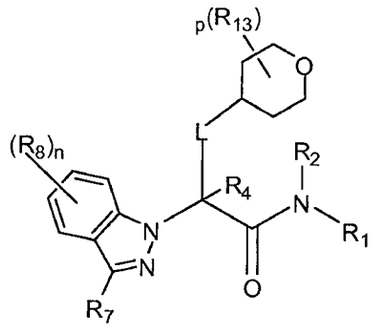
p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring; and

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or

unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring.

10. The compound of claim 1 comprising:



wherein

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

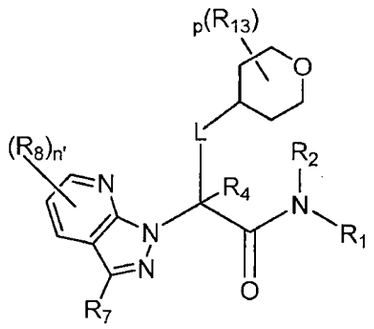
p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring; and

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring.

11. The compound of claim 1 comprising:



wherein

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

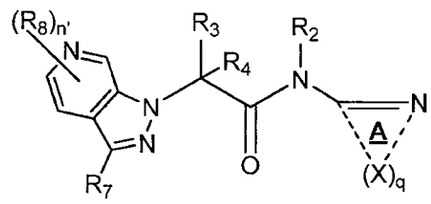
p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring; and

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl,

sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring.

12. The compound of claim 1 comprising:



wherein

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

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

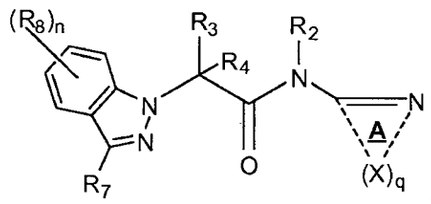
R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and

hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring.

13. The compound of claim 1 comprising:



wherein

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

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl,

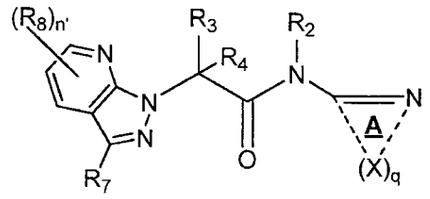
sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring.

14. The compound of claim 1 comprising:



wherein

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

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl,

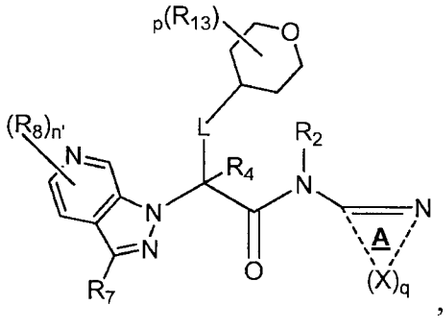
(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring.

15. The compound of claim 1 comprising:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

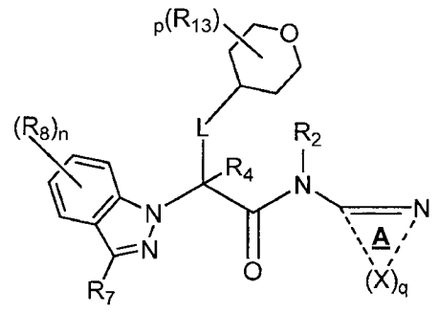
R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino

(C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring.

16. The compound of claim 1 comprising:



wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

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

(C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1-R_{22}$, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

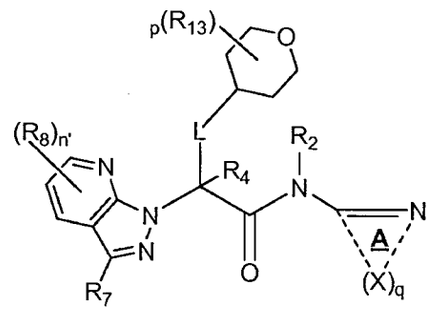
R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring.

17. The compound of claim 1 comprising:



,

wherein

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

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

q is selected from the group consisting of 3, 4 and 5;

each X is independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

R_8 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, (C_{3-12})cycloalkyl sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_8 is $-L_1$-R_{22}, or R_8 and R_7 or two R_8 are taken together to form a substituted or unsubstituted ring;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl,

oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

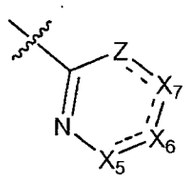
or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring.

18. The compound according to any one of claims 1, 2 and 5-11, wherein R_1 is a substituted or unsubstituted heteroaryl.

19. The compound according to any one of claims 1, 2 and 5-11, wherein R_1 is selected from the group consisting of thiazolyl, pyrazinyl, pyrazolyl and pyridyl, each substituted or unsubstituted.

20. The compound according to any one of claims 1, 2 and 5-11, wherein R_1 is selected from the group consisting of thiazol-2-yl; 2-pyridyl; 5-methyl-thiazol-2-yl; 6-methyl-pyrid-2-yl; 4-methyl-pyrid-2-yl; 5-bromo-6-methyl-pyrid-2-yl; 5-phenyl-pyrid-2-yl; benzothiazol-2-yl; a nictoinic acid methyl ester; 5-bromo-pyrid-2-yl; 2-pyrazinyl; 1-methyl-pyrazol-3-yl and 5-fluoro-thiazol-2-yl.

21. The compound according to any one of claims 1, 2 and 5-11, wherein R_1 comprises:



wherein

X_5, X_6 and X_7 are each independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

Z is selected from the group consisting of $CR_{14}R_{15}$, NR_{16}, O and S;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22};

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring;

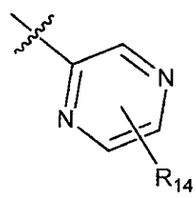
L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy,

carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

22. The compound according to any one of claims 1, 2 and 5-11, wherein R_1 comprises:

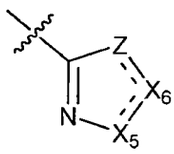


wherein

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl,

halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$.

23. The compound according to any one of claims 1, 2 and 5-11, wherein R_1 comprises:



wherein

X_5 and X_6 are each independently selected from the group consisting of $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO and SO_2;

Z is selected from the group consisting of $CR_{14}R_{15}$, NR_{16}, O and S;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl,

sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{15} is absent when the atom to which it is bound forms part of a double bond; and

R_{16} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, with the proviso that R_{16} is absent when the atom to which it is bound forms part of a double bond,

or any two R_{14}, R_{15} and R_{16} are taken together to form a substituted or unsubstituted ring;

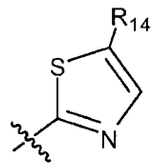
L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl,

imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

24. The compound according to any one of claims 1, 2 and 5-11, wherein R_1 comprises:



wherein

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl,

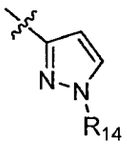
(C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1-R_{22}$;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

25. The compound according to any one of claims 1, 2 and 5-11, wherein R_1 comprises:



wherein

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, carboxamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, oxa(C_{1-5})alkyl, oxo(C_{1-5})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{14} is $-L_1$-R_{22}.

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

26. The compound according to any one of claims 1-25, wherein R_2 is hydrogen.

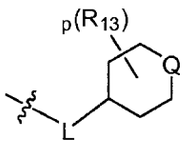
27. The compound according to any one of claims 1, 3, 5-8, 12-14 and 18-26 wherein

R_3 is –L-R_{18};

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C and R_{18} 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

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

28. The compound according to any one of claims 1, 3, 5-8, 12-14 and 18-26 wherein R_3 comprises:



wherein

p is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9;

L is a linker providing 0, 1, 2, 3, 4, 5 or 6 atom separation between the C 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;

Q is selected from the group consisting of O, S, CS, CO, SO, SO_2, $CR_{19}R_{20}$ and NR_{21};

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or two R_{13} are taken together to form a substituted or unsubstituted ring;

R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

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

R_{21} is selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

29. The compound according to any one of claims 1-28, 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-, -$NHCH_2$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-, and -CH_2SC(O)-, each substituted or unsubstituted.

30. The compound according to any one of claims 1-28, wherein

L is selected from the group consisting of –($CR_{24}R_{25}$)$_s$-;

s is selected from the group consisting from the group consisting of 1, 2, 3, 4, 5 and 6; and

R_{24} and R_{25} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl,

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

31. The compound according to any one of claims 1-28, wherein L is–CH_2-.

32. The compound according to any one of claims 1-31, wherein R_4 is hydrogen.

33. The compound according to any one of claims 1-4 and 18-32, wherein R_5 is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

34. The compound according to any one of claims 1-4 and 18-33, wherein R_6 is selected from the group consisting of hydrogen, halo, a substituted or unsubstituted (C_{1-3})alkyl; a substituted or unsubstituted (C_{1-3})alkylsulfonyl and a substituted or unsubstituted (C_{1-6})cycloalkylsulfonyl.

35. The compound according to any one of claims 1-4 and 18-33, wherein

R_6 is –L_1-R_{22};

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,

(C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

36. The compound according to any one of claims 1-35, wherein R_7 is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

37. The compound according to any one of claims 1-35, wherein

R_7 is $-L_1-R_{22}$;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,

(C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

38. The compound according to any one of claims 1-4 and 18-37, wherein R_5 and R_6, together with the atoms to which they are attached, form a substituted or unsubstituted aryl.

39. The compound according to any one of claims 1-4 and 18-37, wherein R_5 and R_6, together with the atoms to which they are attached, form a substituted or unsubstituted heteroaryl.

40. The compound according to any one of claims 6-39, wherein R_8 is selected from the group consisting of hydrogen, halo, a substituted or unsubstituted (C_{1-3})alkyl, a substituted or unsubstituted sulfonyl(C_{1-3})alkyl, a substituted or unsubstituted (C_{1-3})alkylsulfonyl and a substituted or unsubstituted (C_{3-12})cycloalkylsulfonyl.

41. The compound according to any one of claims 6-39, wherein R_8 is selected from the group consisting of sulfonylmethyl, methylsulfonyl, cyclopropylsulfonyl and cyclopentylsulfonyl, each substituted or unsubstituted.

42. The compound according to any one of claims 6-39, wherein

R_8 is $-L_1$-R_{22};

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{22} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

43. The compound according to any one of claims 6-39, wherein R_8 is $-SO_2-R_{22}$; R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{22} is $-NR_{27}R_{28}$; and R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

44. The compound according to any one of claims 6-8, 12-14 and 18-43, wherein R_3 is a substituted or unsubstituted(tetrahydro-2H-pyran-4-yl)methyl and R_8 is a substituted or unsubstituted cyclopropylsulfonyl.

45. The compound according to any one of claims 1-44, wherein R_{22} is selected from the group consisting of a substituted or unsubstituted (C_{1-5})alkyl; a substituted or unsubstituted (C_{3-6})cycloalkyl; a substituted or unsubstituted (C_{4-8})aryl; and a substituted or unsubstituted hetero(C_{1-6})aryl.

46. The compound according to any one of claims 1-44, wherein R_{22} is cyclopropyl.

47. The compound according to any one of claims 1-44, wherein

R_{22} is $-NR_{27}R_{28}$; and

R_{27} and R_{28} are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl,

(C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{27} and R_{28} are taken together to form a substituted or unsubstituted ring.

48. The compound according to any one of claims 1-47, wherein

L_1 is selected from the group consisting of $-(CR_{24}R_{25})_s$-, -NR_{26}-, -O-, -S-, -CO-, -CS-, -SO-, -SO_2-, and combinations thereof;

s is selected from the group consisting from the group consisting of 1, 2, 3, 4, 5 and 6;

R_{24} and R_{25} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{26} is selected from the group consisting of hydrogen, cyano, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

49. The compound according to any one of claims 1-47, wherein L_1 is -SO_2-.

50. The compound according to any one of claims 1-49, wherein the compound is in the form of a pharmaceutically acceptable salt.

51. A pharmaceutical composition comprising as an active ingredient a compound according to any one of claims 1-50, and one or more pharmaceutically acceptable excipients.

52. A kit comprising:

a compound of any one of claims 1-50; 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.

53. An article of manufacture comprising:

a compound of any one of claims 1-50; and

packaging materials.

54. A method of activating glucokinase comprising contacting glucokinase with a compound according to any one of claims 1-50.

55. A compound according to any one of claims 1-50 for use as a medicament.

56. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for activating glucokinase.

57. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating a disease state for which glucokinase possesses activity that contributes to the pathology and/or symptomology of the disease state.

58. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating hyperglycemia.

59. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating diabetes.

60. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating dyslipidaemia.

61. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating obesity.

62. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating insulin resistance.

63. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating metabolic syndrome X.

64. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating impaired glucose tolerance.

65. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating polycystic ovary syndrome.

66. Use of a compound according to any one of claims 1-50 in the manufacture of a medicament for treating cardiovascular disease.

FIGURE 1

[SEQ. I.D. No. 1]

MKLMALTLVEQILAEFQLQEEDLKKVMRRMQKEMDRGLRLETHEEASVKMLPTYVRSTPE
GSEVGDFLSLDLGGTNFRVMLVKVGEGEEGQWSVKTKHQMYSIPEDAMTGTAEMLFDYIS
ECISDFLDKHQMKHKKLPLGFTFSFPVRHEDIDKGILLNWTKGFKASGAEGNNVVGLLRD
AIKRRGDFEMDVVAMVNDTVATMISCYYEDHQCEVGMIVGTGCNACYMEEMQNVELVEGD
EGRMCVNTEWGAFGDSGELDEFLLEYDRLVDESSANPGQQLYEKLIGGKYMGELVRLVLL
RLVDENLLFHGEASEQLRTRGAFETRFVSQVESDTGDRKQIYNILSTLGLRPSTTDCDIV
RRACESVSTRAAHMCSAGLAGVINRMRESRSEDVMRITVGVDGSVYKLHPSFKERFHASV
RRLTPSCEITFIESEEGSGRGAALVSAVACKKACMLGQ

ACTIVADORES DE GLUCOQUINASA

Campo de la invención

[001] La presente invención se refiere a compuestos que se pueden utilizar para activar las hexoquinasas, como así también composiciones del asunto, kits y artículos de fabricación que comprenden estos compuestos. La invención además se refiere a métodos para activar las hexoquinasas y métodos de tratamiento que utilizan compuestos de acuerdo con la presente invención. Además, la invención se refiere a métodos para producir los compuestos de la presente invención, como así también intermediarios útiles en estos métodos. En particular, la presente invención se refiere a activadores de glucoquinasa, composiciones del asunto, kits y artículos de fabricación que comprenden estos compuestos, métodos para activar la glucoquinasa, y métodos para producir los activadores.

Antecedentes de la invención

[002] La glucoquinasa (GK, Hexoquinasa IV) es una de las cuatro hexoquinasas que se encuentran en los mamíferos (Colowick, S. P., in The Enzymes, Vol. 9 (P. Boyer, ed.) Academic Press, New York, N.Y., páginas 1-48, 1973). Las hexoquinasas catalizan el primer paso en el metabolismo de la glucosa, es decir, la conversión de glucosa a glucosa-6-fosfato. La glucoquinasa se halla principalmente en las células β pancreáticas y en células del parénquima hepático, dos tipos de células que se sabe cumplen funciones críticas en la homeostasis de la glucosa corporal total. Específicamente, GK es una enzima que controla la velocidad para el metabolismo de la glucosa en estos dos tipos de células (Chipkin, S. R., Kelly, K. L., y Ruderman, N. B. en Joslin's Diabetes (C. R. Khan y G. C. Wier, eds.), Lea & Febiger, Filadelfia, Pa., páginas 97-115, 1994).

[003] La concentración de glucosa en la cual GK muestra actividad máxima media es aproximadamente 8 mM. Las otras tres hexoquinasas están saturadas con glucosa a concentraciones mucho más inferiores (<1 mM). Por lo tanto, el flujo de glucosa a través de la vía de GK se eleva a medida que la concentración de glucosa en sangre aumenta desde niveles de ayuno (5 mM) hasta niveles posprandiales siguiendo una alimentación que contiene carbohidratos (aproximadamente 10-15 mM) (Printz, R. G., Magnuson, M. A., y Granner, D. K. en Ann. Rev. Nutrition Vol. 13 (R. E. Olson, D. M. Bier, y D. B. McCormick, eds.), Annual Review, Inc., Palo Alto, Calif., páginas 463-496, 1993). Estos hallazgos sugieren que las funciones de GK como sensor de glucosa en células β y hepatocitos (Meglasson, M. D. y Matschinsky, F. M. Amer. J Physiol. 246, E1-E13, 1984).

[004] En forma reciente, estudios en animales transgénicos confirmaron que la GK en

realidad cumple una función crítica en la homeostasis de la glucosa corporal total. Los animales que no expresan GK mueren dentro de los primeros días de nacimiento con diabetes severa, mientras que los animales que sobreexpresan GK tiene tolerante a la glucosa mejorada (Grupe, A., Hultgren, B., Ryan, A. *et al.*, Cell 83, 69-78, 1995; Ferrie, T., Riu, E., Bosch, F. et al., FASEB J., 10, 1213-1218, 1996). Un aumento en la exposición de la glucosa se acopla a través de la GK en células β a la secreción de insulina aumentada y en hepatocitos a la deposición de glucógeno aumentada y tal vez producción de glucosa disminuida.

[005] El hallazgo que la diabetes de inicio en la madurez en el joven tipo 2 (MODY-2) se origina por la pérdida de mutaciones de función en el gen GK sugiere que la GK también funciona como un sensor de la glucosa en los humanos (Liang, Y., Kesavan, P., Wang, L. *et al.*, Biochem. J. 309, 167-173, 1995). Otra evidencia que sostiene una función importante para la GK en la regulación del metabolismo de la glucosa en humanos se aportó mediante la identificación de pacientes que expresan una forma mutante de GK con actividad enzimática aumentada. Estos pacientes exhiben una hipoglucemia de ayuno asociada con un nivel inapropiadamente elevado de insulina en plasma (Glaser, B., Kesavan, P., Heyman, M. *et al.*, New England J. Med. 338, 226-230, 1998). En consecuencia, se espera que los compuestos que activan la GK y, de este modo, aumentan la sensibilidad del sistema sensor de GK sean útiles en el tratamiento de la característica hiperglucémica de toda la diabetes tipo II. Los activadores de glucoquinasa deben aumentar el flujo del metabolismo de la glucosa en las células β y en los hepatocitos, los cuales se acoplarán a la secreción de insulina aumentada.

[006] Existe una constante necesidad de hallar nuevos agentes terapéuticos para tratar las enfermedades humanas. Las hexoquinasas, específicamente pero no limitadas la glucoquinasa, son blancos especialmente atractivos para el descubrimiento de nuevos productos terapéuticos debido a su función importante en la diabetes, hiperglucemia y otras enfermedades.

Síntesis de la invención

[007] La presente invención se refiere a compuestos que activan la glucoquinasa. La presente invención además provee composiciones, artículos de fabricación y kits que comprenden estos compuestos. Además, la invención se refiere a métodos para producir los compuestos de la presente invención, como así también intermediarios útiles en estos métodos.

[008] En una realización, se provee una composición farmacéutica que contiene un activador de glucoquinasa de acuerdo con la presente invención en la forma de principio

activo. Las composiciones farmacéuticas de acuerdo con la invención pueden comprenden opcionalmente 0,001%-100% de uno o más activadores de esta invención. Estas composiciones farmacéuticas se pueden administrar o coadministrar mediante una amplia variedad de vías, que incluyen por ejemplo, oral, parenteral, interaperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposomal, mediante inhalación, vaginal, intraocular, mediante administración local (por ejemplo por catéter o stent), subcutánea, intraadiposa, intraarticular, o intratecal. Las composiciones además se pueden administrar o coadministrar en formas de dosificación de liberación lenta.

[009] La invención además está dirigida un kits y otros artículos de fabricación para tratar estados de enfermedad asociados con la glucoquinasa.

[010] En una realización, se provee un kit que comprende una composición que contiene al menos un activador de glucoquinasa de la presente invención en combinación con las instrucciones. Las instrucciones pueden indicar el estado de enfermedad para el cual la composición debe administrarse, la información de almacenamiento, la información sobre dosificación y/o instrucciones respecto a la forma de administrar la composición. El kit además puede contener materiales de empaque. El material de empaque puede contener un recipiente para almacenar la composición. El kit además puede contener opcionalmente componentes adicionales, tales como jeringas para la administración de la composición. El kit puede contener la composición en formas de dosificación simple o múltiple.

[011] En otra realización, se provee un artículo de fabricación que comprende una composición que contiene al menos un activador de glucoquinasa de la presente invención en combinación con materiales de empaque. El material de empaque puede contener un recipiente para almacenar la composición. El recipiente puede comprender opcionalmente una etiqueta que indica el estado de la enfermedad para la cual la composición debe administrarse, la información de almacenamiento, la información sobre dosificación y/o instrucciones respecto a la forma de administrar la composición. El kit además puede contener opcionalmente componentes adicionales, tales como jeringas para la administración de la composición. El kit puede contener la composición en formas de dosificación simple o múltiple.

[012] Además se proveen métodos para preparar compuestos, composiciones y kits de acuerdo con la presente invención. Por ejemplo, se proveen varios esquemas de síntesis en la presente para sintetizar los compuestos de acuerdo con la presente invención.

[013] Además se proveen métodos para utilizar los compuestos, las composiciones,

los kits y artículos de fabricación de acuerdo con la presente invención.

[014] En una realización, los compuestos, las composiciones, los kits y artículos de fabricación se utilizan para modular la glucoquinasa. En particular, los compuestos, las composiciones, los kits y artículos de fabricación se pueden utilizar para activar la glucoquinasa.

[015] En otra realización, los compuestos, las composiciones, los kits y artículos de fabricación se utilizan para tratar un estado de enfermedad por la cual el aumento de la actividad de la glucoquinasa alivia la patología y/o la sintomatología del estado de enfermedad.

[016] En otra realización, se administra un compuesto a un sujeto donde la actividad de glucoquinasa dentro del sujeto se altera y, en una realización, se aumenta.

[017] En otra realización, una prodroga de un compuesto se administra a un sujeto que se convierte al compuesto *in vivo* donde se activa la glucoquinasa.

[018] En otra realización, se provee un método para activar la glucoquinasa que comprende poner en contacto la glucoquinasa con un compuesto de acuerdo con la presente invención.

[019] En otra realización, se provee un método para activar la glucoquinasa que comprende hacer que un compuesto de acuerdo con la presente invención esté presente en un sujeto para activar la glucoquinasa *in vivo*.

[020] En otra realización, se provee un método para activar la glucoquinasa que comprende administrar un primer compuesto a un sujeto que se convierte *in vivo* a un segundo compuesto donde el segundo compuestos activa la glucoquinasa *in vivo*. Se observa que los compuestos de la presente invención pueden ser los primeros o segundos compuestos.

[021] En otra realización, se provee un método terapéutico que comprende administrar un compuesto de acuerdo con la presente invención.

[022] En otra realización, se provee un método para tratar una afección en un paciente que se sabe está mediado por la glucoquinasa, o el cual se sabe es tratado por los activadores de glucoquinasa, que comprende administrar al paciente una cantidad eficaz para uso terapéutico de un compuesto de acuerdo con la presente invención.

[023] En otra realización, se provee un método para tratar un estado de enfermedad para la cual el aumento de la actividad de glucoquinasa alivia la patología y/o sintomatología del estado de enfermedad, comprendiendo el método: hacer que un compuesto de acuerdo con la presente invención esté presente en un sujeto en una cantidad eficaz para uso terapéutico para el estado de enfermedad.

[024] En otra realización, un método se provee para tratar un estado de enfermedad

para la cual el aumento de la actividad de glucoquinasa alivia la patología y/o sintomatología del estado de enfermedad, comprendiendo el método: administrar un primer compuesto a un sujeto que se convierte *in vivo* a un segundo compuesto de modo que el segundo compuesto está presente en el sujeto en una cantidad eficaz para uso terapéutico para el estado de enfermedad. Se observa que los compuestos de la presente invención pueden ser los primeros o segundos compuestos.

[025] En otra realización, un método se provee para tratar un estado de enfermedad para la cual el aumento de la actividad de glucoquinasa alivia la patología y/o sintomatología del estado de enfermedad, comprendiendo el método: administrar un compuesto de acuerdo con la presente invención a un sujeto de modo que el compuesto está presente en el sujeto en una cantidad eficaz para uso terapéutico para el estado de enfermedad.

[026] En otra realización, se provee un método para utilizar un compuesto de acuerdo con la presente invención a fin de producir un medicamento para uso en el tratamiento de un estado de enfermedad que se sabe es mediado por la glucoquinasa, o que se sabe es tratado por los activadores de glucoquinasa.

[027] Se observa con respecto a todas las realizaciones anteriores que la presente invención intenta abarcar todas las formas ionizadas aceptables para uso farmacéutico (*por ej.*, sales) y solvatos (*por ej.*, hidratos) de los compuestos, sin considerar si estas formas ionizadas y solvatos se especifican dado que es bien conocido en la técnica la administración de agentes farmacéuticos en un forma ionizada o solvatada. Además se observa que a menos que se especifique una estereoquímica particular, el recitado de un compuesto intenta abarcar todos los Estereoisómeros posibles (*por ej.*, enantiómeros o diastereómeros que dependen del número de centros quirales), independientemente si el compuesto está presente en forma de un isómero individual o una mezcla de isómeros. Además, a menos que se especifique lo contrario, el recitado de un compuesto intenta abarcar todas las formas de resonancia posibles y tautómeros. Con respecto a las reivindicaciones, la frase "compuesto que comprende la fórmula" intenta abarcar el compuesto y todas las formas ionizadas y solvatos aceptables para uso farmacéutico, todos los estereoisómeros posibles, y todas las formas de resonancia posibles y tautómeros a menos que se especifique específicamente en la reivindicación particular.

[028] Además se observa que se pueden administrar prodrogas que se alteran *in vivo* y convierten un compuesto de acuerdo con la presente invención. Los diversos métodos para utilizar los compuestos de la presente invención intentan, sin tomar en cuenta si se especifica la administración de la prodroga, abarcar la administración de una prodroga que se convierte *in vivo* a un compuesto de acuerdo con la presente invención. Además

se observa que ciertos compuestos de la presente invención se pueden alterar *in vivo* antes de activar la glucoquinasa y de este modo pueden en sí mismos se prodrogas para otro compuesto. Estas prodrogas de otro compuesto pueden o no tener independientemente actividad de glucoquinasa.

Breve descripción de las figuras

[029] La Figura 1 ilustra la SEC. ID No. 1 que se refiere a esta solicitud.

Definiciones

[030] A menos que se especifique lo contrario, los siguientes términos utilizados en la memoria descriptiva y las reivindicaciones tendrán los siguientes significados a los fines de la presente solicitud.

[031] Se observa que, tal como se utiliza en la memoria descriptiva y las reivindicaciones adjuntas, las formas en singular "un", "una" y "la", "el" incluyen los referentes plurales a menos que el contexto claramente especifique lo contrario. Además, las definiciones de los términos químicos estándar se pueden hallar en los trabajos de referencia, que incluyen Carey & Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. un (2000) y B (2001), Plenum Press, New York. Además, a menos que se especifique lo contrario, se emplean los métodos convencionales de espectroscopía de masa, RMN, HPLC, química de proteínas, bioquímica, técnicas de ADN recombinante y farmacología, dentro de la capacidad de la técnica.

[032] "Alicíclico" significa un resto que comprende una estructura anular no aromática. Los restos alicíclicos pueden ser saturados o parcialmente insaturados con uno, dos o más enlaces dobles o triples. Restos alicíclicos además pueden comprender opcionalmente heteroátomos tales como nitrógeno, oxígeno y azufre. Los átomos de nitrógeno pueden estar opcionalmente cuaternizados u oxidados y los átomos de azufre pueden estar opcionalmente oxidados. Ejemplos de restos alicíclicos incluyen, pero sin limitación restos con anillos (C_{3-8}) tales como ciclopropilo, ciclohexano, ciclopentano, ciclopenteno, ciclopentadieno, ciclohexano, ciclohexeno, ciclohexadieno, cicloheptano, cicloheptено, cicloheptadieno, ciclooctano, cicloocteno, y ciclooctadieno.

[033] "Alifático" significa un resto caracterizado por una disposición de cadena recta o ramificada de átomos de carbono constituyentes y pueden ser saturados o parcialmente insaturados con uno, dos o más enlaces dobles o triples.

[034] "Alquenilo" significa una cadena de carbonos recta o ramificada que contiene al menos un enlace doble carbono-carbono (-CR=CR'- o –CR=CR'R", donde R, R' y R" son cada uno de ellos independientemente hidrógeno u otros sustituyentes). Ejemplos de

alquenilo incluyen vinilo, alilo, isopropenilo, pentenilo, hexenilo, heptenilo, 1-propenilo, 2-butenilo, 2-metil-2-butenilo, y similares. En realizaciones particulares, "alquenilo," ya sea solo o representado junto con otro radical, puede ser un alquenilo (C_{2-20}), un alquenilo (C_{2-15}), un alquenilo (C_{2-10}), un alquenilo (C_{2-5}) o un alquenilo (C_{2-3}). En forma alternativa, "alquenilo," ya sea solo o representado junto con otro radical, puede ser un alquenilo (C_2), un alquenilo (C_3) o un alquenilo (C_4).

[035] "Alquenileno" significa una cadena de carbonos divalentes, recta o ramificada que tiene uno o más enlaces dobles carbono-carbono (-CR=CR'-, donde R y R' son cada uno de ellos independientemente hidrógeno u otros sustituyentes). Ejemplos de alquenileno incluyen eteno-1,2-diilo, propeno-1,3-diilo, metileno-1,1-diilo, y similares. En realizaciones particulares, "alquenileno," ya sea solo o representado junto con otro radical, puede ser un alquenileno (C_{2-20}), un alquenileno (C_{2-15}), un alquenileno (C_{2-10}), un alquenileno (C_{2-5}) o un alquenileno (C_{2-3}). En forma alternativa, "alquenileno," ya sea solo o representado junto con otro radical, puede ser un alquenileno (C_2), un alquenileno (C_3) o un alquenileno (C_4).

[036] "Alcoxi" significa un resto oxígeno que tiene otro sustituyente alquilo. Los grupos alcoxi de la presente invención pueden estar opcionalmente sustituidos.

[037] "Alquilo" representado por sí mismo significa un radical alifático saturado, recto o ramificado que tiene una cadena de átomos de carbono, opcionalmente con uno o más de los átomos de carbono que están reemplazados con oxígeno (ver "oxaalquilo"), un grupo carbonilo (ver "oxoalquilo"), azufre (ver "tioalquilo"), y/o nitrógeno (ver "azaalquilo"). (C_X) alquilo y (C_{X-Y}) alquilo se utilizan típicamente donde X y Y indican el número de átomos de carbono en la cadena. Por ejemplo, alquilo (C_{1-6}) incluye alquilos que tienen una cadena de entre 1 y 6 carbonos (*por ej.*, 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 similares). Alquilo representado junto con otro radical (*por ej.*, como en arilalquilo, heteroarilalquilo y similares) significa un radical divalente alifático saturado o insaturado, recto o ramificado que tiene el número de átomos indicado o cuando no se indiquen átomos significa un enlace (*por ej.*, arilo (C_{6-10}) alquilo (C_{1-3}) incluye, bencilo, fenetilo, 1-feniletilo, 3-fenilpropilo, 2-tienilmetilo, 2-piridinilmetilo y similares). En realizaciones particulares, "alquilo," ya sea solo o representado junto con otro radical, puede ser un alquilo (C_{1-20}), un alquilo (C_{1-15}), un alquilo (C_{1-10}), un alquilo (C_{1-5}) o un alquilo (C_{1-3}). En forma alternativa, "alquilo," ya sea solo o representado junto con otro radical, puede ser un alquilo (C_1), un alquilo (C_2) o un alquilo (C_3).

[038] "Alquileno", a menos que se indique lo contrario, significa un radical divalente

alifático, saturado o insaturado, recto o ramificado. (C_X) alquileno y (C_{X-Y}) alquileno se utilizan típicamente donde X y Y indican el número de átomos de carbono en la cadena. Por ejemplo, alquileno (C_{1-6}) 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 similares. En realizaciones particulares, "alquileno," ya sea solo o representado junto con otro radical, puede ser un alquileno (C_{1-20}), un alquileno (C_{1-15}), un alquileno (C_{1-10}), un alquileno (C_{1-5}) o un alquileno (C_{1-3}). En forma alternativa, "alquileno," ya sea solo o representado junto con otro radical, puede ser un alquileno (C_1), un alquileno (C_2) o un alquileno (C_3).

[039] "Alquilideno" significa un radical alifático saturado o insaturado, recto o ramificado conectado a la molécula principal mediante un enlace doble. (C_X)alquilideno y (C_{X-Y})alquilideno se utilizan típicamente donde X y Y indican el número de átomos de carbono en la cadena. Por ejemplo, alquilideno (C_{1-6}) incluye metileno (=CH_2), etilideno (=$CHCH_3$), isopropilideno (=$C(CH_3)_2$), propilideno (=$CHCH_2CH_3$), alilideno (=CH-CH=CH_2), y similares. En realizaciones particulares, "alquilideno," ya sea solo o representado junto con otro radical, puede ser un alquilideno (C_{1-20}), un alquilideno (C_{1-15}), un alquilideno (C_{1-10}), un alquilideno (C_{1-5}) o un alquilideno (C_{1-3}). En forma alternativa, "alquilideno," ya sea solo o representado junto con otro radical, puede ser un alquilideno (C_1), un alquilideno (C_2) o un alquilideno (C_3).

[040] "Alquinilo" significa una cadena de carbonos recta o ramificada que contiene al menos un enlace triple carbono-carbono (-C≡C- o –C≡CR, donde R es hidrógeno u otro sustituyente). Ejemplos de alquinilo incluyen etinilo, propargilo, 3-metil-1-pentinilo, 2-heptinilo y similares. En realizaciones particulares, "alquinilo," ya sea solo o representado junto con otro radical, puede ser un alquinilo (C_{2-20}), un alquinilo (C_{2-15}), un alquinilo (C_{2-10}), un alquinilo (C_{2-5}) o un alquinilo (C_{2-3}). En forma alternativa, "alquinilo," ya sea solo o representado junto con otro radical, puede ser un alquinilo (C_2), un alquinilo (C_3) o un alquinilo (C_4).

[041] "Alquinileno" significa una cadena de carbonos divalentes, recta o ramificada que tiene uno o más enlaces triples carbono-carbono (-CR≡CR'-, donde R y R' son cada uno de ellos independientemente hidrógeno u otros sustituyentes). Ejemplos de alquinileno incluyen etini-1,2-diilo, propini-1,3-diilo, y similares. En realizaciones particulares, "alquinileno," ya sea solo o representado junto con otro radical, puede ser un alquinileno (C_{2-20}), un alquinileno (C_{2-15}), un alquinileno (C_{2-10}), un alquinileno (C_{2-5}) o un alquinileno (C_{2-3}). En forma alternativa, "alquenileno," ya sea solo o representado junto con otro radical, puede ser un alquinileno (C_2), un alquinileno (C_3) o un alquinileno (C_4).

[042] "Amido" significa el radical -C(=O)-NR-, -C(=O)-NRR', -NR-C(=O)- y/o -NR-C(=O)R', donde cada R y R' son independientemente hidrógeno u otro sustituyente.

[043] "Amino" significa un resto nitrógeno que tiene otros dos sustituyentes donde, por ejemplo, un átomo de hidrógeno o carbono se une al nitrógeno. Por ejemplo, grupos amino representativos incluyen $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH(alquilo (C1-10)), -N(alquilo (C1-10))$_2$, -NH(arilo), -NH(heteroarilo), -N(arilo)$_2$, -N(heteroarilo)$_2$, y similares. Opcionalmente, los dos sustituyentes junto con el nitrógeno además pueden formar un anillo. A menos que se indique lo contrario, los compuestos de la invención que contienen restos amino pueden incluir derivados protegidos de los mismos. Grupos protectores adecuados para restos amino incluyen acetilo, *ter*-butoxicarbonilo, benciloxicarbonilo, y similares.

[044] "Animal" incluye humanos, mamíferos no humanos (*por ej.*, perros, gatos, conejos, Ganado, caballos, ovejas, cabras, credos, ciervos, y similares) y no-mamíferos (*por ej.*, pájaros, y similares).

[045] "Aromático" significa un resto donde los átomos constituyentes conforman un sistema anular insaturado, todos los átomos en el sistema anular están hibridados sp^2 y el número total de electrones pi es igual a 4n+2. Un anillo aromático puede ser tal que los átomos del anillo son sólo átomos de carbono o puede incluir átomos de carbono y no-carbono (ver "heteroarilo").

[046] "Arilo" significa un conjunto anular monocíclico o policíclico donde cada anillo es aromático o cuando se fusiona con uno o más anillos forma un conjunto de anillo aromático. Si uno o más átomos del anillo no es carbono (*por ej.*, N, S), el arilo es un heteroarilo. (C_X)arilo y (C_{X-Y})arilo se utilizan típicamente donde X y Y indican el número de átomos de carbono en el anillo. En realizaciones particulares, "arilo," ya sea solo o representado junto con otro radical, puede ser un arilo (C_{3-14}), un arilo (C_{3-10}), un arilo (C_{3-7}), un arilo (C_{8-10}) o un arilo (C_{5-7}). En forma alternativa, "arilo," ya sea solo o representado junto con otro radical, puede ser un arilo (C_5), un arilo (C_6), un arilo (C_7), un arilo (C_8)., un arilo (C_9) o un arilo (C_{10}).

[047] "Azaalquilo" significa un alquilo, como se definió anteriormente, salvo donde uno o más de los átomos de carbono que forman la cadena alquilo están reemplazados con átomos de nitrógeno sustituido o no sustituido (-NR- o -NRR', donde R y R' son cada uno de ellos independientemente hidrógeno u otros sustituyentes). Por ejemplo, un azaalquilo (C_{1-10}) se refiere a una cadena que comprende entre 1 y 10 carbonos y uno o más átomos de nitrógeno.

[048] "Bicicloalquilo" significa un conjunto anular bicíclico espiro o puenteado, fusionado, saturado o parcialmente insaturado. En realizaciones particulares,

"bicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un bicicloalquilo (C_{4-15}), un bicicloalquilo (C_{4-10}), un bicicloalquilo (C_{6-10}) o un bicicloalquilo (C_{8-10}). En forma alternativa, "bicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un bicicloalquilo (C_8), un bicicloalquilo (C_9) o un bicicloalquilo (C_{10}).

[049] "Bicicloarilo" significa un conjunto anular bicíclico fusionado, espiro o puenteado donde al menos uno de los anillos que comprende el conjunto es aromático. (C_X)bicicloarilo y (C_{X-Y})bicicloarilo se utilizan típicamente donde X y Y indican el número de átomos de carbono en el conjunto anular bicíclico y directamente unido al anillo. En realizaciones particulares, "bicicloarilo," ya sea solo o representado junto con otro radical, puede ser un bicicloarilo (C_{4-15}), un bicicloarilo (C_{4-10}), un bicicloarilo (C_{6-10}) o un bicicloarilo (C_{8-10}). En forma alternativa, "bicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un bicicloarilo (C_8), un bicicloarilo (C_9) o un bicicloarilo (C_{10}).

[050] "Anillo con puente" y "anillo puenteado" como se utiliza en la presente se refieren a un anillo que está unido a otro anillo para formar un compuesto que tiene una estructura bicíclica o policíclica donde dos átomos del anillo que son comunes a ambos anillos no están directamente enlazados entre sí. Ejemplos no exclusivos de compuestos comunes que tienen un anillo con puente incluyen borneol, norbornano, 7-oxabiciclo[2,2,1]heptano, y similares. Uno o ambos anillos del sistema bicíclico también pueden comprender heteroátomos.

[051] "Carbamoílo" significa el radical -OC(O)NRR', donde R y R' son cada uno de ellos independientemente hidrógeno u otros sustituyentes.

[052] "Carbociclo" significa un anillo que consiste de átomos de carbono.

[053] "Carbonilo" significa el radical –C(=O)- y/o –C(=O)R, donde R es hidrógeno u otro sustituyente. Se observa que el radical carbonilo puede estar además sustituido con una variedad de sustituyentes para formar diferentes grupos carbonilo que incluyen ácidos, haluros de ácido, aldehídos, amidas, ésteres y cetonas.

[054] "Carboxi" significa el radical –C(=O)-O- y/o –C(=O)-OR, donde R es hidrógeno u otro sustituyente. Se observa que los compuestos de la invención que contienen restos carboxi pueden incluir derivados protegidos de los mismos, *es decir*, donde el oxígeno es sustituido con un grupo protector. Grupos protectores adecuados para los restos carboxi incluyen bencilo, *ter*-butilo, y similares.

[055] "Ciano" significa el radical -CN.

[056] "Cicloalquilo" significa un conjunto anular no-aromático, saturado o parcialmente insaturado, monocíclico, bicíclico o policíclico. (C_X)cicloalquilo y (C_{X-Y})cicloalquilo se utilizan típicamente donde X y Y indican el número de átomos de carbono en el conjunto anular. Por ejemplo, cicloalquilo (C_{3-10}) 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 similares. En realizaciones particulares, "cicloalquilo," ya sea solo o representado junto con otro radical, puede ser un cicloalquilo (C_{3-14}), un cicloalquilo (C_{3-10}), un cicloalquilo (C_{3-7}), un cicloalquilo (C_{8-10}) o un cicloalquilo (C_{5-7}). En forma alternativa, "cicloalquilo," ya sea solo o representado junto con otro radical, puede ser un cicloalquilo (C_5), un cicloalquilo (C_6), un cicloalquilo (C_7), un cicloalquilo (C_8), un cicloalquilo (C_9) o un cicloalquilo (C_{10}).

[057] "Cicloalquileno" significa un conjunto anular divalente, saturado o parcialmente insaturado, monocíclico, bicíclico o policíclico. (C_X)cicloalquileno y (C_{X-Y})cicloalquileno se utilizan típicamente donde X y Y indican el número de átomos de carbono en el conjunto anular. En realizaciones particulares, "cicloalquileno," ya sea solo o representado junto con otro radical, puede ser un cicloalquileno (C_{3-14}), un cicloalquileno (C_{3-10}), un cicloalquileno (C_{3-7}), un cicloalquileno (C_{8-10}) o un cicloalquileno (C_{5-7}). En forma alternativa, "cicloalquileno," ya sea solo o representado junto con otro radical, puede ser un cicloalquileno (C_5), un cicloalquileno (C_6), un cicloalquileno (C_7), un (C_8)cicloalquileno., un cicloalquileno (C_9) o un cicloalquileno (C_{10}).

[058] "Enfermedad" incluye específicamente cualquier condición no saludable de un animal o parte del mismo e incluye una condición no saludable que puede ser originada por, o debido a, terapia médica o veterinaria aplicada a ese animal, *es decir*, los "efectos colaterales" de esta terapia.

[059] "Anillo fusionado" como se utiliza en la presente se refiere a un anillo que está unido a otro anillo para formar un compuesto que tiene una estructura bicíclica donde los átomos del anillo que son comunes a ambos anillos están directamente enlazados entre sí. Ejemplos no exclusivos de anillo fusionados comunes incluyen decalin, naftaleno, antraceno, fenantreno, indol, furano, benzofurano, quinolina, y similares. Los compuestos que tiene sistemas anulares fusionados pueden ser saturados, parcialmente saturados, carbocíclicos, heterocíclicos, aromáticos, heteroaromáticos, y similares.

[060] "Halo" significa fluoro, cloro, bromo o yodo.

[061] "Heteroalquilo" significa alquilo, según se define en esta solicitud, siempre que uno o más de los átomos dentro de la cadena alquilo es un heteroátomo. En realizaciones particulares, "heteroalquilo," ya sea solo o representado junto con otro radical, puede ser un heteroalquilo (C_{1-20}), un heteroalquilo (C_{1-15}), un heteroalquilo (C_{1-10}), un heteroalquilo (C_{1-5}), un heteroalquilo (C1-3) o un heteroalquilo (C_{1-2}). En forma alternativa, "heteroalquilo," ya sea solo o representado junto con otro radical, puede ser un heteroalquilo (C_1), un heteroalquilo (C_2) o un heteroalquilo (C_3).

[062] "Heteroarilo" significa un grupo aromático monocíclico, bicíclico o policíclico donde al menos un átomo del anillo es un heteroátomo y los átomos restantes del anillo son carbono. Grupos heteroarilo monocíclico incluyen, pero sin limitación, grupos aromáticos cíclicos que tienen cinco o seis átomos del anillo, donde al menos un átomo del anillo es un heteroátomo y los átomos restantes del anillo son 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, pero sin limitación, aquéllos que derivan 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" además incluye, pero sin limitación, anillos bicíclicos o tricíclicos, donde el anillo heteroarilo está fusionado a uno o dos anillos seleccionados independientemente del grupo integrado por un anillo arilo, un anillo cicloalquilo, un anillo cicloalquenilo, y otro anillo heteroarilo monocíclico o heterocicloalquilo. Estos heteroarilos bicíclico o tricíclico incluyen, pero sin limitación, aquéllos que derivan de benzo[b]furano, benzo[b]tiofeno, bencimidazol, imidazo[4,5-c]piridina, quinazolina, tieno[2,3-c]piridina, tieno[3,2-b]piridina, tieno[2,3-b]piridina, indolizina, imidazo[1,2a]piridina, quinolina, isoquinolina, ftalazina, quinoxalina, naftiridina, quinolizina, indol, isoindol, indazol, indolina, benzoxazol, benzopirazol, benzotiazol, imidazo[1,5-a]piridina, pirazolo[1,5-a]piridina, imidazo[1,2-a]pirimidina, imidazo[1,2-c]pirimidina, imidazo[1,5-a]pirimidina, imidazo[1,5-c]pirimidina, pirrolo[2,3-b]piridina, pirrolo[2,3-c]piridina, pirrolo[3,2-c]piridina, pirrolo[3,2-b]piridina, pirrolo[2,3-d]pirimidina, pirrolo[3,2-d]pirimidina, pirrolo[2,3-b]pirazina, pirazolo[1,5-a]piridina, pirrolo[1,2-b]piridazina, pirrolo[1,2-c]pirimidina, pirrolo[1,2-a]pirimidina, pirrolo[1,2-a]pirazina, triazo[1,5-a]piridina, pteridina, purina, carbazol, acridina, fenazina, fenotiazeno, fenoxazina, 1,2-dihidropirrolo[3,2,1-*hi*]indol, indolizina, pirido[1,2-a]indol y 2(1H)-piridinona. Los anillos heteroarilo bicíclicos o tricíclicos pueden unirse a la molécula principal ya sea a través del grupo heteroarilo mismo o el grupo arilo, cicloalquilo, cicloalquenilo o heterocicloalquilo al cual está fusionado. Los grupos heteroarilo de esta invención pueden ser sustituidos o no sustituidos. En realizaciones particulares, "heteroarilo," ya sea solo o representado junto con otro radical, puede ser un heteroarilo (C_{1-13}), un heteroarilo (C_{2-13}), un heteroarilo (C_{2-6}), un heteroarilo (C_{3-9}) o un heteroarilo (C_{5-9}). En forma alternativa, "heteroarilo," ya sea solo o representado junto con otro radical, puede ser un heteroarilo (C_3), un heteroarilo (C_4), un heteroarilo (C_5), un heteroarilo (C_6), un heteroarilo (C_7), un heteroarilo (C_8) o un heteroarilo (C_9).

[063] "Heteroátomo" se refiere a un átomo que no es un átomo de carbono. Ejemplos particulares de heteroátomos incluyen, pero sin limitación, nitrógeno, oxígeno, y azufre.

[064] "Resto heteroátomo" incluye un resto donde el átomo por el cual se une el resto no es un carbono. Ejemplos de restos heteroátomos incluyen -NR-, $-N^{+}(O^{-})=$, -O-, -S- o $-S(O)_2-$, donde R es hidrógeno u otro sustituyente.

[065] "Heterobicicloalquilo" significa bicicloalquilo, según se define en esta solicitud, siempre que uno o más de los átomos dentro del anillo sea un heteroátomo. Por ejemplo heterobicicloalquilo (C_{9-12}) tal como se utiliza en la presente solicitud incluye, pero sin limitación, 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 similares. En realizaciones particulares, "heterobicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un heterobicicloalquilo (C_{1-14}), un heterobicicloalquilo (C_{4-14}), un heterobicicloalquilo (C_{4-9}) o un heterobicicloalquilo (C_{5-9}). En forma alternativa, "heterobicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un heterobicicloalquilo (C_5), heterobicicloalquilo (C_6), heterobicicloalquilo (C_7), heterobicicloalquilo (C_8) o un heterobicicloalquilo (C_9).

[066] "Heterobicicloarilo" significa bicicloarilo, según se define en esta solicitud, siempre que uno o más de los átomos dentro del anillo es un heteroátomo. Por ejemplo, heterobicicloarilo (C_{4-12})tal como se utiliza en la presente solicitud incluye, pero sin limitación, 2-amino-4-oxo-3,4-dihidropteridin-6-ilo, tetrahidroisoquinolinilo, y similares. En realizaciones particulares, "heterobicicloarilo," ya sea solo o representado junto con otro radical, puede ser un heterobicicloarilo (C_{1-14}), un heterobicicloarilo (C_{4-14}), un heterobicicloarilo (C_{4-9}) un heterobicicloarilo (C_{5-9}). En forma alternativa, "heterobicicloarilo," ya sea solo o representado junto con otro radical, puede ser un heterobicicloarilo (C_5), heterobicicloarilo (C_6), heterobicicloarilo (C_7), heterobicicloarilo (C_8) o un heterobicicloarilo (C_9).

[067] "Heterocicloalquilo" significa cicloalquilo, según se define en esta solicitud, siempre que uno o más de los átomos que forman el anillo sea un heteroátomo seleccionado independientemente de N, O, o S. Ejemplos no exclusivos de heterocicloalquilo incluyen piperidilo, 4-morfolilo, 4-piperazinilo, pirrolidinilo, perhidropirrolizinilo, 1,4-diazaperhidroepinilo, 1,3-dioxanilo, 1,4-dioxanilo y similares. En realizaciones particulares, "heterocicloalquilo," ya sea solo o representado junto con otro radical, puede ser un heterocicloalquilo (C_{1-13}), un heterocicloalquilo (C_{1-9}), un heterocicloalquilo (C_{1-6}), un heterocicloalquilo (C_{5-9}) o un heterocicloalquilo (C_{2-6}). En forma alternativa, "heterocicloalquilo," ya sea solo o representado junto con otro radical, puede ser un heterocicloalquilo (C_2), un heterocicloalquilo (C_3), un heterocicloalquilo (C_4), un heterocicloalquilo (C_5), un heterocicloalquilo (C_6), heterocicloalquilo (C_7), heterocicloalquilo (C_8) o un heterocicloalquilo (C_9).

[068] "Heterocicloalquileno" significa cicloalquileno, según se define en esta solicitud,

siempre que uno o más de los átomos de carbono miembros del anillo sea reemplazado por un heteroátomo. En realizaciones particulares, "heterocicloalquileno," ya sea solo o representado junto con otro radical, puede ser un heterocicloalquileno (C_{1-13}), un heterocicloalquileno (C_{1-9}), un heterocicloalquileno (C_{1-6}), un heterocicloalquileno (C_{5-9}) o un heterocicloalquileno (C_{2-6}). En forma alternativa, "heterocicloalquileno," ya sea solo o representado junto con otro radical, puede ser un heterocicloalquileno (C_2), un heterocicloalquileno (C_3), un heterocicloalquileno (C_4), un heterocicloalquileno (C_5), un heterocicloalquileno (C_6), heterocicloalquileno (C_7), heterocicloalquileno (C_8) o un heterocicloalquileno (C_9).

[069] "Hidroxi" significa el radical -OH.

[070] "IC_{50}" significa la concentración molar de un inhibidor que produce 50% de inhibición de la enzima blanco.

[071] "Imino" significa el radical –CR(=NR') y/o –C(=NR')-, donde R y R' son cada uno de ellos independientemente hidrógeno u otro sustituyente.

[072] "Isómeros" significa compuestos que tienen fórmulas moleculares idénticas pero que difieren en la naturaleza o secuencia de enlace de sus átomos o en la disposición de sus átomos en el espacio. Los isómeros que difieren en la disposición de sus átomos en el espacio se denominan "estereoisómeros." Los estereoisómeros que son imágenes espejo uno de otro se denominan "diastereómeros" y estereoisómeros que son imágenes espejo que no se superponen denominadas "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 las dos formas enantioméricas se denomina una "mezcla racémica". Un compuesto que tiene más de un centro quiral tiene pares enantioméricos 2^{n-1}, donde *n* es el número de centros quirales. Los compuestos con más de un centro quiral pueden existir como otro diastereómero individual o como una mezcla de diastereómeros, denominada una "mezcla diastereomérica". Cuando un centro quiral está presente un estereoisómero puede estar caracterizado por la configuración absoluta de ese centro quiral. La configuración absoluta se refiere a la disposición en espacio de los sustituyentes unidos al centro quiral. Los enantiómeros están caracterizados por la configuración absoluta de sus centros quirales y se describen por las normas de secuenciamiento R y S de Cahn, Ingold y Prelog. Las convenciones para la nomenclatura estereoquímica, los métodos para la determinación de la estereoquímica y la separación de los estereoisómeros son bien conocidos en la técnica (*por ej.*, ver "Advanced Organic Chemistry", 4º edición, Marczo, Jerry, John Wiley & Sons, New York, 1992).

[073] "Grupo saliente" significa el grupo con el significado asociado convencionalmente con él en la química orgánica de síntesis, es decir, un átomo o grupo desplazable bajo condiciones de reacción (*por ej.*, alquilantes). Ejemplos de grupos salientes incluyen, pero sin limitación, halo (*por ej.*, F, Cl, Br y I), alquilo (*por ej.*, metilo y etilo) y sulfoniloxi (*por ej.*, mesiloxi, etansulfoniloxi, bencenosulfoniloxi y tosiloxi), tiometilo, tieniloxi, dihalofosfinoíloxi, tetrahalofosfoxi, benciloxi, isopropiloxi, aciloxi, y similares.

[074] "Resto que suministra la separación del átomo X" y "conector que provee la separación del átomo X" entre los otros dos restos significa que la cadena de átomos que enlaza directamente los otros dos restos es X átomos de longitud. Cuando X se da como un rango (*por ej.*, X_1-X_2), entonces la cadena de átomos es al menos X_1 y no más de X_2 átomos de longitud. Se entiende que la cadena de átomos puede formarse a partir de una combinación de átomos que incluye, por ejemplo, átomos de carbono, nitrógeno, azufre y oxígeno. Además, cada átomos puede unirse opcionalmente a uno o más sustituyentes, como lo permitan las valencias. Además, la cadena de átomos puede formar parte de un anillo. En consecuencia, en una realización, un resto que provee X la separación del átomo X entre dos restos (R y R') puede estar representado por R-$(L)_X$-R' donde cada L se selecciona independientemente del grupo integrado por CR''R''', NR'''', O, S, CO, CS, C=NR''''', SO, SO_2, y similares, donde cualquiera de dos o más de R'', R''', R'''' y R''''' pueden ser tomados juntos para formar un anillo sustituido o no sustituido.

[075] "Nitro" significa el radical -NO_2.

[076] "Oxalquilo" significa un alquilo, como se definió anteriormente, salvo donde uno o más de los átomos de carbono que forman la cadena alquilo están reemplazados con átomos de oxígeno (-O- o –OR, donde R es hidrógeno u otro sustituyente). Por ejemplo, un oxaalquilo (C1-10) se refiere a una cadena que comprende entre 1 y 10 carbonos y uno o más átomos de oxígeno.

[077] "Oxalquilo" significa un alquilo, como se definió anteriormente, salvo donde uno o más de los átomos de carbono que forman la cadena alquilo están reemplazados con grupos carbonilo (-C(=O)- o –C(=O)-R, donde R es hidrógeno u otro sustituyente). El grupo carbonilo puede ser un aldehído, cetona, éster, amida, ácido o haluro ácido. Por ejemplo, un oxoalquilo (C_{1-10}) se refiere a una cadena que comprende entre 1 y 10 átomos de carbono y uno o más grupos carbonilo.

[078] "Oxi" significa el radical -O- o –OR, donde R es hidrógeno u otro sustituyente. En consecuencia, se observa que el radical oxi puede estar además sustituido con una variedad de sustituyentes para formar diferentes grupos oxi que incluyen hidroxi, alcoxi, ariloxi, heteroariloxi o carboniloxi.

[079] "Aceptable para uso farmacéutico" significa aquél que es útil en la preparación

de una composición farmacéutica que en general es segura, no tóxica y no es indeseable biológicamente y de ningún otro modo e incluye aquél el cual es aceptable para uso veterinario como así también uso farmacéutico humano.

[080] "Sales aceptables para uso farmacéutico" significa sales de los compuestos de la presente invención las cuales son aceptables para uso farmacéutico, como se definió anteriormente, y que proveen la actividad farmacológica deseada. Estas sales incluyen sales de adición de ácido formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares; o con ácidos orgánicos tales como ácido acético, ácido propiónico, ácido hexanoico, ácido heptanoico, ácido ciclopentanopropiónico, 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 cinnámico, ácido mandélico, ácido metansulfónico, ácido etansulfónico, ácido 1,2-etandisulfónico, ácido 2-hidroxietansulfónico, ácido bencenosulfónico, ácido *p*-clorobencenosulfónico, ácido 2-naftalenosulfónico, ácido *p*-toluenosulfónico, ácido alcanforsulfónico, ácido 4-metilbiciclo[2,2,2]oct-2-eno-1-carboxílico, ácido glucoheptónico, ácido 4,4'-metilenobis(3-hidroxi-2-eno-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido butilacético terciario, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicíclico, ácido esteárico, ácido mucónico y similares.

[081] Las sales aceptables para uso farmacéutico también incluyen sales de adición de base las cuales se pueden formar cuando los protones ácidos 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, trometamina, *N*-metilglucamina y similares.

[082] "Anillo policíclico" incluye anillos bicíclicos y multi-cíclicos. Los anillos individuales que comprenden el anillo policíclico pueden ser fusionados, espiros o de puente.

[083] "Prodroga" significa un compuesto que puede convertirse metabólicamente *in vivo* en un inhibidor de acuerdo con la presente invención. La prodroga misma puede o no tener además actividad con respecto a una proteína blanco dada. Por ejemplo, un compuesto que comprende un grupo hidroxi se puede administrar en forma de un éster que se convierte por hidrólisis *in vivo* al compuesto hidroxi. Los ésteres adecuados que se pueden convertir *in vivo* en compuestos hidroxi incluyen acetatos, citratos, lactatos, fosfatos, tartratos, malonatos, oxalatos, salicilatos, propionatos, succinatos, fumaratos,

maleatos, metileno-bis-b-hidroxinaftoatos, gentisatos, isetionatos, di-*p*-toluoiltartratos, metansulfonatos, etansulfonatos, bencenosulfonatos, p-toluenosulfonatos, ciclohexilsulfamatos, quinatos, ésteres de aminoácidos, y similares. De manera similar, un compuesto que comprende un grupo amina se puede administrar en forma de una amida que se convierte por hidrólisis *in vivo* al compuesto amina.

[084] "Derivados protegidos" significa derivados de inhibidores en los cuales un sitio o sitios reactivos se bloquean con grupos protectores. Los derivados protegidos son útiles en la preparación de inhibidores o en sí mismos pueden ser activos como inhibidores. Una lista extensa de grupos protectores adecuados se puede encontrar en T.W. Greene, *Protecting Groups in Organic Synthesis*, 3º edición, John Wiley & Sons, Inc. 1999.

[085] "Anillo" y "conjunto anular" significa un sistema carbocíclico o heterocíclico e incluye sistemas aromáticos y non-aromáticos. El sistema puede ser monocíclico, bicíclico o policíclico. Además, para los sistemas bicíclicos y policíclicos, los anillos individuales que comprenden el anillo policíclico pueden ser anillos fusionados, espiros o de puentes.

[086] "Sujeto" y "paciente" incluyen humanos, mamíferos no humanos (*por ej.*, perros, gatos, conejos, ganado, caballos, ovejas, cabras, cerdos, ciervos, y similares) y no-mamíferos (*por ej.*, pájaros, y similares).

[087] "Sustituyente que puede convertirse a hidrógeno *in vivo*" significa cualquier grupo que puede convertirse a un átomo de hidrógeno por medios enzimológicos o químicos incluyendo, pero sin limitación, hidrólisis e hidrogenólisis. Ejemplos incluyen grupos hidrolizables, tales como grupos acilo, grupos que tienen un grupo oxicarbonilo, residuos de aminoácidos, residuos peptídicos, o-nitrofenilsulfenilo, trimetilsililo, tetrahidro-piranilo, difenilfosfinilo, y similares. Ejemplos de grupos acilo incluyen formilo, acetilo, trifluoroacetilo, y similares. Ejemplos de grupos que tienen un grupo oxicarbonilo incluyen etoxicarbonilo, t-butoxicarbonilo [$(CH_3)_3C$-OCO-], benciloxicarbonilo, p-metoxibenciloxicarbonilo, viniloxicarbonilo, β-(p-toluenosulfonil)etoxicarbonilo, y similares. Ejemplos de residuos aminoácidos adecuados incluyen residuos aminoácidos *per se y* residuos aminoácidos que están protegidos con un grupo protector. Los residuos aminoácidos adecuados incluyen, pero sin limitación, residuos de Gly (glicina), Ala (alanina; $CH_3CH(NH_2)CO$-), Arg (arginina), Asn (asparagina), Asp (ácido aspártico), Cys (cisteína), Glu (ácido glutámico), His (histidina), Ile (isoleucina), Leu (leucina; $(CH_3)_2CHCH_2CH(NH_2)CO$-), Lys (lisina), Met (metionina), Fe (fenilalanina), Pro (prolina), Ser (serina), Thr (treonina), Trp (triptófano), Tyr (tirosina), Val (valina), Nva (norvalina), Hse (homoserina), 4-Hyp (4-hidroxiprolina), 5-Hilo (5-hidroxilisina), Orn (ornitina) y β-Ala. Ejemplos de grupos protectores adecuados incluyen aquéllos típicamente empleados en

síntesis peptídico, que incluyen grupos acilo (tales como formilo y acetilo), grupos arilmetiloxicarbonilo (tales como grupos benciloxicarbonilo y p-nitrobenciloxicarbonilo), t-butoxicarbonilo [$(CH_3)_3C$-OCO-], y similares. Los residuos peptídicos adecuados incluyen residuos peptídicos que comprenden dos a cinco, y opcionalmente dos a tres, de los residuos aminoácidos mencionados anteriormente. Ejemplos de estos residuos peptídicos incluyen, pero sin limitación, residuos de péptidos tales como Ala-Ala [$CH_3CH(NH_2)$CO-NHCH(CH_3)CO-], Gli-Fe, Nva-Nva, Ala-Fe, Gli-Gli, Gli-Gli-Gli, Ala-Met, Met-Met, Leu-Met y Ala-Leu. Los residuos de estos aminoácidos o péptidos pueden estar presentes en configuraciones estereoquímicas de la forma D, la forma L o mezclas de las mismas. Además, el residuo aminoácido o péptido puede tener un átomo de carbono asimétrico. Ejemplos de residuos aminoácidos adecuados que tienen un átomo de carbono asimétrico incluyen residuos de Ala, Leu, Fe, Trp, Nva, Val, Met, Ser, Lys, Thr y Tyr. Los residuos peptídicos que tienen un átomo de carbono asimétrico incluyen residuos peptídicos que tienen uno o más residuos aminoácidos constituyentes que tiene un átomo de carbono asimétrico. Ejemplos de grupos protectores aminoácidos adecuados incluyen aquéllos típicamente empleados en síntesis peptídico, incluyendo grupos acilo (tales como formilo y acetilo), grupos arilmetiloxicarbonilo (tales como benciloxicarbonilo y p-nitrobenciloxicarbonilo), grupos t-butoxicarbonilo [$(CH_3)_3C$-OCO-], y similares. Otros ejemplos de sustituyentes "que pueden convertirse a hidrógeno *in vivo*" incluyen grupos hidrogenolizables que pueden eliminarse por reducción. Ejemplos de grupos hidrogenolizables que pueden eliminarse por reducción incluyen, pero sin limitación, arilsulfonilo grupos (tal como o-toluenosulfonilo); grupos metilo sustituidos con fenilo o benciloxi (tales como bencilo, tritilo y benciloximetilo); grupos arilmetoxicarbonilo (tales como benciloxicarbonilo y o-metoxi-benciloxicarbonilo); y grupos halogenoetoxicarbonilo (tales como β,β,β-tricloroetoxicarbonilo y β-yodoetoxicarbonilo).

[088] "Sustituido o no sustituido" significa que un resto dado puede consistir solo de constituyentes hidrógeno a través de valencias disponibles (no sustituido) o además puede comprender uno o más sustituyentes no-hidrógeno a través de valencias disponibles (sustituido) que no se especifican de otro modo por el nombre del resto dado. Por ejemplo, isopropilo es un ejemplo de un resto etileno que es sustituido por $-CH_3$. En general, un sustituyente no-hidrógeno puede ser cualquier sustituyente que puede estar unido a un átomo del resto dado que se especifica para ser sustituido. Ejemplos de sustituyentes incluyen, pero sin limitación, aldehído, alicíclico, alifático, alquilo (C_{1-10}), alquileno, alquilideno, amida, amino, aminoalquilo, aromático, arilo, bicicloalquilo, bicicloarilo, carbamoílo, carbociclilo, carboxilo, grupo carbonilo, cicloalquilo, cicloalquileno, éster, halo, heterobicicloalquilo, heterocicloalquileno, heteroarilo, heterobicicloarilo,

heterocicloalquilo, oxo, hidroxi, iminocetona, cetona, nitro, oxaalquilo, y restos oxoalquilo, cada uno de los cuales puede estar además sustituido o no sustituido. En una realización particular, ejemplos de sustituyentes incluyen, pero sin limitación, hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino (C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}), haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}), carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquilo (C_{3-12}) alquilo (C_{1-5}), heterocicloalquilo (C_{3-12}) alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroarilo (C_{1-10}) alquilo (C_{1-5}), bicicloarilo (C_{9-12}) alquilo (C_{1-5}), heterobicicloarilo (C8-12)–alquilo (C_{1-5}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{1-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}). Además, el sustituyente está opcionalmente sustituido por otro sustituyente. En una realización particular, ejemplos del otro sustituyente incluyen, pero sin limitación, hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino (C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}), carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquilo (C_{3-12}) alquilo (C_{1-5}), heterocicloalquilo (C_{3-12}) alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroarilo (C_{1-10}) alquilo (C_{1-5}), bicicloarilo (C_{9-12}) alquilo (C_{1-5}), heterobicicloarilo (C8-12)–alquilo (C_{1-5}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{1-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}).

[089] "Sulfinilo" significa el radical –SO- y/o –SO-R, donde R es hidrógeno u otro sustituyente. Se observa que el radical sulfinilo puede estar además sustituido con una variedad de sustituyentes para formar diferentes grupos sulfinilo que incluyen ácidos sulfínicos, sulfinamidas, ésteres de sulfinilo, y sulfóxidos.

[090] "Sulfonilo" significa el radical -SO_2- y/o –SO_2-R, donde R es hidrógeno u otro sustituyente. Se observa que el radical sulfonilo puede estar además sustituido con una variedad de sustituyentes para formar diferentes grupos sulfonilo que incluyen ácidos sulfónicos, sulfonamidas, ésteres de sulfonato, y sulfonas.

[091] "Cantidad eficaz para uso terapéutico" significa esa cantidad la cual, cuando se administra a un animal para tratar una enfermedad, es suficiente para efectuar el tratamiento de la enfermedad.

[092] "Tio" denota el reemplazo de un oxígeno por un azufre e incluye, pero sin limitación, grupos que contienen -SR, -S- y =S.

[093] "Tioalquilo" significa un alquilo, como se definió anteriormente, salvo donde uno

o más de los átomos de carbono que forman la cadena alquilo están reemplazados con átomos de azufre (-S- o –S-R, donde R es hidrógeno u otro sustituyente). Por ejemplo, un tioalquilo (C_{1-10}) se refiere a una cadena que comprende entre 1 y 10 carbonos y uno o más átomos de azufre.

[094] "Tiocarbonilo" significa el radical –C(=S)- y/o –C(=S)-R, donde R es hidrógeno u otro sustituyente. Se observa que el radical tiocarbonilo puede estar además sustituido con una variedad de sustituyentes para formar diferentes grupos tiocarbonilo que incluyen tioácidos, tioamidas, tioésteres, y tiocetonas.

[095] "Tratamiento" o "que trata" significa cualquier administración de un compuesto de la presente invención e incluye:

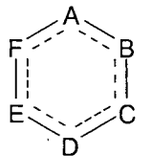
(1) prevenir que aparezca la enfermedad en un animal que puede estar predispuesto a la enfermedad pero no aún no la experimenta o muestra la patología o sintomatología de la enfermedad,

(2) inhibir la enfermedad en un animal que está experimentando o mostrando la patología o sintomatología de la enfermedad (*es decir*, detener el desarrollo posterior de la patología y/o sintomatología), o

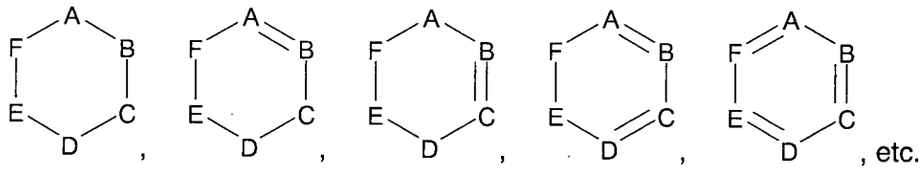
(3) aliviar la enfermedad en un animal que está experimentando o mostrando la patología o sintomatología de la enfermedad (*es decir*, revertir la patología y/o sintomatología).

[096] Se observa con respecto a todas las definiciones suministradas en la presente que las definiciones deben ser interpretadas como con un final abierto en el sentido que se pueden incluir otros sustituyentes más allá de los especificados. Por lo tanto, un alquilo C_1 indica que hay un átomo de carbono pero no indica cuáles son los sustituyentes sobre el átomo de carbono. Por lo tanto, un alquilo (C_1) comprende metilo (*es decir*, $-CH_3$) como así también -CRR'R" donde R, R', y R" pueden ser cada uno de ellos independientemente hidrógeno u otro sustituyente donde el átomo unido al carbono es un heteroátomo o ciano. Por lo tanto, CF_3, CH_2OH y CH_2CN, por ejemplo, son todos alquilos (C_1). De manera similar, los términos tales como alquilamino y similares comprenden dialquilamino y similares.

[097] Un compuesto que tiene una fórmula que está representada con un enlace punteado intenta incluir las fórmulas que tienen opcionalmente cero, uno o más enlaces dobles, como se ejemplifica y se muestra a continuación:



representa



, etc.

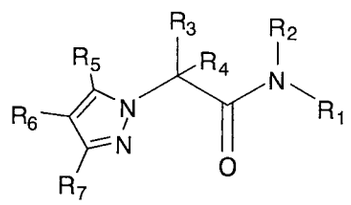
[098] Además, los átomos que componen los compuestos de la presente invención incluyen todas las formas isotópicas de estos átomos. Los isótopos, como se utiliza en la presente, incluyen aquellos átomos que tienen el mismo número atómico pero diferentes números de masa. A modo de ejemplo general y sin limitación, los isótopos de hidrógeno incluyen tritio y deuterio, y los isótopos de carbono incluyen ^{13}C y ^{14}C.

Descripción detallada de la invención

[099] La presente invención se refiere a compuestos que se pueden utilizar para modular una hexoquinasa y, en particular, a compuestos que activan la glucoquinasa (denominada en la presente "GK"). La presente invención además se refiere a composiciones farmacéuticas, kits y artículos de fabricación que comprenden estos compuestos. Además, la presente invención se refiere a métodos e intermediarios útiles para producir los compuestos. Además, la presente invención se refiere a métodos para utilizar dichos compuestos. Se observa que los compuestos de la presente invención también pueden poseer actividad para otros miembros de la familia de la hexoquinasa y de este modo se pueden utilizar para apuntar sobre estados de enfermedad asociados con estos otros miembros de la familia.

Activadores de glucoquinasa

[0100] En una realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



o un polimorfo, solvato, éster, tautómero, enantiómero, sal o prodroga de los

mismos aceptable para uso farmacéutico, donde

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5),

heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es $–L_1-R_{22}$;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1-R_{22}$;

o cualquiera dos R_5, R_6 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que

suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

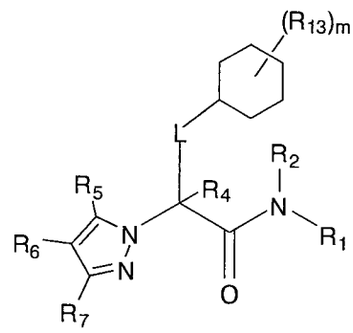
R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo

(C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00101] En una variante de la realización anterior, R_1 no es 5-(3-acetamidociclobutil)-1H-pirazol-3-ilo cuando R_5 y R_6, junto con el anillo al cual ellos están unidos, forman un indazol-1-ilo no sustituido. En otra variante de la realización anterior, R_1 no es 5-(2-clorobencil)tiazol-2-ilo cuando R_3 es fenilo y R_2, R_4, R_5, R_6 y R_7 son todos hidrógeno.

[00102] En otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



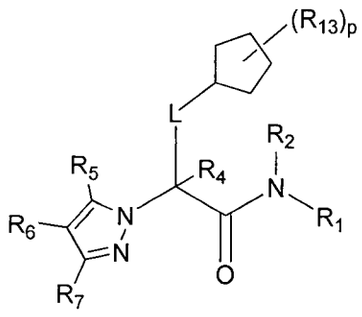
donde

m se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 y 11;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00103] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



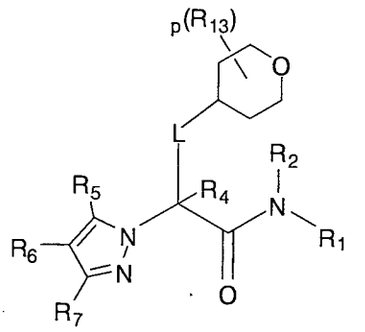
donde

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00104] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

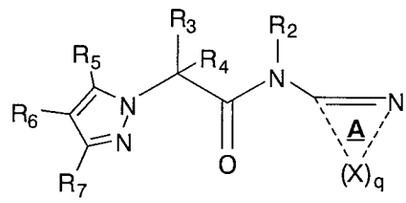
p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10),

sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00105] En otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



,

donde

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10),

sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

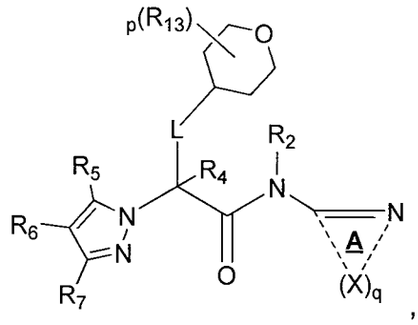
R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido, y

las variables restantes son como las que se describieron anteriormente.

[00106] En una variante de la realización anterior, el anillo A no es 5-(3-acetamidociclobutil)-1H-pirazol-3-ilo cuando R_5 y R_6, junto con el anillo al cual ellos están unidos, forman un indazol-1-ilo no sustituido. En otra variante de la realización anterior, anillo A no es 5-(2-clorobencil)tiazol-2-ilo cuando R_3 es fenilo y R_2, R_4, R_5, R_6 y R_7 son todos hidrógeno.

[00107] En otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

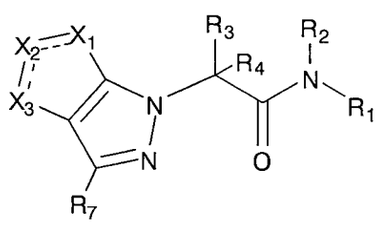
R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido, y

las variables restantes son como las que se describieron anteriormente.

[00108] En otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

X_1, X_2 y X_3 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

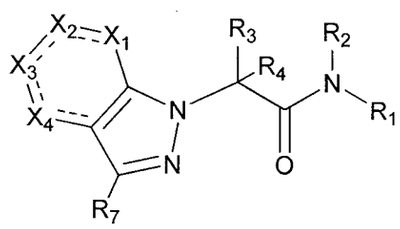
R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10),

sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido.

[00109] En otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

X_1, X_2, X_3 y X_4 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-

10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo

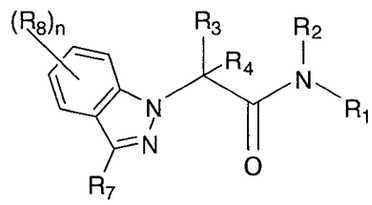
(C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00110] Incluso en otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

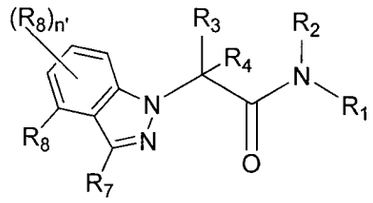
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo

(C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00111] En una variante de la realización anterior, R_1 no es 5-(3-acetamidociclobutil)-1H-pirazol-3-ilo cuando R_7 y cada R_8 son todos hidrógeno.

[00112] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

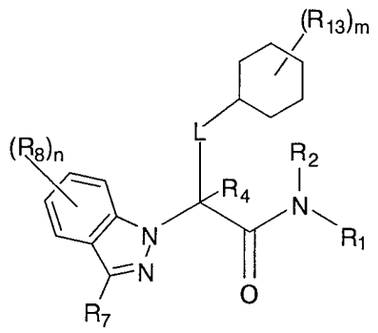
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00113] En una variante de la realización anterior, R_1 no es 5-(3-acetamidociclobutil)-1H-pirazol-3-ilo cuando R_7 y cada R_8 son todos hidrógeno.

[00114] Incluso en otra realización, los activadores de glucoquinasa de la presente

invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

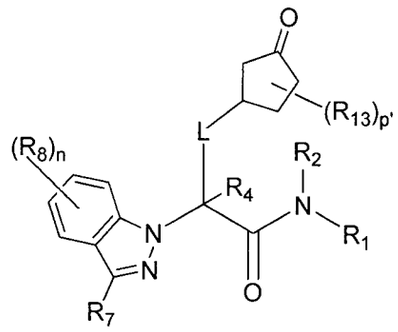
m se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 y 11;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00115] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

p' se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6 y 7;

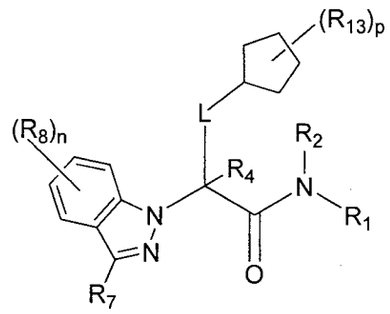
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada

uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00116] En otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

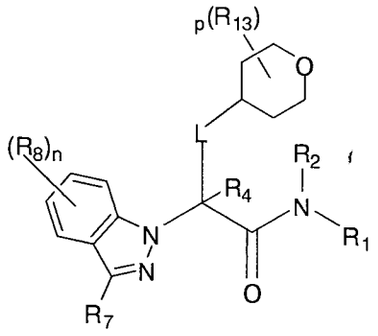
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1$-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12),

heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00117] Incluso en otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

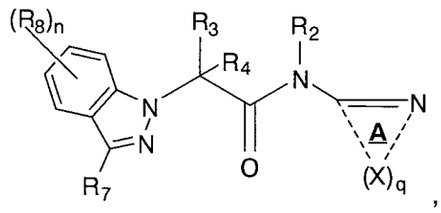
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo

(C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00118] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



,

donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3),

sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

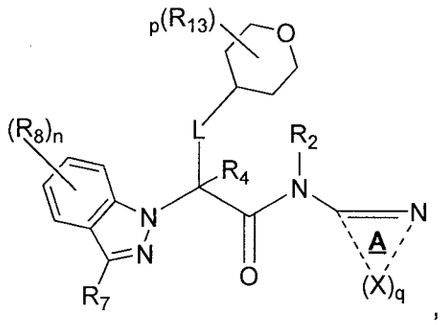
R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00119] En una variante de la realización anterior, anillo A no es 5-(3-acetamidociclobutil)-1H-pirazol-3-ilo cuando R_7 y cada R_8 son todos hidrógeno.

[00120] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo

(C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

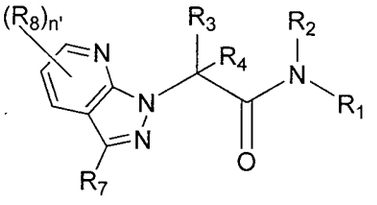
R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-

5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00121] En otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



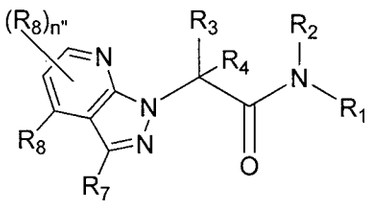
donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00122] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



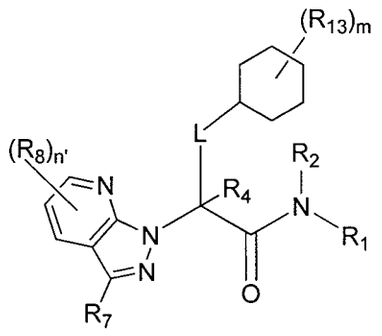
donde

n" se selecciona del grupo integrado por 0, 1 y 2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00123] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

m se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 y 11;

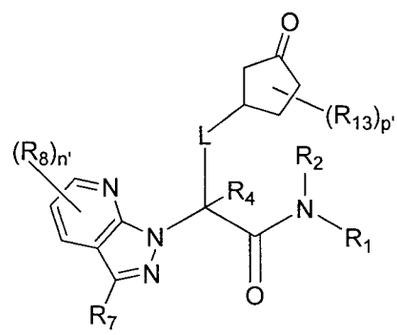
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo

(C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00124] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

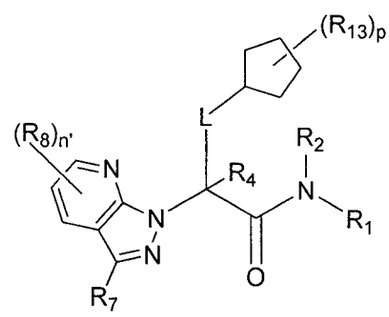
p' se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6 y 7;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00125] En otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

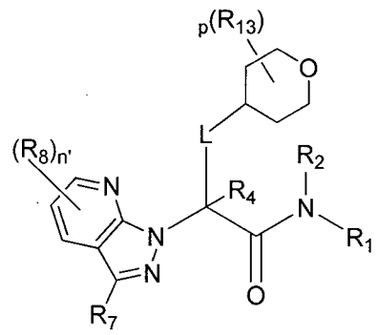
p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00126] Incluso en otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

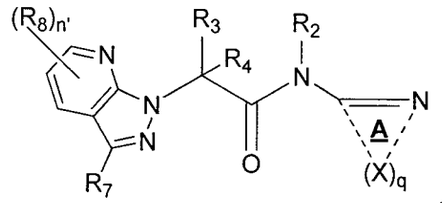
p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00127] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada

uno sustituido o no sustituido, o R_{14} es $-L_1-R_{22}$;

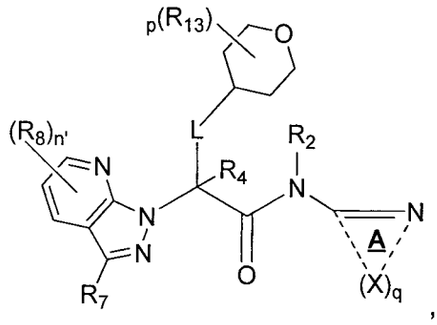
R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00128] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada

uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

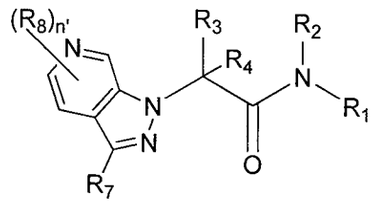
R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-

12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00129] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



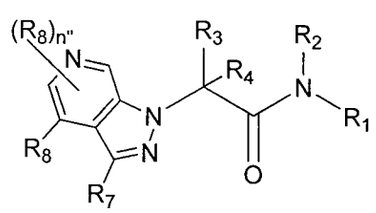
donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00130] En otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



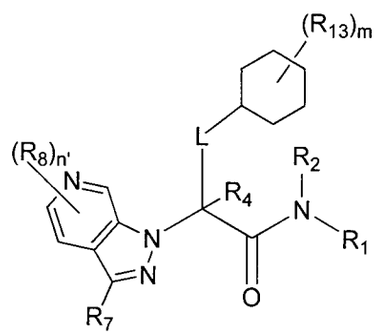
donde

n'' se selecciona del grupo integrado por 0, 1 y 2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00131] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

m se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 y 11;

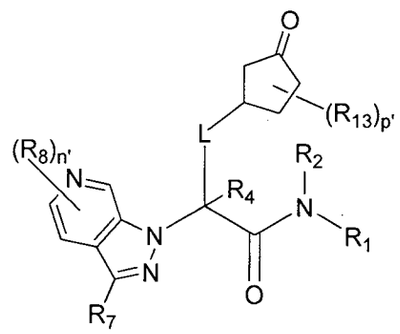
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5),

cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00132] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

p' se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6 y 7;

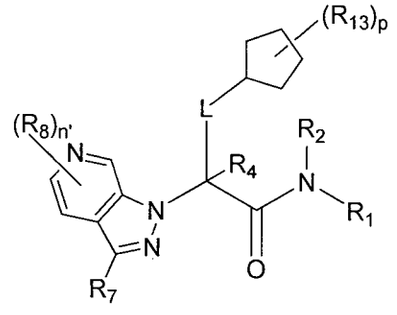
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10),

iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00133] En otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

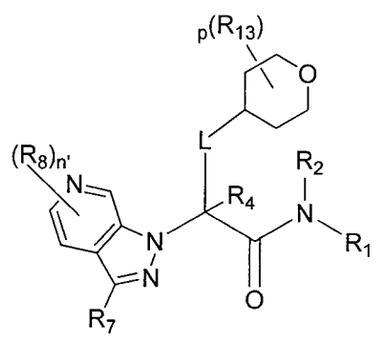
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo

(C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00134] Incluso en otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

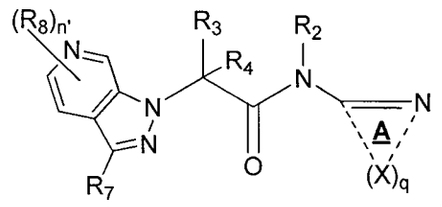
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio,

hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00135] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



,

donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$,

CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es –L_1-R_{22};

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-

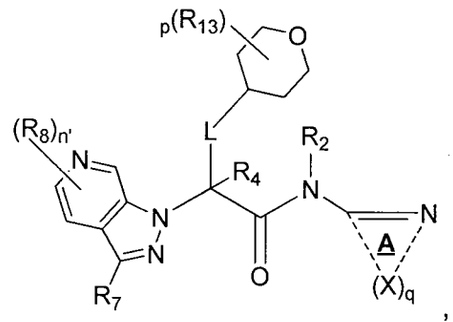
12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00136] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



,

donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo

(C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es –L_1-R_{22};

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10),

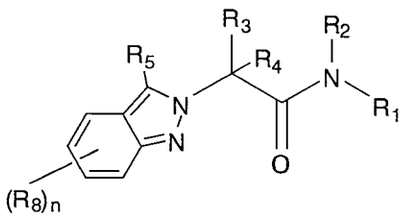
sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00137] En otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

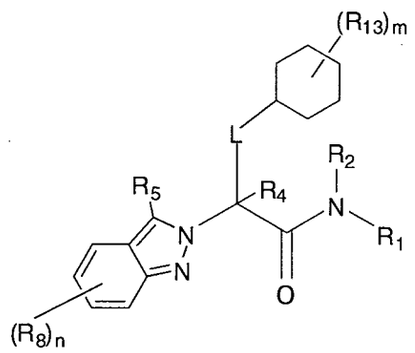
n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio,

hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_5 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00138] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

m se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 y 11;

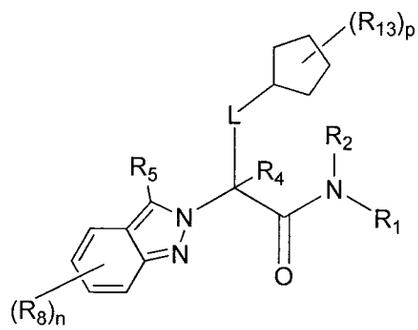
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y

heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_5 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00139] En otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

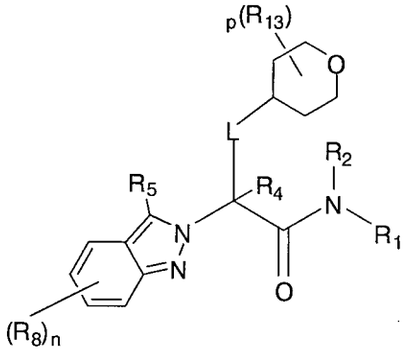
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5),

cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_5 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00140] Incluso en otra realización más, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

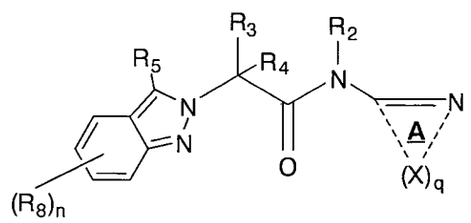
R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10),

iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_5 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00141] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



,

donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo

(C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_5 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $-L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

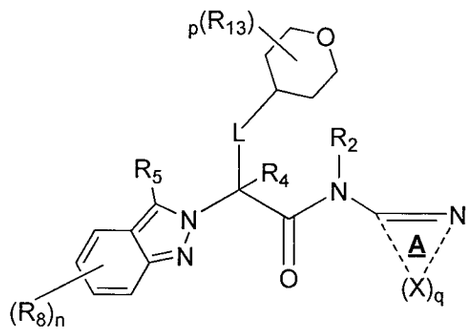
R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi,

heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00142] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5),

bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es –L_1-R_{22}, o R_8 y R_5 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es –L_1-R_{22};

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-

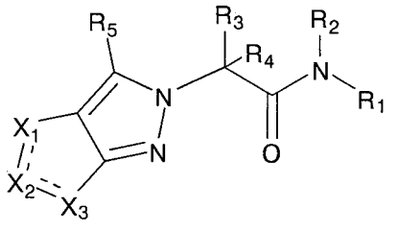
12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido; y

las variables restantes son como las que se describieron anteriormente.

[00143] Incluso en otra realización, los activadores de glucoquinasa de la presente invención tienen la fórmula:



donde

X_1, X_2 y X_3 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo

(C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12),

heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

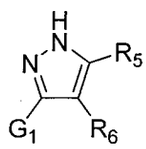
R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_5, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido; y

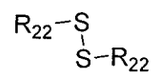
las variables restantes son como las que se describieron anteriormente.

[00144] En otro de sus aspectos, la presente invención se refiere a métodos para producir compuestos que son útiles como activadores de glucoquinasa. En una realización, los métodos comprenden los pasos de:

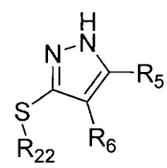
hacer reaccionar un compuesto que tiene la fórmula



con un compuesto que tiene la fórmula

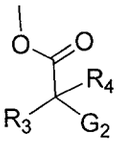


para formar un primer producto de reacción que tiene la fórmula

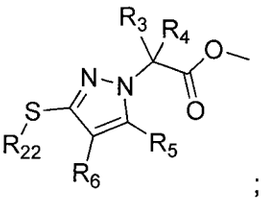


;

hacer reaccionar el primer producto de reacción con un compuesto que tiene la fórmula

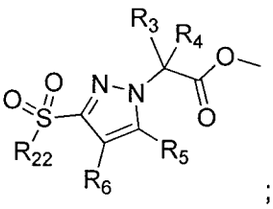


para formar un segundo producto de reacción que tiene la fórmula



;

tratar el segundo producto de reacción para formar un tercer producto de reacción que tiene la fórmula

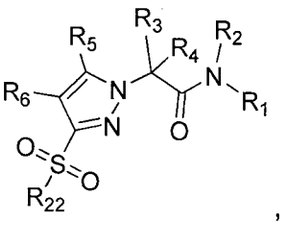


; y

hacer reaccionar el tercer producto de reacción con un compuesto que tiene la fórmula

NHR_1R_2

para formar un cuarto producto de reacción que tiene la fórmula



,

donde

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12),

heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5),

heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es $-L_1-R_{22}$;

o R_5 y R_6 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo

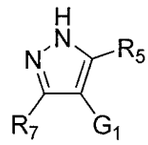
(C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido; y

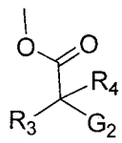
G_1 y G_2 son cada uno de ellos independientemente un grupo saliente.

[00145] En otra realización, los métodos comprenden los pasos de:

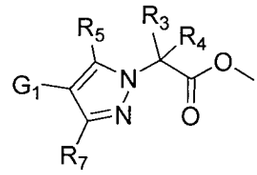
hacer reaccionar un compuesto que tiene la fórmula



con un compuesto que tiene la fórmula



para formar un primer producto de reacción que tiene la fórmula

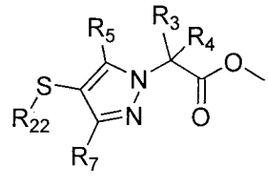


;

hacer reaccionar el primer producto de reacción con un compuesto que tiene la fórmula

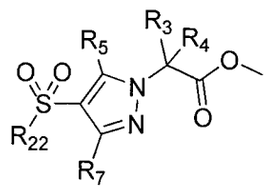
SHR_{22}

para formar un segundo producto de reacción que tiene la fórmula



;

tratar el segundo producto de reacción para formar un tercer producto de reacción que tiene la fórmula

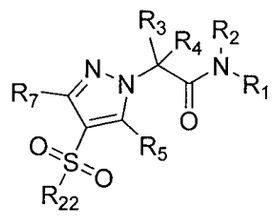


; y

hacer reaccionar el tercer producto de reacción con un compuesto que tiene la fórmula

NHR_1R_2

para formar un cuarto producto de reacción que tiene la fórmula



,

donde

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es $-L-R_{18}$;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1–R_{22}$;

o R_5 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de

átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

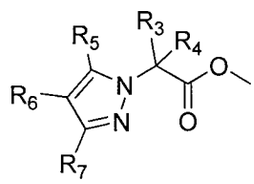
R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo

(C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido; y

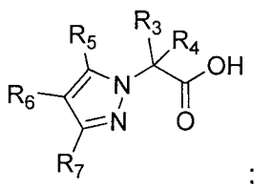
G_1 y G_2 son cada uno de ellos independientemente un grupo saliente.

[00146] Incluso en otra realización, los métodos comprenden los pasos de:

tratar un compuesto que tiene la fórmula

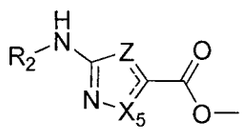


para formar un primer producto de reacción que tiene la fórmula

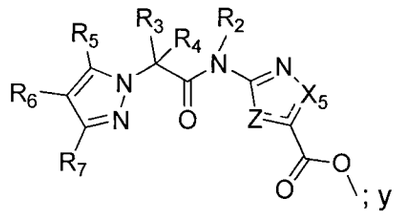


;

hacer reaccionar el primer producto de reacción con un compuesto que tiene la fórmula

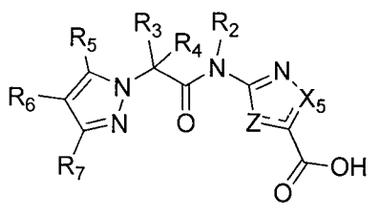


para formar un segundo producto de reacción que tiene la fórmula



; y

tratar el segundo producto de reacción para formar un tercer producto de reacción que tiene la fórmula



,

donde

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10),

oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es $–L_1-R_{22}$;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1-R_{22}$;

o cualquiera dos R_5, R_6 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

X_5 se selecciona del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-

10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

Z se selecciona del grupo integrado por $CR_{14}R_{15}$, NR_{16}, O y S;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10),

iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $-L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; y

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

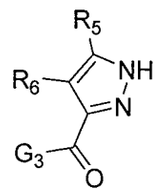
R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12),

heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00147] Incluso en otra realización, los métodos comprenden los pasos de:

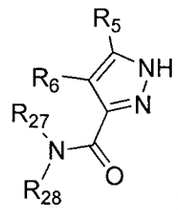
hacer reaccionar un compuesto que tiene la fórmula



con un compuesto que tiene la fórmula

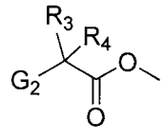
$$NHR_{27}R_{28}$$

para formar un primer producto de reacción que tiene la fórmula

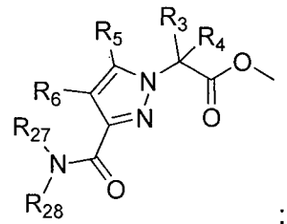


;

hacer reaccionar el primer producto de reacción con un compuesto que tiene la fórmula

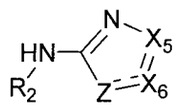


para formar un segundo producto de reacción que tiene la fórmula

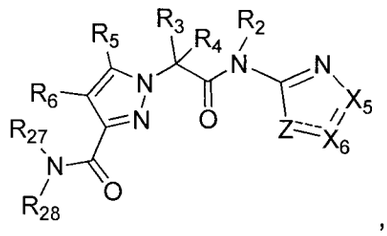


; y

hacer reaccionar el segundo producto de reacción con un compuesto que tiene la fórmula



para formar un tercer producto de reacción que tiene la fórmula



donde

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es $-L_1-R_{22}$;

o R_5 y R_6 se toman juntos para formar un anillo sustituido o no sustituido;

X_5 y X_6 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y

heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

Z se selecciona del grupo integrado por $CR_{14}R_{15}$, NR_{16}, O y S;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10),

oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

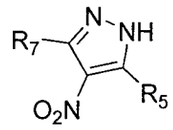
R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido; y

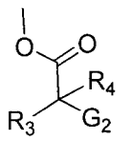
G_2 y G_3 son cada uno de ellos independientemente un grupo saliente.

[00148] En otra realización más, los métodos comprenden los pasos de:

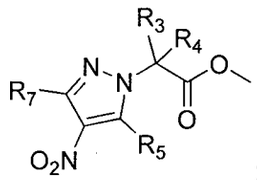
hacer reaccionar un compuesto que tiene la fórmula



con un compuesto que tiene la fórmula

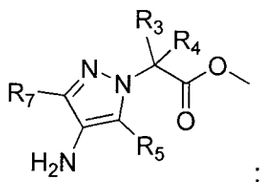


para formar un primer producto de reacción que tiene la fórmula



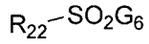
;

tratar el primer producto de reacción para formar un segundo producto de reacción que tiene la fórmula

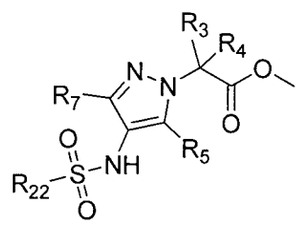


;

hacer reaccionar el segundo producto de reacción con un compuesto que tiene la fórmula

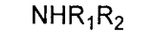


para formar un tercer producto de reacción que tiene la fórmula

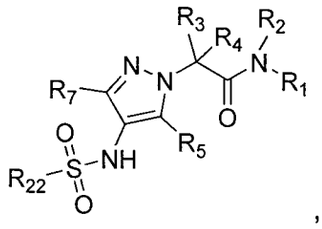


; y

hacer reaccionar el tercer producto de reacción con un compuesto que tiene la fórmula



para formar un cuarto producto de reacción que tiene la fórmula



donde

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-

12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $-L_1-R_{22}$;

o R_5 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-

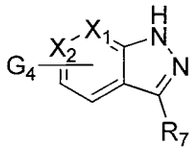
10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido; y

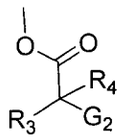
G_2 y G_6 son cada uno de ellos independientemente un grupo saliente.

[00149] Incluso en otra realización más, los métodos comprenden los pasos de:

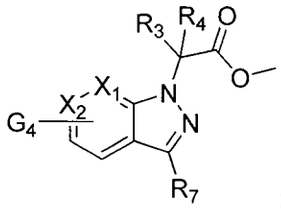
hacer reaccionar un compuesto que tiene la fórmula



con un compuesto que tiene la fórmula

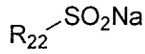


para formar un primer producto de reacción que tiene la fórmula

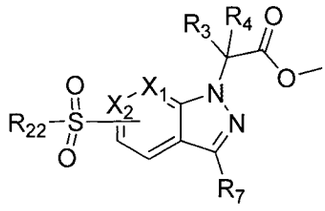


;

hacer reaccionar el primer producto de reacción con un compuesto que tiene la fórmula

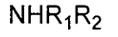


para formar un segundo producto de reacción que tiene la fórmula

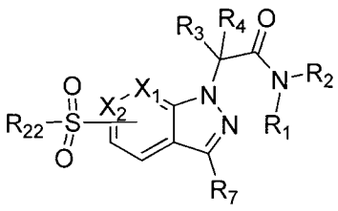


; y

hacer reaccionar el segundo producto de reacción con un compuesto que tiene la fórmula



para formar un tercer producto de reacción que tiene la fórmula



,

donde

X_1 y X_2 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–

alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1–R_{22}$;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-

12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi,

carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

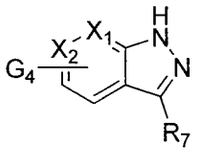
R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$;

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido; y

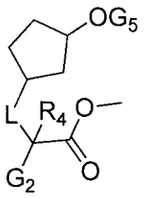
G_2 y G_4 son cada uno de ellos independientemente un grupo saliente.

[00150] Incluso en otra realización, los métodos comprenden los pasos de:

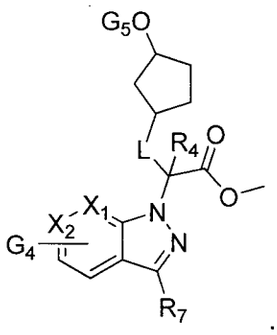
hacer reaccionar un compuesto que tiene la fórmula



con un compuesto que tiene la fórmula

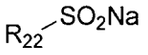


para formar un primer producto de reacción que tiene la fórmula

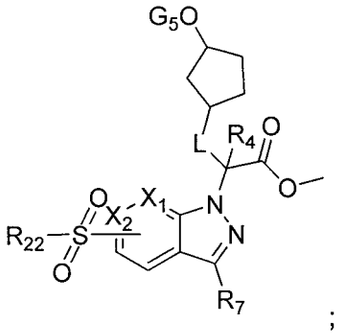


;

hacer reaccionar el primer producto de reacción con un compuesto que tiene la fórmula

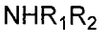


para formar un segundo producto de reacción que tiene la fórmula

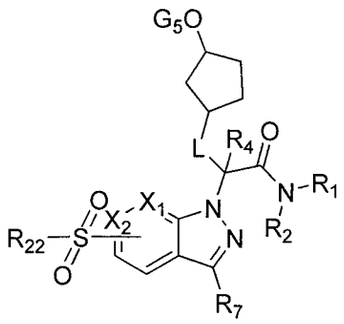


;

hacer reaccionar el segundo producto de reacción con un compuesto que tiene la fórmula

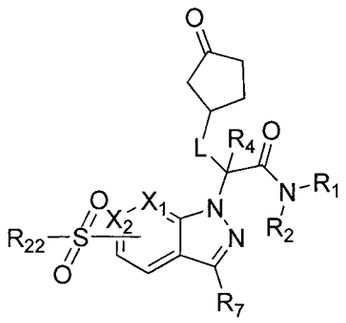


para formar un tercer producto de reacción que tiene la fórmula



; y

tratar el tercer producto de reacción para formar un cuarto producto de reacción que tiene la fórmula



,

donde

X_1 y X_2 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

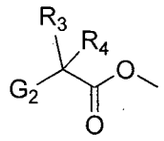
R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10),

oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $-L_1-R_{22}$;

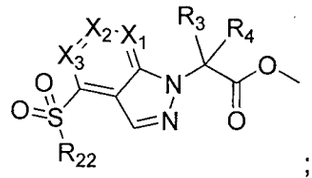
R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5),



para formar un cuarto producto de reacción que tiene la fórmula

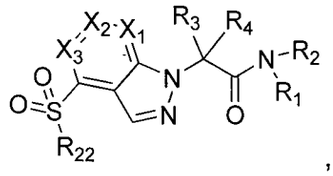


; y

hacer reaccionar el cuarto producto de reacción con un compuesto que tiene la fórmula

$$NHR_1R_2$$

para formar un quinto producto de reacción que tiene la fórmula



,

donde

X_1, X_2 y X_3 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es $-L-R_{18}$;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–

alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5),

oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1-R_{22}$;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5),

heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y

heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

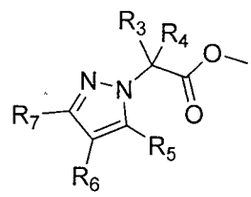
R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido;

G_2 y G_4 son cada uno de ellos independientemente un grupo saliente; y

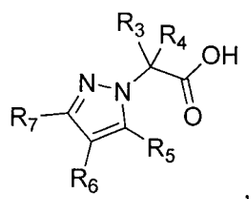
G_5 es un grupo protector.

[00151] En otra realización, los métodos comprenden el paso de:

tratar un primer producto de reacción que tiene la fórmula



en condiciones suficientes para formar un segundo producto de reacción que tiene la fórmula



,

donde

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es $-L-R_{18}$;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es $–L_1-R_{22}$;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10),

oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $-L_1-R_{22}$;

o cualquiera dos R_5, R_6 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

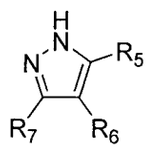
R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y

heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

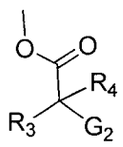
R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00152] En una variante de la realización anterior, los métodos además comprenden el paso de:

hacer reaccionar un compuesto que tiene la fórmula



con un compuesto que tiene la fórmula



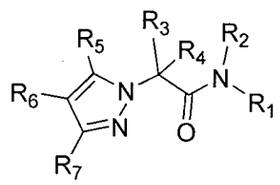
para formar la primera reacción, donde G_2 es un grupo saliente.

[00153] En otra variante de la realización anterior y variante, los métodos además comprenden el paso de:

hacer reaccionar el segundo producto de reacción con un compuesto que tiene la fórmula

$$NHR_1R_2$$

para formar un tercer producto de reacción que tiene la fórmula



,

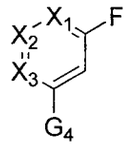
donde

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

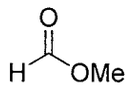
R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*.

[00154] Incluso en otra realización, los métodos comprenden los pasos de:

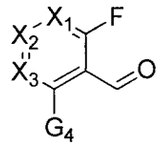
hacer reaccionar un compuesto que tiene la fórmula



con un compuesto que tiene la fórmula

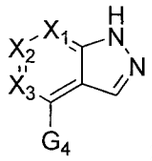


para formar un primer producto de reacción que tiene la fórmula



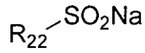
;

tratar el primer producto de reacción en condiciones suficientes para formar un segundo producto de reacción que tiene la fórmula

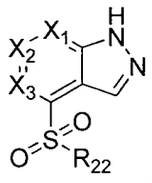


;

hacer reaccionar el segundo producto de reacción con un compuesto que tiene la fórmula

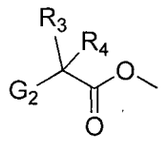


para formar un tercer producto de reacción que tiene la fórmula

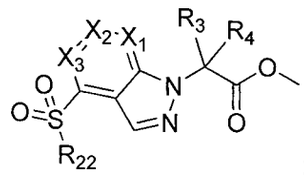


;

hacer reaccionar el tercer producto de reacción con un compuesto que tiene la fórmula



para formar un cuarto producto de reacción que tiene la fórmula

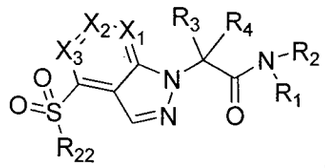


; y

hacer reaccionar el cuarto producto de reacción con un compuesto que tiene la fórmula

$$NHR_1R_2$$

para formar un quinto producto de reacción que tiene la fórmula



,

donde

X_1, X_2 y X_3 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es $-L-R_{18}$;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–

alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5),

heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10),

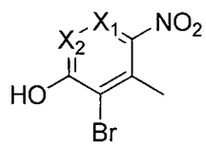
oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido; y

G_2 y G_4 son cada uno de ellos independientemente un grupo saliente.

[00155] Incluso en otra realización, los métodos comprenden los pasos de:

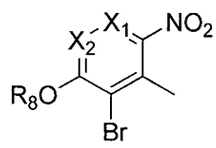
hacer reaccionar un compuesto que tiene la fórmula



con un compuesto que tiene la fórmula

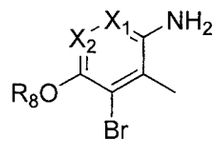


para formar un primer producto de reacción que tiene la fórmula



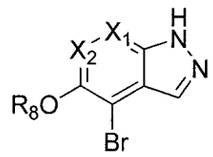
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tratar el primer producto de reacción en condiciones suficientes para formar un segundo producto de reacción que tiene la fórmula



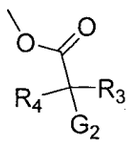
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tratar el segundo producto de reacción en condiciones suficientes para formar un tercer producto de reacción que tiene la fórmula

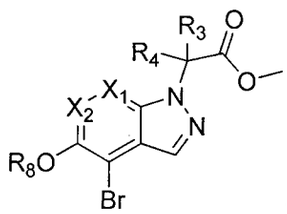


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hacer reaccionar el tercer producto de reacción con un compuesto que tiene la fórmula

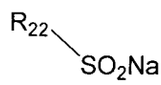


para formar un cuarto producto de reacción que tiene la fórmula

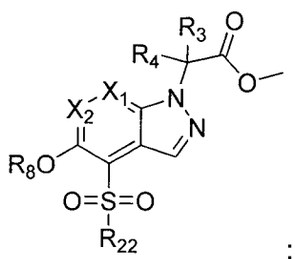


;

hacer reaccionar el cuarto producto de reacción con un compuesto que tiene la fórmula



para formar un quinto producto de reacción que tiene la fórmula

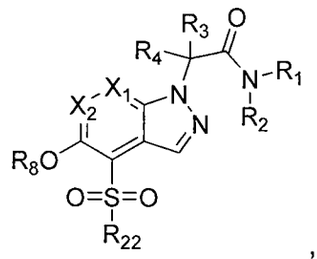


; y

hacer reaccionar el quinto producto de reacción con un compuesto que tiene la fórmula

NHR_1R_2

para formar un sexto producto de reacción que tiene la fórmula



donde

X_1 y X_2 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es $–L-R_{18}$;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo

(C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5),

heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi,

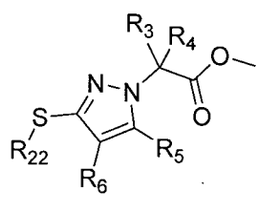
carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido;

G_2 es un grupo saliente; y

G_5 es un grupo protector.

[00156] Incluso en otro de sus aspectos, la presente invención se refiere a intermediarios que son útiles para producir activadores de glucoquinasa. En una realización, los intermediarios comprenden:



donde

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10),

heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es –L_1-R_{22};

o R_5 y R_6 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

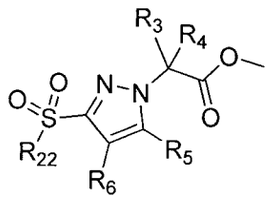
R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo

(C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00157] En otra realización, los intermediarios comprenden:



donde

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-

12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es $–L_1-R_{22}$;

o R_5 y R_6 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

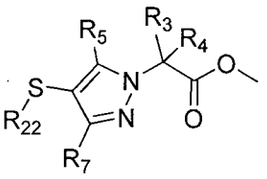
R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-

10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00158] Incluso en otra realización, los intermediarios comprenden:



donde

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es $-L-R_{18}$;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–

alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $-L_1-R_{22}$;

o R_5 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

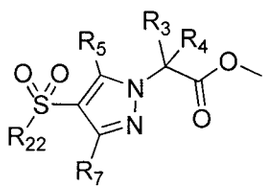
R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo,

amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00159] Incluso en otra realización, los intermediarios comprenden:



donde

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5),

heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $-L_1-R_{22}$;

o R_5 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

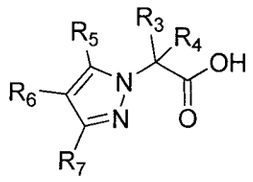
R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo

(C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00160] En otra realización más, los intermediarios comprenden:



donde

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5),

heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es $–L_1-R_{22}$;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1-R_{22}$;

o cualquiera dos R_5, R_6 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

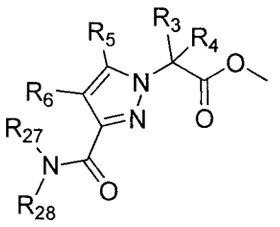
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00161] Incluso en otra realización más, los intermediarios comprenden:



donde

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo,

amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es $-L_1-R_{22}$;

o R_5 y R_6 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

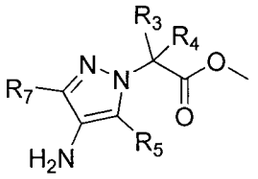
R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5),

heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00162] Incluso en otra realización, los intermediarios comprenden:



donde

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es $-L-R_{18}$;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $-L_1-R_{22}$;

o R_5 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

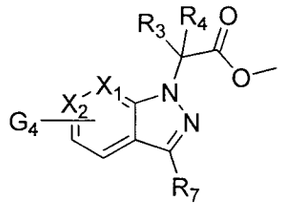
R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5),

heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00163] En otra realización, los intermediarios comprenden:



donde

X_1 y X_2 se seleccionan cada uno de ellos independientemente del grupo integrado por

CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es $-L-R_{18}$;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $-L_1-R_{22}$;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo

(C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-

12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

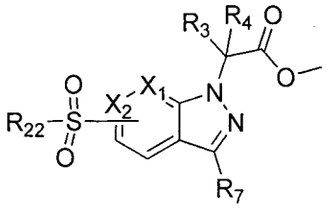
R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12),

heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es –$NR_{27}R_{28}$;

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido; y

G_4 es un grupo saliente.

[00164] Incluso en otra realización, los intermediarios comprenden:



donde

X_1 y X_2 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo

(C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1-R_{22}$;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5),

heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del

conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

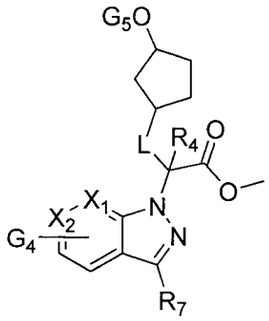
R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5),

bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00165] Incluso en otra realización, los intermediarios comprenden:



donde

X_1 y X_2 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1-R_{22}$;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-

10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

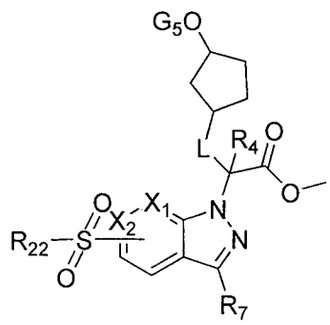
R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo

integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido;

G_4 es un grupo saliente; y

G_5 es un grupo protector.

[00166] En otra realización más, los intermediarios comprenden:



donde

X_1 y X_2 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo,

amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $-L_1-R_{22}$;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10),

sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

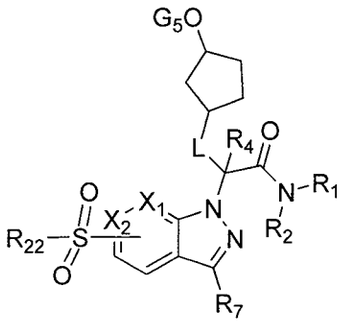
R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5),

heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido; y

G_5 es un grupo protector.

[00167] Incluso en otra realización más, los intermediarios comprenden:



donde

X_1 y X_2 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1-R_{22}$;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-

10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$;

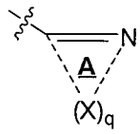
R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido; y

G_5 es un grupo protector.

[00168] En una variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 es un heteroarilo sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 se selecciona del grupo integrado por tiazolilo, pirazinilo, pirazolilo y piridilo, cada uno sustituido o no sustituido.

Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 se selecciona del grupo integrado por tiazol-2-ilo; 2-piridilo; 5-metil-tiazol-2-ilo; 6-metil-pirid-2-ilo; 4-metil-pirid-2-ilo; 5-bromo-6-metil-pirid-2-ilo; 5-fenil-pirid-2-ilo; benzotiazol-2-ilo; un metil éster del ácido nicotínico; y 5-bromo-pirid-2-ilo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 es un 2-pirazinilo sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 es un 1-metil-pirazol-3-ilo sustituido o no sustituido. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 es un 5-fluoro-tiazol-2-ilo sustituido o no sustituido.

[00169] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo

(C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido;

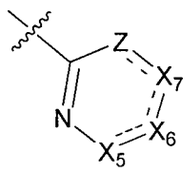
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo,

amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00170] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

X_5, X_6 y X_7 se seleccionan cada uno de ellos independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

Z se selecciona del grupo integrado por $CR_{14}R_{15}$, NR_{16}, O y S;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1$-R_{22};

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5),

bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido;

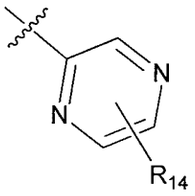
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo

integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

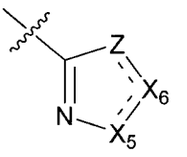
[00171] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$.

[00172] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

X_5 y X_6 se seleccionan cada uno de ellos independientemente del grupo integrado por

$CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

Z se selecciona del grupo integrado por $CR_{14}R_{15}$, NR_{16}, O y S;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1$-R_{22};

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido;

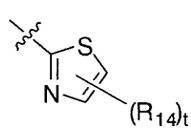
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de

átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00173] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

t se selecciona del grupo integrado por 0, 1 y 2; y

cada R_{14} se selecciona independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$, o dos R_{14} se toman juntos para formar un anillo sustituido o no sustituido;

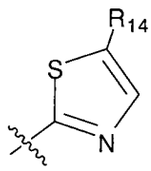
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5),

bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00174] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

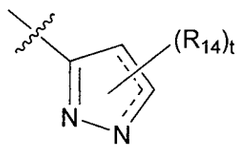
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12),

heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00175] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

t se selecciona del grupo integrado por 0, 1 y 2; y

cada R_{14} se selecciona independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $-L_1$-R_{22}, o dos R_{14} se toman juntos para formar un anillo sustituido o no sustituido;

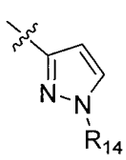
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de

átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00176] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

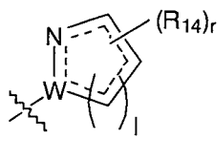
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5),

cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00177] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

I se selecciona del grupo integrado por 1 y 2;

r se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7 y 8;

W se selecciona del grupo integrado por CR_{17} o N;

cada R_{14} se selecciona independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$, o dos R_{14} se toman juntos para formar un anillo sustituido o no sustituido;

R_{17} se selecciona del grupo integrado por hidrógeno, halo, alquilo (C1-3), arilo y heteroarilo, cada uno sustituido o no sustituido, o R_{17} y R_{14} se toman juntos para formar un anillo, con la condición que R_{17} esté ausente cuando el átomo al cual él está unido forma parte de un enlace doble;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

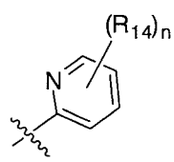
R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido,

imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00178] En una variante de las variantes anteriores que contiene W, W es CR_{17}. En otra variante de las variantes anteriores que contienen W, W es N.

[00179] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_1, R_1 comprende:



donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

cada R_{14} se selecciona independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10),

carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1$-R_{22}, o dos R_{14} se toman juntos para formar un anillo sustituido o no sustituido;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y

heterobiciclоarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00180] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen el anillo **A**, el anillo **A** es un heteroarilo sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen el anillo **A**, el anillo **A** se selecciona del grupo integrado por tiazolilo, pirazinilo, pirazolilo y piridilo, cada uno sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen **A**, **A** es un 2-pirazinilo sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen **A**, **A** es un 1-metil-pirazol-3-ilo sustituido o no sustituido. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen **A**, **A** es un 5-fluoro-tiazol-2-ilo sustituido o no sustituido.

[00181] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen Z, Z es S.

[00182] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen X_1, X_1 es –CH=. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen X_1, X_1 es –N=.

[00183] En otra variante de cada una de las realizaciones anteriores y variantes que contienen X_2, X_2 es –CH=. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen X_2, X_2 es –N=.

[00184] En otra variante de cada una de las realizaciones anteriores y variantes que contienen X_3, X_3 es $–CR_9=$. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen X_3, X_3 es –CH=.

[00185] En otra variante de cada una de las realizaciones anteriores y variantes que contienen X_4, X_4 es $–CR_9=$. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen X_4, X_4 es –CH=.

[00186] En otra variante de cada una de las realizaciones anteriores y variantes que contienen X_1, X_2, X_3 y X_4, X_1 es –CH=, X_2 es –N=, X_3 es –CH= y X_4 es $–CR_9=$. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen X_1, X_2, X_3 y X_4, X_1 es –CH=, X_2 es –CH=, X_3 es $–C\ R_9=$ y X_4 es $–CR_9=$.

[00187] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen X_5, X_5 es –CH=.

[00188] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen X_6, X_6 es –CH=.

[00189] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen X_7, X_7 es –CH=. En otra variante de cada una de las realizaciones

anteriores y variantes que contienen X_7, X_7 es –N=.

[00190] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_2, R_2 es hidrógeno.

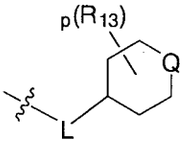
[00191] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3,

R_3 es –L-R_{18};

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; y

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

[00192] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 comprende:



donde

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

Q se selecciona del grupo integrado por O, S, CS, CO, SO, SO_2, $CR_{19}R_{20}$ y NR_{21};

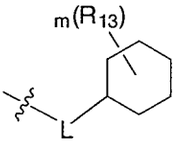
R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo,

sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{19} y R_{20} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

R_{21} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

[00193] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 comprende:



donde

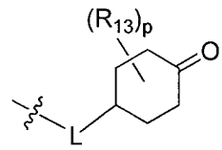
m se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 y 11;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el

anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; y

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido.

[00194] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 comprende:



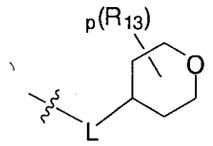
donde

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; y

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido.

[00195] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 comprende:



donde

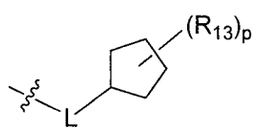
p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; y

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido.

[00196] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 se selecciona del grupo integrado por alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

[00197] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 comprende:



donde

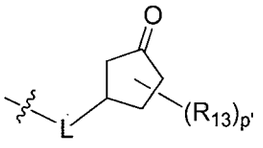
p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el

anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; y

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido.

[00198] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 comprende:



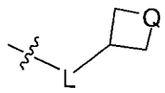
donde

p' se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6and 7;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; y

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido.

[00199] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 comprende:



donde

Q se selecciona del grupo integrado por O, S, CS, CO, SO, SO_2, $CR_{19}R_{20}$ y NR_{21};

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{19} y R_{20} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

R_{21} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

[00200] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 se selecciona del grupo integrado por alquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), y heteroarilalquilo (C1-5), cada uno sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 se selecciona del grupo integrado por butilo; hexilmetilo; bencilo; imidazol-4-ilmetilo, fenilo y (tetrahidro-2H-piran-4-il)metilo. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 es un (tetrahidro-2H-piran-4-il)metilo sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 se selecciona del grupo integrado por butilo; hexilmetilo; bencilo;

imidazol-4-ilmetilo y fenilo. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3, R_3 se selecciona del grupo integrado por alquilo, cicloalquilo-alquilo, dihaloaril-alquilo, alcoxiaril-alquilo, alcoxicicloalquil-alquilo, tetrahidrofuranoil-alquilo, furanoil-alquilo y tetrahidro-2H-piranil-alquilo, cada uno sustituido o no sustituido.

[00201] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen L, L es $-CH_2-$. En otra variante de cada una de las realizaciones anteriores y variantes que contienen L, L se selecciona del grupo integrado por $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2C(O)-$, $-CH_2-C(O)CH_2-$, $-CH_2CH_2C(O)-$,$-CH_2O-$, $-CH_2OCH_2-$, $-CH_2CH_2O-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-CH_2CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-CH_2S-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$,$-CH_2C(O)S-$ y $-CH_2SC(O)-$, cada uno sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen L, L se selecciona del grupo integrado por $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, $-NH-C(O)-$, $-NCH_3-C(O)-$, $-C(O)NH-$, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, $-S-$, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, $-C(O)S-$, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, y $-CH_2SC(O)-$, cada uno sustituido o no sustituido.

[00202] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen L,

L se selecciona del grupo integrado por $-(CR_{24}R_{25})_s-$;

s se selecciona del grupo integrado por 1, 2, 3, 4, 5 y 6; y

R_{24} y R_{25} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada

uno sustituido o no sustituido.

[00203] En otra variante de cada una de las realizaciones anteriores y variantes que contienen Q, Q es $-CR_{19}R_{20}-$. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen Q, Q es $-CH_2-$. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen Q, Q es $-NR_{21}-$. En otra variante de cada una de las realizaciones anteriores y variantes que contienen Q, Q es -NH-. En otra variante de cada una de las realizaciones anteriores y variantes que contienen Q, Q es -O-.

[00204] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_4, R_4 se selecciona del grupo integrado por carbonilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

[00205] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_4, R_4 se selecciona del grupo integrado por hidrógeno, alquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), y heteroarilalquilo (C1-5), cada uno sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_4, R_4 se selecciona del grupo integrado por alquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), y heteroarilalquilo (C1-5), cada uno sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_4, R_4 se selecciona del grupo integrado por hidrógeno; butilo; ciclohexilmetilo; bencilo; imidazol-4-ilmetilo y fenilo. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_4, R_4 se selecciona del grupo integrado por butilo; ciclohexilmetilo; bencilo; imidazol-4-ilmetilo y fenilo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_4, R_4 es hidrógeno.

[00206] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_5, R_5 es hidrógeno. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_5, R_5 es halo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_5, R_5 es un alquilo (C1-3) sustituido o no sustituido.

[00207] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es hidrógeno. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es halo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es un alquilo (C1-3) sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es un alquilo (C1-3)-sulfonilo sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es un cicloalquilo (C1-6)-sulfonilo sustituido o no sustituido. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 se selecciona del grupo integrado por metilsulfonilo, ciclopropilsulfonilo y ciclopentilsulfonilo, cada uno sustituido o no sustituido.

[00208] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6,

R_6 es $-L_1-R_{22}$;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-

3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00209] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es $–SO_2-R_{22}$; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00210] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es $–CO-R_{22}$; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10),

carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00211] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es $-NH-SO_2-R_{22}$; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo

(C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00212] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es -NH-CO-R_{22}; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00213] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_6, R_6 es -CO-NH-R_{22}; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo

(C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00214] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_7, R_7 es hidrógeno. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_7, R_7 es halo. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_7, R_7 es un alquilo (C1-3) sustituido o no sustituido.

[00215] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_7,

R_7 es $-L_1$-R_{22};

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo

(C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es –$NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00216] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_7, R_7 es –CO-R_{22}; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es –$NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-

12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclcloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00217] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_7, R_7 es -NH-SO_2-R_{22}; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclcloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es –$NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclcloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido..

[00218] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_5 y R_6, R_5 y R_6, junto con los átomos al cual ellos están unidos, forman un arilo sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_5 y R_6, R_5 y R_6, junto con los átomos al cual ellos están unidos, forman un fenilo sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_5 y R_6, R_5 y R_6, junto con los átomos al cual ellos están unidos, forman un heteroarilo sustituido o no sustituido.

[00219] Incluso en otra variante de cada una de las realizaciones anteriores y variantes

que contienen R_6 y R_7, R_6 y R_7, junto con los átomos al cual ellos están unidos, forman un arilo sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6 y R_7, R_6 y R_7, junto con los átomos al cual ellos están unidos, forman un fenilo sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_6 y R_7, R_6 y R_7, junto con los átomos al cual ellos están unidos, forman un heteroarilo sustituido o no sustituido.

[00220] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es hidrógeno. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es halo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es un alquilo (C1-3) sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es un sulfonilalquilo (C1-3) sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es un alquilo (C1-3)-sulfonilo sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es un cicloalquilo (c3-12)-sulfonilo sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 se selecciona del grupo integrado por sulfonilmetilo, metilsulfonilo, ciclopropilsulfonilo y ciclopentilsulfonilo, cada uno sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es un ciclopropilsulfonilo sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es ciano. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es un alcoxi (C1-6) sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es metoxi.

[00221] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8,

R_8 es $-L_1-R_{22}$;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo

(C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00222] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es $-SO_2-R_{22}$; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi,

heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00223] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es $–CO-R_{22}$; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $–NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00224] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es $-NH-SO_2-R_{22}$; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino,

sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00225] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es -NH-CO-R_{22}; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3),

cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00226] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_8, R_8 es -CO-NH-R_{22}; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es –$NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00227] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3 y R_8, R_3 es un (tetrahidro-2H-piran-4-il)metilo sustituido o no sustituido y R_8 es un ciclopropilsulfonilo sustituido o no sustituido.

[00228] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_9, R_9 es un ciclopropilsulfonilo sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_9, R_9 es un alcoxi (C1-3) sustituido o no sustituido. Incluso en otra variante de cada una de las

realizaciones anteriores y variantes que contienen R_9, R_9 es metoxi.

[00229] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_3 y R_9, R_3 es un (tetrahidro-2H-piran-4-il)metilo sustituido o no sustituido y R_9 es un ciclopropilsulfonilo sustituido o no sustituido.

[00230] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{10}, R_{10} es hidrógeno. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{10}, R_{10} es halo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{10}, R_{10} es un alquilo (C1-3) sustituido o no sustituido.

[00231] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{11}, R_{11} es hidrógeno. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{11}, R_{11} es un alquilo (C1-3) sustituido o no sustituido.

[00232] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{12}, R_{12} es hidrógeno. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{12}, R_{12} es un alquilo (C1-3) sustituido o no sustituido.

[00233] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{13}, R_{13} es hidrógeno. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{13}, R_{13} es halo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{13}, R_{13} es un alquilo (C1-3) sustituido o no sustituido.

[00234] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, cada R_{14} se selecciona independientemente del grupo integrado por hidrógeno, halo, un alquilo (C1-5) sustituido o no sustituido y un carboxamido sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, al menos un R_{14} es un carboxamido sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, al menos un R_{14} es hidrógeno. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_{14}, al menos un R_{14} es halo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, al menos un R_{14} es flúor. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, al menos un R_{14} es cloro. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, al menos un R_{14} es un alquilo (C1-5) sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, al menos un R_{14} es metilo. Incluso

en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, dos R_{14}, junto con los átomos al cual ellos están unidos, se toman juntos para formar un anillo sustituido o no sustituido.

[00235] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, R_{14} es oxaalquilo (C1-5). Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, R_{14} es oxoalquilo (C1-5). En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, R_{14} es $-L_1-R_{22}$, donde L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00236] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{14}, R_{14} se selecciona del grupo integrado por hidrógeno, halo, ciano, $-OR_{22}$, $-SO_2-R_{22}$, $-NH-SO_2-R_{22}$ y $-SO_2-NH-R_{22}$; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10),

sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_{14}, R_{14} se selecciona del grupo integrado por halo, alquilo (C1-5), oxaalquilo (C1-5) y oxoalquilo (C1-5), cada uno sustituido o no sustituido.

[00237] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{15}, R_{15} es hidrógeno. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{15}, R_{15} es halo. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_{15}, R_{15} es un alquilo (C1-5) sustituido o no sustituido.

[00238] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{16}, R_{16} es alquilo (C1-5). En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{16}, R_{16} es metilo.

[00239] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{17}, R_{17} está ausente. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{17}, R_{17} es hidrógeno. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{17}, R_{17} es alquilo (C13). En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{17}, R_{17} es metilo. En otra variante de cada una de las realizaciones anteriores

y variantes que contienen R_{17}, R_{17} es halo.

[00240] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{18}, R_{18} se selecciona del grupo integrado por alquilo, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, cada uno sustituido o no sustituido.

[00241] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{19}, R_{19} es hidrógeno. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{19}, R_{19} es halo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{19}, R_{19} es un alquilo (C1-3) sustituido o no sustituido.

[00242] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{20}, R_{20} es hidrógeno. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{20}, R_{20} es halo. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{20}, R_{20} es un alquilo (C1-3) sustituido o no sustituido.

[00243] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{21}, R_{21} es hidrógeno. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{21}, R_{21} es un alquilo (C1-3) sustituido o no sustituido.

[00244] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{22}, R_{22} es un alquilo (C1-5) sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{22}, R_{22} es un cicloalquilo (C3-6) sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{22}, R_{22} es un arilo (C4-8) sustituido o no sustituido. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{22}, R_{22} es un fenilo sustituido o no sustituido. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen R_{22}, R_{22} es un heteroarilo (C1-6) sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{22}, R_{22} es ciclopropilo.

[00245] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{22},

R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10),

iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

[00246] Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen L_1,

L_1 se selecciona del grupo integrado por $-(CR_{24}R_{25})_s-$, $-NR_{26}-$, -O-, -S-, -CO-, -CS-, -SO-, $-SO_2-$, y combinaciones de los mismos;

s se selecciona del grupo integrado por 1, 2, 3, 4, 5 y 6;

R_{24} y R_{25} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

R_{26} se selecciona del grupo integrado por hidrógeno, ciano, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-

12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

[00247] En otra variante de cada una de las realizaciones anteriores y variantes que contienen L_1, L_1 es $-SO_2-$. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen L_1, L_1 es $-C(O)-NR_{26}-$ y R_{26} se selecciona del grupo integrado por hidrógeno, ciano, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

[00248] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen L_1, L_1 es $-C(S)-NR_{26}-$ y R_{26} se selecciona del grupo integrado por hidrógeno, ciano, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

[00249] En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{24}, R_{24} se selecciona del grupo integrado por H y un alquilo (C1-5) sustituido o no sustituido.

[00250] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{25}, R_{25} se selecciona del grupo integrado por H y un alquilo (C1-5) sustituido o no sustituido.

[00251] Incluso en otra variante más de cada una de las realizaciones anteriores y

variantes que contienen R_{26}, R_{26} se selecciona del grupo integrado por hidrógeno y un alquilo (C1-10) sustituido o no sustituido.

[00252] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{27}, R_{27} es un cicloalquilo (C3-12) sustituido o no sustituido. En otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{27}, R_{27} es un ciclopropilo sustituido o no sustituido.

[00253] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen R_{28}, R_{28} es hidrógeno.

[00254] En otra variante de cada una de las realizaciones anteriores y variantes que contienen l, l es 1.

[00255] Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen m, m es 0. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen m, m es 1. En otra variante de cada una de las realizaciones anteriores y variantes que contienen m, m es 2.

[00256] En otra variante de cada una de las realizaciones anteriores y variantes que contienen n, n es 0. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen n, n es 1. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen n, n es 2.

[00257] En otra variante de cada una de las realizaciones anteriores y variantes que contienen n', n' es 0. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen n', n' es 1. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen n', n' es 2.

[00258] En otra variante de cada una de las realizaciones anteriores y variantes que contienen n'', n'' es 0. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen n'', n'' es 1. Incluso en otra variante más de cada una de las realizaciones anteriores y variantes que contienen n'', n'' es 2.

[00259] En otra variante de cada una de las realizaciones anteriores y variantes que contienen p, p es 0. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen p, p es 1. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen p, p es 2.

[00260] En otra variante de cada una de las realizaciones anteriores y variantes que contienen p', p' es 0. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen p', p' es 1. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen p', p' es 2.

[00261] En otra variante de cada una de las realizaciones anteriores y variantes que contienen q, q es 3. Incluso en otra variante de cada una de las realizaciones anteriores y

variantes que contienen q, q es 4.

[00262] En otra variante de cada una de las realizaciones anteriores y variantes que contienen r, r es 1.

[00263] En otra variante de cada una de las realizaciones anteriores y variantes que contienen s, s es 0. Incluso en otra variante de cada una de las realizaciones anteriores y variantes que contienen s, s es 1.

[00264] En otra variante de cada una de las realizaciones anteriores y variantes que contienen t, t es 1.

[00265] Se observa que los compuestos de la presente invención may be en la forma de una sal, éster biohidrolizable, amida biohidrolizable, carbamato biohidrolizable, solvato, hidrato o prodroga del los mismos aceptables para uso farmacéutico. Por ejemplo, el compuesto opcionalmente comprende un sustituyente que es ese que puede convertirse *in vivo* a un diferente sustituyente, tal como hidrógeno. Además se observa que el compuesto puede estar presente en una mezcla de estereoisómeros, o el compuesto puede comprender un único estereoisómero.

[00266] La presente invención además provee una composición farmacéutica que comprende en la forma de principio activo un compuesto de acuerdo con cualquiera de las realizaciones y variantes anteriores. En una variante particular, la composición es una formulación sólida adaptada para administración oral. En otra variante particular, la composición es una formulación líquida adaptada para administración oral. Incluso en otra variante particular, la composición es un comprimido. Incluso en otra variante particular más, la composición es una formulación líquida adaptada para parenteral administración.

[00267] En otro de sus aspectos, se provee una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las realizaciones y variantes anteriores, donde la composición es adaptada para administración mediante una vía seleccionada del grupo integrado por oral, parenteral, interaperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposomal, mediante inhalación, vaginal, intraocular, mediante administración local (por ejemplo por catéter o stent), subcutánea, intraadiposa, intraarticular, e intratecal.

[00268] Incluso en otro de sus aspectos, se provee un kit que comprende un compuesto de cualquiera de las realizaciones y variantes anteriores; e instrucciones las cuales comprenden una o más formas de información seleccionada del grupo que consiste en indicar un estado de enfermedad por el cual la composición debe administrarse, información de almacenamiento para la composición, información de dosificación e instrucciones respecto a la forma de administrar la composición. En una variante

particular, el kit comprende el compuesto en una forma de dosificación múltiple.

[00269] Incluso en otro de sus aspectos, se provee un artículo de fabricación que comprende un compuesto de cualquiera de las realizaciones y variantes anteriores; y materiales de empaque. En una variante, el material de empaque comprende un recipiente para alojar el compuesto. En una variante particular, el recipiente comprende una etiqueta que indica uno o más componentes del grupo que consiste de un estado de enfermedad por el cual el compuesto debe administrarse, información de almacenamiento, información de dosificación y/o instrucciones respecto a la forma de administrar el compuesto. En otra variante, el artículo de fabricación comprende el compuesto en una forma de dosificación múltiple.

[00270] En otro de sus aspectos, se provee un método terapéutico que comprende administrar un compuesto de cualquiera de las realizaciones y variantes anteriores a un sujeto.

[00271] En otro de sus aspectos, se provee un método para activar glucoquinasa que comprende poner en contacto glucoquinasa con un compuesto de cualquiera de las realizaciones y variantes anteriores.

[00272] Incluso en otro de sus aspectos, se provee un método para activar glucoquinasa que comprende hacer que un compuesto de cualquiera de las realizaciones y variantes anteriores esté presente en a sujeto para activar la glucoquinasa *in vivo*.

[00273] En otro de sus aspectos, se provee un método para activar glucoquinasa que comprende administrar un primer compuesto a un sujeto que se convierte *in vivo* a un segundo compuesto donde el segundo compuesto activa la glucoquinasa *in vivo*, siendo el segundo compuesto un compuesto de acuerdo con cualquiera de las realizaciones y variantes anteriores.

[00274] En otro de sus aspectos, se provee un método para tratar un estado de enfermedad para la cual el aumento de la actividad de glucoquinasa alivia la patología y/o sintomatología del estado de enfermedad, el método que comprende hacer que un compuesto de cualquiera de las realizaciones y variantes anteriores esté presente en un sujeto en una cantidad eficaz para uso terapéutico para el estado de enfermedad.

[00275] Incluso en otro de sus aspectos, se provee un método para tratar un estado de enfermedad para la cual el aumento de la actividad de glucoquinasa alivia la patología y/o sintomatología del estado de enfermedad, el método que comprende administrar un compuesto de cualquiera de las realizaciones y variantes anteriores a un sujeto, donde el compuesto está presente en el sujeto en una cantidad eficaz para uso terapéutico para el estado de enfermedad.

[00276] En otro de sus aspectos, se provee un método para tratar un estado de

enfermedad para la cual el aumento de la actividad de glucoquinasa alivia la patología y/o sintomatología del estado de enfermedad, el método que comprende administrar un primer compuesto a un sujeto que se convierte *in vivo* a un segundo compuesto donde el segundo compuesto activa la glucoquinasa *in vivo*, siendo el segundo compuesto un compuesto de acuerdo con cualquiera de las realizaciones y variantes anteriores.

[00277] En una variante de cada uno de los métodos anteriores el estado de enfermedad se selecciona del grupo integrado por hiperglucemia, diabetes, dislipidemia, obesidad, resistencia a la insulina, síndrome metabólico X, intolerancia a la glucosa, síndrome del ovario poliquístico, y enfermedad cardiovascular.

Sales, hidratos, y prodrogas de activadores de glucoquinasa

[00278] Debe reconocerse que los compuestos de la presente invención pueden estar presentes y opcionalmente administrarse en 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 convertir los compuestos de la presente invención y usarlos en la forma de sus sales aceptables para uso farmacéutico que derivan de varios ácidos orgánicos e inorgánicos y base de acuerdo con procedimientos bien conocidos en la técnica.

[00279] Cuando los compuestos de la presente invención poVern una forma de base libre, los compuestos se pueden preparar en la forma de una sal de adición de ácido aceptable para uso farmacéutico haciendo reaccionar la forma de base libre del compuesto con un ácido orgánico o inorgánico aceptable para uso farmacéutico, *por ej.*, hidrohaluros tales como clorhidrato, bromhidrato, yohidrato; otros ácidos minerales y sus correspondientes sales tales como sulfato, nitrato, fosfato, etc.; y alquilo y monoarilsulfonatos tales como etansulfonato, toluenosulfonato y bencenosulfonato; y otros ácidos orgánicos y sus correspondientes sales tales como acetato, tartrato, maleato, succinato, citrato, benzoato, salicilato y ascorbato. Otras sales de adición de ácido de la presente invención incluyen, pero sin limitación: adipato, alginato, arginato, aspartato, bisulfato, bisulfito, bromuro, butirato, alcanforato, alcanforsulfonato, caprilato, cloruro, clorobenzoato, ciclopentanopropionato, digluconato, dihidrógenofosfato, dinitrobenzoato, dodecilsulfato, fumarato, galacterato (del ácido múcico), galacturonato, glucoheptoato, gluconato, glutamato, glicerofosfato, hemisuccinato, hemisulfato, heptanoato, hexanoato, hippurato, clorhidrato, bromhidrato, yohidrato, 2-hidroxietansulfonato, yoduro, isetionato, iso-butirato, lactato, lactobionato, malato, malonato, mandelato, metafosfato, metansulfonato, metilbenzoato, monohidrógenofosfato, 2-naftalenosulfonato, nicotinato, nitrato, oxalato, oleato, pamoato, pectinato, persulfato, fenilacetato, 3-fenilpropionato, fosfato, fosfonato y

ftalato. Debe reconocerse que las formas de base libre diferirán típicamente de sus formas de sal respectivas de algún modo en las propiedades físicas tales como solubilidad en solventes polares, pero de otro modo las sales son equivalentes a sus respectivas formas de base libre a los fines de la presente invención.

[00280] Cuando los compuestos de la presente invención poVer una forma de ácido libre, una sal de adición de base aceptable para uso farmacéutico se puede preparar haciendo reaccionar la forma de ácido libre del compuesto con una base orgánica o inorgánica aceptable para uso farmacéutico. Ejemplos de estas bases son hidróxidos de metal alcalino que incluye hidróxidos de potasio, sodio y litio; hidróxido de metal alcalinotérreo tales como bario e hidróxidos de calcio; alcóxido de metal alcalino, por ej., etanolato de potasio y propanolato de sodio; y varias bases orgánicas tales como hidróxido de amonio, piperidina, dietanolamina y N-metilglutamina. Además se incluyen las sales de aluminio de los compuestos de la presente invención. Otras sales de base de la presente invención incluyen, pero sin limitación: sales de cobre, férrica, ferrosa, litio, magnesio, mangánica, manganosa, potasio, sodio y zinc. Las sales de base orgánica incluyen, pero sin limitación, sales de aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen aminas sustituidas que se producen en forma natural, aminas cíclicas y resinas de intercambio iónico básicas, *por ej.*, arginina, betaína, cafeína, cloroprocaína, colina, N,N'-dibenciletilendiamina (benzatina), diciclohexilamina, dietanolamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilendiamina, N-etilmorfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, iso-propilamina, lidocaína, lisina, meglumina, N-metil-D-glucamina, morfolina, piperazina, piperidina, poliamina resinas, procaína, purinas, teobromina, trietanolamina, trietilamina, trimetilamina, tripropilamina y tris-(hidroximetil)-metilamina (trometamina). Debe reconocerse que las formas de ácido libre diferirán típicamente de sus formas de sal respectivas de algún modo en las propiedades físicas tales como solubilidad en solventes polares, pero de otro modo las sales son equivalentes en sus respectivas formas de ácido libre a los fines de la presente invención.

[00281] Los compuestos de la presente invención que comprenden grupos que contienen nitrógeno básico se pueden cuaternizar con agentes tales como haluros de alquilo (C_{1-4}), *por ej.*, cloruros, bromuros y yoduros de metilo, etilo, iso-propilo y ter-butilo,; sulfatos de dialquilo (C_{1-4}), *por ej.*, sulfatos de dimetilo, dietilo y diamilo; haluros de alquilo (C_{10-18}), *por ej.*, cloruros, bromuros y yoduros de decilo, dodecilo, laurilo, miristilo y estearilo; y haluros de arilalquilo (C_{1-4}), *por ej.*, cloruro de bencilo y bromuro de fenetilo. Estas sales permiten la preparación tanto de compuestos hidrosolubles como solubles en aceite de la presente invención.

[00282] Los N-óxidos de los compuestos de acuerdo con la presente invención se pueden preparar mediante métodos conocidos por los expertos en la técnica. Por ejemplo, *los N-óxidos* se pueden preparar tratando una forma no oxidada del compuesto con un agente oxidante (*por ej.*, ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido *meta*-cloroperoxibenzoico, o similares) en un solvente orgánico inerte adecuado (*por ej.*, un hidrocarburo halogenado tal como diclorometano) a aproximadamente 0 °C. En forma alternativa, los N-óxidos de los compuestos se pueden preparar a partir del N-óxido de un material de partida apropiado.

[00283] Los derivados de prodroga de los compuestos de acuerdo con la presente invención se pueden preparar modificando los sustituyentes de los compuestos de la presente invención que se convierten a continuación *in vivo* a un diferente sustituyente. Se observa que en muchos casos, las prodrogas mismas están dentro del alcance del rango de los compuestos de acuerdo con la presente invención. Por ejemplo, las prodrogas se pueden preparar haciendo reaccionar un compuesto con un agente de carbamilación (*por ej.*, 1,1-aciloxialquilocarbonocloridrato, *para*-nitrofenilo carbonato, o similar) o un agente de acilación. Otros ejemplos de métodos para producir prodrogas se describen en Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, pág. 1985.

[00284] Los derivados protegidos de los compuestos de la presente invención también se pueden producir. Ejemplos de técnicas aplicables a la creación de grupos protectores y su eliminación se pueden hallar en T.W. Greene, *Protecting Groups in Organic Synthesis*, 3° edición, John Wiley & Sons, Inc. 1999.

[00285] Los compuestos de la presente invención también se pueden preparar en forma conveniente, o formarse durante el proceso de la invención, en forma de solvatos (*por ej.*, hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar en forma conveniente mediante la recristalización de una mezcla solvente acuosa/orgánica, utilizando solventes orgánicos tales como dioxina, tetrahidrofurano o metanol.

[00286] Una "sal aceptable para uso farmacéutico", como se utiliza en la presente, abarca cualquier compuesto de acuerdo con la presente invención que se utiliza en la forma de una sal del mismo, especialmente donde la sal confiere sobre el compuesto propiedades farmacocinéticas mejoradas en comparación con la forma libre del compuesto o una forma de sal diferente del compuesto. La sal aceptable para uso farmacéutico además puede conferir inicialmente propiedades farmacocinéticas deseables sobre el compuesto que no poseía previamente, e incluso puede afectar en forma positiva la farmacodinámica del compuesto con respecto a su actividad terapéutica en el cuerpo. Un ejemplo de una propiedad farmacocinética que puede afectar en forma favorable es la manera en la cual

el compuesto se transporta a través de la membrana celular, lo cual a su vez puede afectar directa y positivamente la absorción, distribución, biotransformación y excreción del compuesto. Mientras que la vía de administración de la composición farmacéutica es importante, y varios factores anatómicos, fisiológicos y patológicos pueden afectar en forma crítica la biodisponibilidad, la solubilidad del compuesto, usualmente depende del carácter de la forma de la sal particular del mismo, que se utiliza. Un experto en la técnica apreciará que una solución acuosa del compuesto suministrará la absorción más rápida del compuesto en el cuerpo de un sujeto que se está tratando, mientras que las soluciones y suspensiones lípidas, como así también las formas de dosificación sólida, darán por resultado una absorción más lenta del compuesto.

Composiciones que comprenden activadores de glucoquinasa

[00287] Una amplia variedad de composiciones y métodos de administración se puede utilizar junto con los compuestos de la presente invención. Estas composiciones pueden incluir, además de los compuestos de la presente invención, excipientes farmacéuticos convencionales, y otros agentes convencionales inactivos para uso farmacéutico. Además, las composiciones pueden incluir agentes activos además de los compuestos de la presente invención. Estos agentes activos adicionales pueden incluir compuestos adicionales de acuerdo con la invención, y/o uno o más de otros agentes activos para uso farmacéutico.

[00288] Las composiciones pueden estar en forma gaseosa, líquida, semi-líquida o sólida, formulada de una manera adecuada para la vía de administración a ser utilizada. Para la administración oral, se utilizan típicamente cápsulas y comprimidos. Para la administración parenteral, se utiliza típicamente la reconstitución de un polvo liofilizado, preparado como se describe en la presente.

[00289] Las composiciones que comprenden los compuestos de la presente invención se pueden administrar o coadministrar por vía oral, parenteral, interaperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposomal, mediante inhalación, vaginal, intraocular, mediante administración local (por ejemplo por catéter o stent), subcutánea, intraadiposa, intraarticular, e intratecal. Los compuestos y/o composiciones de acuerdo con la invención además se pueden administrar o coadministrar en formas de dosificación de liberación lenta.

[00290] Los activadores de glucoquinasa y las composiciones que los comprenden se pueden administrar o coadministrar en cualquier forma de dosificación convencional. La co-administración en el contexto de esta invención significa la administración de más de un agente terapéutico, uno de los cuales incluye una activador de glucoquinasa, en el

curso de un tratamiento coordinado para obtener un resultado clínico mejorado. Esta co-administración además puede ser coextensiva, es decir, producirse durante períodos de tiempo superpuestos.

[00291] Las soluciones o suspensiones que se utilizan para aplicación parenteral, intradérmica, subcutánea, o tópica puede incluir opcionalmente incluyen 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 parabenos de metilo; antioxidantes, tales como ácido ascórbico y bisulfito de sodio; agentes quelantes, tales como ácido etilendiaminatetraacético (EDTA); buffers, tales como acetatos, citratos y fosfatos; agentes para el ajuste de la tonicidad tales como cloruro de sodio o dextrosa, y agentes APRA ajustar la acidez o alcalinidad de la composición, tales como agentes alcalinos o de acidificación o buffers del tipo carbonatos, bicarbonatos, fosfatos, ácido clorhídrico, y ácidos orgánicos del tipo acético y ácido cítrico. Las preparaciones parenterales pueden estar opcionalmente incluidas en ampollas, jeringas descartables o frascos de dosificación simple o múltiple fabricados de vidrio, plástico u otro material adecuado.

[00292] Cuando los compuestos de acuerdo con la presente invención exhiben solubilidad insuficiente, se pueden utilizar métodos para solubilizar los compuestos. Estos métodos son conocidos por los expertos en la técnica, e incluyen, pero sin limitación, el uso de cosolventes, tales como dimetilsulfóxido (DMSO), el uso de tensoactivos, tales como TWEEN, o disolución en bicarbonato de sodio acuoso. Los derivados de los compuestos, tales como prodrogas de los compuestos también se pueden utilizar en la formulación de composiciones farmacéuticas efectivas.

[00293] Al mezclar o agregar los compuestos de acuerdo con la presente invención a una composición, se puede formar una solución, suspensión, emulsión o similar. La forma de la composición resultante dependerá de una cantidad de factores, que incluyen el modo de administración deseado, y la solublidad del compuesto en el vehículo o portador seleccionado. La concentración necesaria para aliviar la enfermedad que se está tratando se puede determinar empíricamente.

[00294] Las composiciones de acuerdo con la presente invención se proveen opcionalmente para su administración a humanos y animales en formas de dosificación unitaria, tales como comprimidos, cápsulas, píldoras, polvos, polvos secos para inhaladores, gránulos, soluciones o suspensiones parenterales estériles, y soluciones o suspensiones orales, y emulsiones de aceite-agua que contienen cantidades adecuadas de los compuestos, en particular las sales aceptables para uso farmacéutico, con preferencia las sales de sodio, de los mismos. Los compuestos activos para uso

farmacéutico y terapéutico y sus derivados se formulan típicamente y se administran en forma de dosificación unitaria o múltiple. Las formas de dosificación unitaria, como se utiliza en la presente, se refiere a unidades físicamente discretas adecuadas 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 activo para uso terapéutico suficiente para producir el efecto terapéutico deseado, en asociación con el vehículo, portador o diluyente farmacéutico requerido. Ejemplos de formas de dosificación unitaria incluyen ampollas y jeringas, comprimidos o cápsulas envasadas en forma individual. Las formas de dosificación unitaria se pueden administrar en fracciones o en forma múltiple. Una forma de dosificación múltiple es una pluralidad de formas de dosificación unitaria idéntica envasada en un solo recipiente para ser administrada en la forma de dosificación unitaria segregada. Ejemplos de formas de dosificación múltiple incluyen frascos, botellas de comprimidos o cápsulas o botellas de pinta o galones. Por lo tanto, la forma de dosificación múltiple es una forma múltiple de dosificación unitaria que no está segregada en envases.

[00295] Además de uno o más compuestos de acuerdo con la presente invención, la composición puede comprender: un diluyente tal como lactosa, sacarosa, fosfato dicálcico, o carboximetilcelulosa; un lubricante, tal como estearato de magnesio, estearato de calcio y talco; y un aglutinante tal como almidón, gomas naturales, tales como acacia gelatina de goma, glucosa, molazas, polvinilpirrolidina, celulosas y sus derivados, povidona, crospovidonas y otros aglutinantes de este tipo conocidos por los expertos en la técnica. Las composiciones líquidas que se administran para uso farmacéutico, por ejemplo, se pueden preparar por disolución, dispersión o de otro modo mezclando un compuesto activo como se definió anteriormente y adyuvantes farmacéuticos opcionales en un vehículo, tal como, por ejemplo, agua, solución salina, dextrosa acuosa, glicerol, glicoles, etanol, y similares, para formar una solución o suspensión. Si se desea, la composición farmacéutica a ser administrada puede contener menores cantidades de sustancias auxiliares tales como agentes humectantes, agentes emulsionantes, o agentes solubilizantes, agentes de buffer de pH y similares, por ejemplo, acetato, citrato de sodio, derivados de ciclodextrina, sorbitan monolaurato, trietanolamina, acetato de sodio, trietanolamina oleato, y otros agentes de este tipo. Los métodos reales para preparar estas formas de dosificación son conocidos en la técnica, o serán evidentes, para los expertos en la técnica; por ejemplo, ver Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15º Edición, 1975. La composición o formulación a ser administrada contendrá, en cualquier caso, una cantidad suficiente de un activador de la presente invención para aumentar la actividad de glucoquinasa *in vivo*, por lo tanto para

tratar el estado de enfermedad del sujeto.

[00296] Las formas de dosificación o composiciones pueden comprender opcionalmente uno o más compuestos de acuerdo con la presente invención en el rango de 0,005% a 100% (peso/peso) con el equilibrio que comprenden sustancias adicionales tales como las que se describen en la presente. Para administración oral, una composición aceptable para uso farmacéutico puede comprender opcionalmente cualquiera de uno o más excipientes empleados normalmente, tales *como,* por ejemplo grados farmacéuticos de manitol, lactosa, almidón, estearato de magnesio, talco, derivados de celulosa, croscarmelosa sódica, glucosa, sacarosa, carbonato de magnesio, sacarina de sodio, talco. Estas composiciones incluyen soluciones, suspensiones, comprimidos, cápsulas, polvos, polvos secos para inhaladores y formulaciones de liberación sostenida, tales como pero sin limitación, implantes y sistemas de administración microencapsulados, y polímeros biodegradables y biocompatibles, tales como colágeno, etilen vinil acetato, polianhídridos, ácido poliglicólico, poliortoésteres, ácido polilláctico y otros. Los métodos para preparar estas formulaciones son conocidos por los expertos en la técnica. Las composiciones pueden contener opcionalmente 0,01%-100% (peso/peso) de uno o más activadores de glucoquinasa, opcionalmente 0,1-95%, y opcionalmente 1-95%.

[00297] Las sales, con preferencia sales de sodio, de los activadores se pueden preparar con vehículos que protegen el compuesto contra la eliminación rápida del cuerpo, tales como las formulaciones o recubrimientos de liberación por tiempo. Las formulaciones pueden incluir además otros compuestos activos para obtener las combinaciones de propiedades deseadas.

Formulaciones para administración oral

[00298] Las formas de dosificación farmacéutica pueden estar en forma sólida, de gel o líquida. Ejemplos de formas de dosificación sólidas incluyen, pero sin limitación comprimidos, cápsulas, gránulos y polvos a granel. Ejemplos más específicos de comprimidos orales incluyen pastillas comprimidas y para chupar, y comprimidos que pueden ser recubiertos entéricos, recubiertos con azúcar o recubiertos con película. Ejemplos de cápsulas incluyen cápsulas de gelatina blanda o dura. Los gránulos y polvos se pueden suministrar en formas efervescentes o no efervescentes. Cada uno puede estar combinada con otros principios conocidos por los expertos en la técnica.

[00299] En ciertas realizaciones, los compuestos de acuerdo con la presente invención se proveen en formas de dosificación sólida, con preferencia cápsulas o comprimidos. Los comprimidos, las píldoras, cápsulas, sellos y similares pueden contener opcionalmente uno o más de los siguientes principios, o compuestos de naturaleza similar: un

aglutinante; un diluyente; un agente desintegrante; un lubricante; un deslizante; un agente endulzante; y un agente saborizante.

[00300] Ejemplos de aglutinantes que se pueden utilizar incluyen, pero sin limitación, celulosa microcristalina, goma tragacanto, solución de glucosa, acacia mucilaginosa, solución de gelatina, sacarosa y pasta de almidón.

[00301] Ejemplos de lubricantes que se pueden utilizar incluyen, pero sin limitación, talco, almidón, estearato de magnesio o calcio, licopodio y ácido esteárico.

[00302] Ejemplos de diluyentes que se pueden utilizar incluyen, pero sin limitación, lactosa, sacarosa, almidón, caolina, sal, manitol y fosfato dicálcico.

[00303] Ejemplos de deslizantes que se pueden utilizar incluyen, pero sin limitación, dióxido de silicio coloidal.

[00304] Ejemplos de agentes desintegrantes que se pueden utilizar incluyen, pero sin limitación, croscarmelosa sódica, glicolato de almidón sódico, ácido algínico, almidón de maíz, almidón de papa, bentonita, metilcelulosa, agar y carboximetilcelulosa.

[00305] Ejemplos de agentes colorantes que se pueden utilizar incluyen, pero sin limitación, cualquiera de las tintas FD y C hidrosolubles certificadas y aprobadas, sus mezclas; y tintas FD y C insolubles en agua suspendidas en alúmina hidrato.

[00306] Ejemplos de agentes endulzantes que se pueden utilizar incluyen, pero sin limitación, sacarosa, lactosa, manitol y agentes endulzantes artificiales tales como ciclamato de sodio y sacarina, y cualquier número de saborizantes secos por aspersión.

[00307] Ejemplos de agentes saborizantes que se pueden utilizar incluyen, pero sin limitación, saborizantes naturales extraídos de plantas tales como frutas y mezclas sintéticas de compuestos que producen una sensación agradable, tales como, pero sin limitación pimienta y salicilato de metilo.

[00308] Ejemplos de agentes humectantes que se pueden utilizar incluyen, pero sin limitación, propilenglicol monoestearato, sorbitan monooleato, dietilenglicol monolaurato y polioxietilen lauril éter.

[00309] Ejemplos de recubrimientos ani eméticos que se pueden utilizar incluyen, pero sin limitación, ácidos grasos, grasas, ceras, lacas, laca amoniaca y acetatos ftalatos de celulosa.

[00310] Ejemplos de recubrimientos de película que se pueden utilizar incluyen, pero sin limitación, hidroxietilcelulosa, carboximetilcelulosa sódica, polietilenglicol 4000 y acetato ftalato de celulosa.

[00311] Si se desea la administración oral, la sal del compuesto se puede proveer opcionalmente en una composición que la protege del medio ácido del estómago. Por ejemplo, la composición puede ser formulada en un recubrimiento entérico que mantiene

su integridad en el estómago y libera el compuesto activo en el intestino. La composición además se puede formular en combinación con un antiácido u otro principio.

[00312] Cuando la forma de dosificación unitaria es una cápsula, puede contener opcionalmente un vehículo líquido tal como un aceite graso. Además, las formas de dosificación unitaria pueden contener opcionalmente varios materiales que modifican la forma física de la unidad de dosificación, por ejemplo, recubrimientos de azúcar y otros agentes entéricos.

[00313] Los compuestos de acuerdo con la presente invención también se pueden administrar como un componente de un elixir, suspensión, jarabe, galleta, rocíos, goma de mascar o similar. Un jarabe puede comprender opcionalmente, además de los compuestos activos, sacarosa como agente endulzante y ciertos conservantes, tintes y colorantes y saborizantes.

[00314] Los compuestos de la presente invención además se pueden mezclar con otros materiales activos que no desequilibran la acción deseada, o con materiales que suplementan la acción deseada, tales como antiácidos, bloqueadores de H2 y diuréticos. Por ejemplo, si un compuesto se utiliza para tratar asma o hipertensión, se puede utilizar con otros broncodilatadores y agentes antihipertensos, respectivamente.

[00315] Ejemplos de vehículos aceptables para uso farmacéutico que se pueden incluir en los comprimidos que comprenden compuestos de la presente invención incluyen, pero sin limitación aglutinantes, lubricantes, diluyentes, agentes desintegrantes, agentes colorantes, agentes saborizantes, y agentes humectantes. Los comprimidos recubiertos entéricos, debido al recubrimiento entérico, resisten la acción ácida del estómago y se disuelven o se desintegran en los intestinos neutros o alcalinos. Los comprimidos recubiertos con azúcar pueden ser comprimidos a los cuales se aplican diferentes capas de sustancias aceptables para uso farmacéutico. Los comprimidos recubiertos con película pueden ser comprimidos que han sido recubiertos con polímeros u otro recubrimiento adecuado. Los comprimidos múltiples pueden ser comprimidos producidos por más de un ciclo de compresión utilizando las sustancias aceptables para uso farmacéutico mencionadas previamente. Los agentes colorantes también se pueden utilizar en los comprimidos. Los agentes saborizantes y endulzantes se pueden utilizar en los comprimidos y son especialmente útiles en la formación de comprimidos y pastillas para chupar.

[00316] Ejemplos de formas de dosificación oral líquidas que se pueden utilizar incluyen, pero sin limitación, soluciones acuosas, emulsiones, suspensiones, soluciones y/o suspensiones reconstituidas a partir de gránulos no efervescentes y preparaciones efervescentes reconstituidas a partir de gránulos efervescentes.

[00317] Ejemplos de soluciones acuosas que se pueden utilizar incluyen, pero sin limitación, elixires y jarabes. Como se utiliza en la presente, los elixires se refieren a preparaciones transparentes, endulzadas, hidroalcohólicas. Ejemplos de vehículos aceptables para uso farmacéutico que se pueden utilizar en los elixires incluyen, pero sin limitación solventes. Ejemplos particulares de solventes que se pueden utilizar incluyen glicerina, sorbitol, alcohol etílico y jarabe. Como se utiliza en la presente, los jarabes se refieren a soluciones acuosas concentradas de un azúcar, por ejemplo, sacarosa. Además los jarabes pueden contener opcionalmente un conservante.

[00318] Las emulsiones se refieren a sistemas bifásicos en los cuales un líquido se dispersa en la forma de pequeños glóbulos a través de otro líquido. Las emulsiones pueden ser opcionalmente emulsiones de aceite-en-agua o agua-en-aceite. Ejemplos de vehículos aceptables para uso farmacéutico que se pueden utilizar en las emulsiones incluyen, pero sin limitación líquidos no acuosos, agentes emulsionantes, y conservantes.

[00319] Ejemplos de sustancias aceptables para uso farmacéutico que se pueden utilizar en gránulos no efervescentes, a ser reconstituidos en una forma de dosificación oral líquida, incluyen diluyentes, endulzantes y agentes humectantes.

[00320] Ejemplos de sustancias aceptables para uso farmacéutico que se pueden utilizar en gránulos efervescentes, a ser reconstituidos en una forma de dosificación oral líquida, incluyen ácidos orgánicos y una fuente de dióxido de carbono.

[00321] Los agentes colorantes y saborizantes se pueden utilizar opcionalmente en todas las formas de dosificación anteriores.

[00322] Ejemplos particulares de conservantes que se pueden utilizar incluyen glicerina, metilo y propilparaben, ácido benzoico, benzoato de sodio y alcohol.

[00323] Ejemplos particulares de líquidos no acuosos que se pueden utilizar in emulsiones incluyen aceite mineral y aceite de semilla de algodón.

[00324] Ejemplos particulares de agentes emulsionantes que se pueden utilizar incluyen gelatina, acacia, tragacanto, bentonita, y tensoactivos tal como polioxietilen sorbitan monooleato.

[00325] Ejemplos particulares de agentes de suspensión que se pueden utilizar incluyen carboximetilcelulosa sódica, pectina, tragacanto, Veegum y acacia. Los diluyentes incluyen lactosa y sacarosa. Los agentes endulzantes incluyen sacarosa, jarabes, glicerina y agentes endulzantes artificiales tales como ciclamato de sodio y sacarina.

[00326] Ejemplos particulares de agentes humectantes que se pueden utilizar incluyen propilenglicol monoestearato, sorbitan monooleato, dietilenglicol monolaurato y polioxietilen lauril éter.

[00327] Ejemplos particulares de ácidos orgánicos que se pueden utilizar incluyen ácido

cítrico y tartárico.

[00328] Fuentes de dióxido de carbono que se pueden utilizar en composiciones efervescentes incluyen bicarbonato de sodio y carbonato de sodio. Los agentes colorantes incluyen cualquiera de las tintas FD y C hidrosolubles certificadas y aprobadas y sus mezclas.

[00329] Ejemplos particulares de agentes saborizantes que se pueden utilizar incluyen saborizantes naturales extraídos de plantas tales como frutas y mezclas sintéticas de los compuestos que producen una sensación de sabor agradable.

[00330] Para una forma de dosificación sólida, la solución o suspensión, en por ejemplo propilen carbonato, aceites vegetales o triglicéridos, está preferentemente encapsulada en una cápsula de gelatina. Estas soluciones y la preparación y encapsulación de las mismas, se divulgan en las Patentes Estadounidenses Nos. 4,328,245; 4,409,239; y 4,410,545. Para una forma de dosificación líquida, la solución, *por ej.*, por ejemplo, en un polietilenglicol, se puede diluir con una cantidad suficiente de un vehículo líquido aceptable para uso farmacéutico, *por ej.*, agua, para ser fácilmente medida para su administración.

[00331] En forma alternativa, las formulaciones orales líquidas o semi-líquidas se pueden preparar disolviendo o dispersando el compuesto activo o sal en aceites vegetales, glicoles, triglicéridos, propilenglicol ésteres (por ej., propilen carbonato) y otros vehículos de este tipo, y encapsulando estas soluciones o suspensiones en cápsulas de gelatina dura o blanda. Otras formulaciones útiles incluyen las que se establecen en las Patentes Estadounidenses Nos. Re 28,819 y 4,358,603.

Inyectables, soluciones y emulsiones

[00332] La presente invención además está dirigida a composiciones diseñadas para administrar los compuestos de la presente invención por administración parenteral, en general caracterizada por inyección subcutánea, intramuscular o intravenosa. Los inyectables se pueden preparar en cualquier forma convencional, por ejemplo en forma de soluciones o suspensiones líquidas, formas sólidas adecuadas para la solución o suspensión en líquido previo a la inyección, o en forma de emulsiones.

[00333] Ejemplos de excipientes que se pueden utilizar en conjunto con inyectables de acuerdo con la presente invención incluyen, pero sin limitación agua, solución salina, dextrosa, glicerol o etanol. Las composiciones inyectables además pueden comprender opcionalmente cantidades menores de sustancias auxiliares no tóxicas tales como agentes humectantes o emulsionantes, agentes de buffer de pH, estabilizantes, mejoradores de la solubilidad, y otros agentes de este tipo, tales como por ejemplo,

acetato de sodio, sorbitan monolaurato, trietanolamina oleato y ciclodextrinas. La implantación de un sistema de liberación lenta o liberación sostenida, de modo que un nivel constante de dosificación se mantiene (ver, *por ej.*, Patente Estadounidense No. 3,710,795) también se contempla en la presente. El porcentaje de compuesto activo contenido en estas composiciones parenterales depende enormemente de la naturaleza específica de la misma, como así también la actividad del compuesto y las necesidades del sujeto.

[00334] La administración parenteral de las formulaciones incluye administraciones intravenosa, subcutánea e intramuscular. Las preparaciones para la administración parenteral incluyen soluciones estériles listos para la inyección, productos solubles secos estériles, tales como los polvos liofilizados descriptos en la presente, listos para ser combinados con un solvente justo antes de su uso, incluyendo comprimidos hipodérmicos, suspensiones estériles listas para inyección, productos insolubles secos estériles listos para ser combinados con un vehículo justo antes de su uso y emulsiones estériles. Las soluciones pueden ser acuosas o no acuosas.

[00335] Cuando se administran por vía intravenosa, ejemplos de vehículos adecuados incluyen, pero sin limitación solución salina fisiológica o solución salina tamponada con fosfato (PBS), y soluciones que contienen agentes espesantes y solubilizantes, tales como glucosa, polietilenglicol, y polipropilenglicol y mezclas de los mismos.

[00336] Ejemplos de vehículos aceptables para uso farmacéutico que se pueden utilizar opcionalmente en preparaciones parenterales incluyen, pero sin limitación vehículos acuosos, vehículos no acuosos, agentes antimicrobianos, agentes isotónicos, buffers, antioxidantes, anestésicos locales, agentes de suspensión y dispersión, agentes emulsionantes, agentes secuestrantes o quelantes y otras sustancias aceptables para uso farmacéutico.

[00337] Ejemplos de vehículos acuosos que pueden ser utilizados opcionalmente incluyen inyección de cloruro de sodio, inyección Ringers, inyección de dextrosa isotónica, inyección de agua estéril, dextrosa e inyección Ringers de lactato.

[00338] Ejemplos de vehículos parenterales no acuosos que se pueden utilizar y opcionalmente incluyen aceites fijos de origen vegetal, aceite de semilla de algodón, aceite de maíz, aceite de sésamo y aceite de maní.

[00339] Agentes antimicrobianos en concentraciones bacteriostáticas o fungistáticos se pueden agregar a las preparaciones parenterales, en particular cuando las preparaciones se envasan en recipientes de múltiples dosis y de este modo diseñadas para ser almacenadas y múltiples alícuotas para ser eliminadas. Ejemplos de agentes antimicrobianos que se pueden utilizar incluyen fenoles o cresoles, mercuriales, alcohol

bencílico, clorobutanol, metilo y propilo, ésteres del ácido p-hidroxibenzoico, timerosal, cloruro de benzalconio y cloruro de bencetonio.

[00340] Ejemplos de agentes isotónicos que se pueden utilizar incluyen cloruro de sodio y dextrosa. Ejemplos de buffers que se pueden utilizar incluyen fosfato y citrato. Ejemplos de antioxidantes que se pueden utilizar incluyen bisulfato de sodio. Ejemplos de anestésicos locales que se pueden utilizar incluyen clorhidrato de procaína. Ejemplos de agentes de suspensión y dispersión que se pueden utilizar incluyen carboximetilcelulosa sódica, hidroxipropil metilcelulosa y polivinilpirrolidona. Ejemplos de agentes emulsionantes que se pueden utilizar incluyen Polisorbato 80 (TWEEN 80). Un agente secuestrante o quelante de iones metálicos incluye EDTA.

[00341] Los vehículos farmacéuticos además pueden incluir opcionalmente alcohol etílico, polietilenglicol y propilenglicol para vehículos miscibles en agua e hidróxido de sodio, ácido clorhídrico, ácido cítrico o ácido láctico para ajuste del pH.

[00342] La concentración de un activador en la formulación parenteral se puede ajustar de modo que una inyección administra una cantidad eficaz para uso farmacéutico suficiente para producir el efecto farmacológico deseado. La concentración exacta de un activador y/o dosificación a ser utilizada dependerá finalmente de la edad, el peso y la condición del paciente o animal como se sabe en la técnica.

[00343] Las preparaciones parenterales de dosis única se pueden envasar en una ampolla, un frasco o una jeringa con una aguja. Todas las preparaciones para la administración parenteral deben ser estériles, como es bien conocido y practicado en la técnica.

[00344] Los inyectables se pueden diseñar para administración local y sistémica. Típicamente, una dosificación eficaz para uso terapéutico es formulada de modo que contenga una concentración de al menos aproximadamente 0,1% p/p hasta aproximadamente 90% p/p o más, con preferencia más de 1% p/p del activador de glucoquinasa al tejido o tejidos tratados. El activador puede ser administrado inmediatamente, o se puede dividir en una cantidad de dosis más pequeñas para ser administrada a intervalos de tiempo. Se entiende que la dosificación precisa y la duración del tratamiento será una función de la ubicación de donde la composición debe administrarse por vía parenteral, el vehículo y otras variables que pueden determinar empíricamente utilizando los protocolos de ensayo conocidos o por extrapolación de datos de ensayo *in vivo* o *in vitro*. Se observa que las concentraciones y los valores de dosificación también pueden variar con la edad del individuo tratado. Además debe entenderse que para cualquier sujeto particular, los regímenes de dosificación específicos deben ser ajustados en el tiempo de acuerdo con la necesidad individual y el criterio

profesional de la persona que administra o supervisa la administración de las formulaciones. Por lo tanto, los rangos de concentración establecidos en la presente son a modo de ejemplo y no intentan limitar el alcance o la práctica de las formulaciones reivindicadas.

[00345] El activador de glucoquinasa puede ser opcionalmente suspendido en forma micronizada u otra forma adecuada o puede ser derivatizado para producir un producto activo más soluble o para producir una prodroga. La forma de la mezcla resultante depende de un número de factores, que incluyen el modo deseado de administración y la solubilidad del compuesto en el portador o vehículo seleccionado. La concentración eficaz es suficiente para aliviar los síntomas del el estado de enfermedad y se puede determinar empíricamente.

Polvos liofilizados

[00346] Los compuestos de la presente invención además se pueden preparar en forma de polvos liofilizados, los cuales e pueden reconstituir para administración en forma de soluciones, emulsiones y otras mezclas. Los polvos liofilizados se pueden formular además en forma de sólidos o geles.

[00347] El polvo liofilizado, estéril, se puede preparar disolviendo el compuesto en una solución de buffer de fosfato de sodio que contiene dextrosa u otro excipiente adecuado. La filtración estéril subsiguiente de la solución seguida de liofilización en condiciones estándar conocidas por los expertos en la técnica provee la formulación deseada. En pocas palabras. El polvo liofilizado se puede preparar opcionalmente disolviendo dextrosa, sorbitol, fructosa, jarabe de maíz, xilitol, glicerina, glucosa, sacarosa u otro agente adecuado, aproximadamente 1-20%, con preferencia aproximadamente 5 a 15%, en un buffer adecuado, tales como citrato, fosfato de sodio o potasio u otro buffer de este tipo conocido por los expertos en la técnica, típicamente a aproximadamente pH neutro. A continuación, se agrega un activador de glucoquinasa a la mezcla resultante, con preferencia por encima de temperatura ambiente, con mayor preferencia a aproximadamente 30-35°C, y se agita hasta que se disuelve. La mezcla resultante se diluye agregando más buffer a una concentración deseada. La mezcla resultante se filtra estéril o se trata para eliminar las partículas y para asegurar la esterilidad, y se divide en frascos para liofilización. Cada frasco puede contener una dosificación simple o dosificaciones múltiples del activador.

Administración tópica

[00348] Los compuestos de la presente invención además se pueden administrar en forma

de mezclas tópicas. Las mezclas tópicas se pueden utilizar para administración local y sistémica. La mezcla resultante puede ser una solución, suspensión, emulsiones o similares y se formulan como cremas, geles, ungüentos, emulsiones, soluciones, elixires, lociones, suspensiones, tinturas, pastas, espumas, aerosoles, irrigaciones, esprays, supositorios, vendajes, parches dérmicos o cualquier otra formulación adecuada para administración tópica.

[00349] Los activadores de glucoquinasa se pueden formular en forma de aerosoles para aplicación tópica, tales como por inhalación (ver, Patentes Estadounidenses Nos. 4,044,126, 4,414,209, y 4,364,923, las cuales describen aerosoles para la administración de un esteroide útiles para el tratamiento de enfermedades inflamatorias, en particular asma). Estas formulaciones para administración al tracto respiratorio pueden estar en la forma de un aerosol o solución para un nebulizador, o en forma de polvo microfino para insuflación, sola o en combinación con un vehículo inerte tal como lactosa. En ese caso, las partículas de la formulación tendrán, típicamente, diámetros inferiores a 50 micrones, con preferencia inferiores a 10 micrones.

[00350] Los activadores se pueden formular para aplicación local o tópica, tales como para aplicación tópica a la piel y a las membranas mucosas, tal como en el ojo, en la forma de geles, cremas, y lociones y para aplicación al ojo o para aplicación intracisterna o intraespinal. La administración tópica se contempla para administración transdérmica y además para administración a los ojos o mucosa, o para terapias de inhalación. Las soluciones nasales del activador de glucoquinasa solas o en combinación con otros excipientes aceptables para uso farmacéutico también se pueden administrar.

Formulaciones para otras vías de administración

[00351] Dependiendo del estado de enfermedad a ser tratada, otras vías de administración, tales como aplicación tópica, parches transdérmicos, y administración rectal, también se pueden utilizar. Por ejemplo, las formas de dosificación farmacéutica para administración rectal son supositorios rectales, cápsulas y comprimidos para efecto sistémico. Los supositorios rectales se utilizan en la presente como cuerpos sólidos para inserción en el recto que se funden o derriten a la temperatura corporal liberando uno o más principios activos para uso farmacológico o terapéutico. Las sustancias aceptables para uso farmacéutico utilizadas en los supositorios rectales son bases o vehículos y agentes para elevar el punto de fusión. Ejemplos de bases incluyen manteca cacao (aceite teobroma), glicerina-gelatina, carbowax, (polioxietilenglicol) y mezclas apropiadas de mono-, di- y triglicéridos de ácidos grasos. Se pueden utilizar combinaciones de varias bases. Los agentes para elevar el punto de fusión de los supositorios incluyen

espermaceti. Los supositorios rectales se pueden preparar ya sea mediante el método de compresión o mediante moldeado. El peso típico de un supositorio rectal es aproximadamente 2 a 3 gramos. Los comprimidos y cápsulas para administración rectal se pueden producir utilizando la misma sustancia aceptable para uso farmacéutico y mediante los mismos métodos para las formulaciones para administración oral.

Ejemplos de formulaciones

[00352] Los siguientes son ejemplos particulares de formulaciones orales, intravenosas y comprimidos que se pueden utilizar opcionalmente con compuestos de la presente invención. Se observa que estas formulaciones pueden variar dependiendo del compuesto particular compuesto que se utiliza y la indicación para la cual la formulación se va a utilizar.

FORMULACIÓN ORAL

Compuesto de la presente invención	10-100 mg
Monohidrato de ácido cítrico	105 mg
Hidróxido de sodio	18 mg
Saborizante	
Agua	c.s. hasta 100 ml

FORMULACIÓN INTRAVENOSA

Compuesto de la presente invención	0,1-10 mg
Monohidrato Dextrosa	c.s. para hacerla isotónica
Monohidrato de ácido cítrico	1,05 mg
Hidróxido de sodio	0,18 mg
Agua para inyección	c.s. hasta 1,0 ml

FORMULACIÓN DEL COMPRIMIDO

Compuesto de la presente invención	1%
Celulosa microcristalina	73%
Ácido esteárico	25%
Sílice coloidal	1%.

Kits que contienen activadores de glucoquinasa

[00353] La invención además está dirigida a kits y otros artículos de fabricación para tratar enfermedades asociadas con la glucoquinasa. Se observa que las enfermedades

intentan cubrir todas las condiciones por las cuales el aumento de la actividad de glucoquinasa (*por ej.*, regulación por aumento de glucoquinasa) alivia la patología y/o sintomatología de la afección.

[00354] En una realización, se provee un kit que comprende una composición que contiene al menos un activador de la presente invención en combinación con las instrucciones. Las instrucciones pueden indicar el estado de enfermedad por el cual la composición debe administrarse, información de almacenamiento, información de dosificación y/o instrucciones respecto a la forma de administrar la composición. El kit además puede contener materiales de empaque. El material de empaque puede comprender un recipiente para alojar la composición. El kit además puede comprender opcionalmente componentes adicionales, tales como jeringas para administración de la composición. El kit puede comprender la composición en formas de dosificaciones simples o múltiples.

[00355] En otra realización, un artículo de fabricación se provee que comprende una composición que comprende al menos un activador de la presente invención en combinación con materiales de empaque. El material de empaque puede comprender un recipiente para alojar la composición. El recipiente puede comprender opcionalmente una etiqueta que indica el estado de enfermedad por el cual la composición debe administrarse, información de almacenamiento, información de dosificación y/o instrucciones respecto a la forma de administrar la composición. El kit además puede comprender opcionalmente componentes adicionales, tales como jeringas para la administración de la composición. El kit puede comprender la composición en formas de dosificaciones simples o múltiples.

[00356] Se observa que el material de empaque utilizado en los kits y en los artículos de fabricación 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 tener cualquier forma convencional conocida en la técnica la cual está producida de un material aceptable para uso farmacéutico, por ejemplo un papel o una caja de cartón, una botella o tarro de vidrio o plástico, una bolsa que puede cerrarse(por ejemplo, para mantener un "relleno" de comprimidos para colocar en un recipiente diferente), o un blister con dosificaciones individuales para presionar el paquete de acuerdo con un programa terapéutico. El recipiente que se emplea dependerá de la forma de dosificación exacta involucrada, por ejemplo una caja de cartón convencional se utilizaría, en general, para mantener una suspensión líquida. Es factible que se pueda utilizar más de un recipiente juntos en un único envase para comercializar una forma de dosificación simple. Por ejemplo, los comprimidos pueden estar contenidos en una botella que a su vez está contenida en una caja. Típicamente, el kit incluye direcciones para la

administración de los componentes separados. La forma de kit, en particular, es ventajosa cuando los componentes separados se administran, con preferencia, en formas de dosificación diferentes (*por ej.*, oral, tópica, transdérmica y parenteral), se administran a intervalos de dosificación diferentes, o cuando la titulación de los componentes individuales de la combinación está prescripta por el profesional actuante.

[00357] Un ejemplo particular de un kit de acuerdo con la presente invención es el denominado blister. Los blisteres son bien conocidos en la industria del envasado y se utilizan ampliamente para el envasado de formas de dosificación unitaria farmacéutica (comprimidos, cápsulas, y similares). En general, los blisteres consisten de una lámina de material relativamente rígido cubierto con una lámina de metal de material plástico preferentemente transparente. Durante el proceso de empaque se forman huecos en la lámina plástica. Los huecos tienen el tamaño y la forma de loa comprimidos o las cápsulas individuales a ser envasadas o pueden tener la forma y el tamaño para acomodar los múltiples comprimidos y/o cápsulas a ser envasadas. A continuación, los comprimidos o las cápsulas se colocan en los huecos y la lámina de material relativamente rígido se sella contra la lámina de materiál plástico en el frente de la lámina de aluminio la cual está opuesta a la dirección en la cual se forman los huecos. Como resultado, los comprimidos o las cápsulas se sellan en forma individual o colectiva, según se deVer, en el huecos entre la lámina de aluminio y la lámina de plástico. Con preferencia la resistencia de la lámina es tal que los comprimidos o las cápsulas pueden ser removidas del blister en forma manual aplicando presión en los huecos por lo que se forma una abertura en la lámina en el lugar del hueco. El comprimido o la cápsula se puede remover a través de dicha abertura.

[00358] Otra realización específica de un kit es a expendedor diseñado para distribuir las dosificaciones diarias una por vez en el orden del uso destinado. Con preferencia, el expendedor está equipado con una ayuda memoria, para facilitar el cumplimiento con el régimen. Un ejemplo de este tipo de ayuda memoria es un contador mecánico que indica la cantidad de dosis diarias que han sido distribuidas. Otro ejemplo de este tipo de ayuda memoria es una memoria con micro-chip alimentada por batería acoplada con un lector de cristal líquido, o una señal recordatoria audible la cual, por ejemplo, lee la fecha en que se ha tomado la última dosis diaria y/o recuerda cuando debe tomarse la próxima dosis.

Dosificación, huésped y seguridad

[00359] Los compuestos de la presente invención son estables y se pueden utilizar en forma segura. En particular, los compuestos de la presente invención son útiles como activadores de glucoquinasa para una variedad de sujetos (*por ej.*, humanos, mamíferos

no humanos y no-mamíferos). La dosis óptima puede variar dependiendo de estas condiciones, tales como, por ejemplo, el tipo de sujeto, el peso corporal del sujeto, la vía de administración, y las propiedades específicas del compuesto particular que se utiliza. En general, la dosis diaria para administración oral a un adulto (peso corporal de aproximadamente 60 kg) es aproximadamente 1 a 1000 mg, aproximadamente 3 a 300 mg, o aproximadamente 10 a 200 mg. Se apreciará que la dosis diaria se puede dar en una administración simple o en porciones múltiples (*por ej.*, 2 o 3) al día.

Terapias combinadas

[00360] Una amplia variedad de agentes terapéuticos pueden tener un efecto aditivo terapéutico o sinérgico con los activadores de GK de acuerdo con la presente invención. En particular, la presente invención además se refiere al uso de los activadores de GK de la presente invención en combinación con uno o más compuestos antidiabéticos. Ejemplos de estos compuestos antidiabéticos incluyen, pero sin limitación proteasas S9, del tipo inhibidores de dipeptidil peptidasa IV (DPP-IV); moduladores de la vía de señalización de insulina, del tipo inhibidores de la proteína tirosina fosfatasa (PTPasa), e inhibidores de glutamina-fructosa-6-fosfato amidotransferasa (GFAT); compuestos que influyen una producción de glucosa hepática desregulada, del tipo inhibidores de glucosa-6-fosfatasa (G6Pasa), inhibidores de fructosa-1,6-bisfosfatasa (F-1,6-BPasa), glucogen fosforilasa (GP), antagonistas del receptor glucagon e inhibidores de fosfoenolpiruvato carboxiquinasa (PEPCK); inhibidores de piruvato dehidrogenoasa quinasa (PDHK); mejoradores de la sensibilidad a la insulina (sensibilizadores de insulina); mejoradores de la secreción de insulina (secretagogos de insulina); inhibidores de alfa-glucosidasa; inhibidores de vaciamiento gástrico; otros activadores de glucoquinasa (GK); agonistas del receptor GLP-1; moduladores de UCP; moduladores de RXR; inhibidores de GSK-3; moduladores de PPAR; metformina; insulina; y antagonistas α_2-adrenérgicos.

[00361] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente inhibidores de DPP-IV seleccionados del grupo integrado por Alogliptin (Nesina; Takeda Pharmaceutical Company Limited), Sitagliptin (Januvia; Merck), Saxagliptin (Ongliza; Bristol Myers Squibb), y Vildagliptin (Galvus; Novartis). Además, el uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente inhibidores de DPP-IV combinados con metformina tales como, por ejemplo, Alogliptin más metformina (Takeda Pharmaceutical Company Limited), Sitagliptin más metformina (Janumet; Merck), Saxagliptin más metformina (Bristol Myers Squibb), y Vildagliptin más metformina

(Eucreas; Novartis).

[00362] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente seleccionados del grupo integrado por inhibidores de proteína tirosina fosfatasa, inhibidores de glutamina-fructosa-6-fosfato amidotransferasa, inhibidores de glucosa-6-fosfatasa, inhibidores de fructosa-1,6-bisfosfatasa, inhibidores de glucógeno fosforilasa, antagonistas del receptor glucagon, inhibidores de fosfoenolpiruvato carboxiquinasa, inhibidores de piruvato dehidrogenoasa quinasa, inhibidores de alfa-glucosidasa, inhibidores de vaciamiento gástrico, activadores de glucoquinasa, agonistas del receptor GLP-1, agonistas del receptor GLP-2, moduladores de UCP, moduladores de RXR, inhibidores de GSK-3, moduladores de PPAR, metformina, insulina, y antagonistas α_2-adrenérgicos.

[00363] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente seleccionados del grupo integrado por inhibidores de GSK-3, agonistas receptor del retinoide X, agonistas de Beta-3 AR, moduladores de UCP, tiazolidindionas antidiabéticas, agonistas de PPAR gamma del tipo no-glitazona, agonistas duales PPAR gamma/PPAR alfa, compuestos que contiene vanadio antidiabético y biguanidas.

[00364] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente tiazolidindionas seleccionadas del grupo integrado por (S)-(3,4-dihidro-2-(fenil-metil)-2H-1-benzopiran-6-il)metil-tiazolidin-2,4-diona, 5-{[4-(3-(5-metil-2-fenil-4-oxazolil)-1-oxo-propil)-fenil]-metil}-tiazolidin-2,4-diona, 5-{[4-(1-metil-ciclohexil)metoxi)-fenil]metil]-tiazolidin-2,4-diona, 5-{[4-(2-(1-indolil)etoxi)fenil]metil}-tiazolidin-2,4-diona, 5-{4-[2-(5-metil-2-fenil-4-oxazolil)-etoxi)]bencil}-tiazolidin-2,4-diona, 5-(2-naftilsulfonil)-tiazolidin-2,4-diona, bis{4-[(2,4-dioxo-5-tiazolidinil)-metil]fenil}metan, 5-{4-[2-(5-metil-2-fenil-4-oxazolil)-2-hidroxietoxi]-bencil}- -tiazolidin-2,4-diona, 5-[4-(1-fenil-1-ciclopropancarbonilamino)-bencil]-tiazolidin-2,4-diona, 5-{[4-(2-(2,3-dihidroindol-1-il)etoxi)fenilmetil)-tiazolidin-2,4-diona, 5-[3-(4-cloro-fenil])-2-propinil]-5-fenilsulfonil)tiazolidin-2,4-diona, 5-[3-(4-clorofenil])-2-propinil]-5-(4-fluorofenil-sulfonil)tiazolidin-2,4-diona,5-{[4-(2-(metil-2-piridinil-amino)-etoxi)fenil]metil}-tiazolidin-2,4-diona, 5-{[4-(2-(5-etil-2-piridil)etoxi)fenil]-metil}-tiazolidin-2,4-diona, 5-{[4-(3,4-dihidro-6-hidroxi-2,5,7,8-tetrametil-2H-1-benzopiran-2-il)metoxi)-fenil]-metil)-tiazolidin-2,4-diona, 5-[6-(2-fluoro-benciloxi)-naftalen-2-ilmetil]-tiazolidin-2,4-diona, 5-([2-(2-naftil)-benzoxazol-5-il]-metil}tiazolidin-2,4-diona y 5-(2,4-dioxotiazolidin-5-ilmetil)-2-metoxi-N-(4-trifluorometil-bencil)benzamida, incluyendo cualquier sal aceptable para uso farmacéutico de los mismos.

[00365] En una variante, el uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención incluye metformina. En una variante particular, la metformina en esta combinación comprende una o más sales aceptables para uso farmacéutico sales de la misma. En otra variante particular, la metformina en esta combinación comprende una sal HCl metformina. Incluso en otra variante particular más, la metformina en esta combinación es administrada en una dosis diaria entre 125 y 2550 mg. Incluso en otra variante, la metformina en esta combinación es administrada en una dosis diaria entre 250 y 2550 mg.

[00366] En otra variante, el uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención incluye uno o más derivados de sulfonil urea.

[00367] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente seleccionados del grupo integrado por glisoxepid, gliburide, glibenclamida, acetohexamida, cloropropamida, glibornuride, tolbutamida, tolazamida, glipizide, carbutamida, gliquidone, glihexamida, fenbutamida, tolciclamida, glimepiride y gliclazida, que incluye cualquiera de las sales aceptables para uso farmacéutico de los mismos. En una variante, el uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención incluye glimepiride.

[00368] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente seleccionados del grupo integrado por hormonas incretina o imitadores de las mismas, antagonistas del receptor imidazolina de la célula beta, y secretagogos de insulina de corta acción.

[00369] En otra variante, el uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención incluyen insulina.

[00370] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente uno o más agonistas de GLP-1 que incluyen, por ejemplo, extendatide.

[00371] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente uno o más agonistas de GLP-2 que incluyen, por ejemplo, GLP-2 recombinante humano.

[00372] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente uno o más derivados de D-fenilalanina antidiabética.

[00373] El uno o más compuestos antidiabéticos administrados en combinación con los

activadores de GK de la presente invención pueden ser además opcionalmente seleccionados del grupo integrado por repaglinide, mitiglinide, y nateglinide, que incluye cualquiera de las sales aceptables para uso farmacéutico de los mismos. En una variante, el uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención incluyen hidrato de sal de calcio de mitiglinide.

[00374] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente uno o más inhibidores de alfa-glucosidasa.

[00375] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente seleccionados del grupo integrado por acarbose, voglibose y miglitol, que incluye cualquiera de las sales aceptables para uso farmacéutico de los mismos. En una variante, el uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención incluye voglibose. En otra variante, el voglibose en esta combinación es administrado en una dosis diaria entre 0,1 y 1 mg.

[00376] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente rosiglitazone, que incluye cualquiera de las sales aceptables para uso farmacéutico de los mismos. En una variante, la rosiglitazone en esta combinación comprende una sal maleato de rosiglitazone.

[00377] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente tesaglitazar, muraglitazar o naveglitazar, que incluye cualquiera de las sales aceptables para uso farmacéutico de los mismos.

[00378] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención pueden ser además opcionalmente pioglitazona, que incluye cualquiera de las sales aceptables para uso farmacéutico de los mismos. En una variante, la pioglitazona en esta combinación comprende una sal HCl de pioglitazona. En otra variante, la pioglitazona en esta combinación es administrada en una dosis diaria entre 7,5 y 60 mg. Incluso en otra variante, la pioglitazona en esta combinación es administrada en una dosis diaria entre 15 y 45 mg.

[00379] El uno o más compuestos antidiabéticos administrados en combinación con los activadores de GK de la presente invención además pueden comprender opcionalmente metformina y pioglitazona. En una variante, la pioglitazona en esta combinación comprende una o más de sus sales aceptables para uso farmacéutico. En otra variante,

la pioglitazona en esta combinación comprende una sal HCl de pioglitazona. Incluso en otra variante, la pioglitazona en esta combinación es administrada en una dosis diaria entre 7,5 y 60 mg. Incluso en otra variante, la pioglitazona en esta combinación es administrada en una dosis diaria entre 15 y 45 mg. En otra variante de cada una de las variantes anteriores, la metformina en esta combinación comprende una o más de sus sales aceptables para uso farmacéutico. En una variante particular, la metformina en esta combinación comprende una sal HCl de metformina. En otra variante particular, la metformina en esta combinación es administrada en una dosis diaria entre 125 y 2550 mg. Incluso en otra variante, la metformina en esta combinación es administrada en una dosis diaria entre 250 y 2550 mg.

[00380] En el caso de la terapia combinada con compuestos de la presente invención, el otro compuesto antidiabético se puede administrar (*por ej.*, vía y forma de dosificación) de una manera conocida per se para dicho compuesto. Los compuestos de la presente invención y el otro compuesto antidiabético se pueden administrar en forma secuencial (*es decir*, en tiempo separados) o al mismo, ya sea uno detrás de otro en forma separada en dos formas de dosificación separadas o en una sola forma de dosificación combinada. En una realización particular, el otro compuesto antidiabético se administra con los compuestos de la presente invención en forma de una dosificación sola combinada. La dosis del compuesto antidiabético se puede seleccionar del rango conocido a ser empleado clínicamente para dicho compuesto. Cualquiera de los compuestos terapéuticos de las complicaciones diabéticas, compuestos antihiperlipidémicos o compuestos antiobésicos se pueden utilizar en combinación con los compuestos de la presente invención del mismo modo que los compuestos antidiabéticos anteriores.

EJEMPLOS

Preparación de activadores de glucoquinasa

[00381] Se pueden desarrollar varios métodos para sintetizar los compuestos de acuerdo con la presente invención. Los métodos representativos para sintetizar estos compuestos se proveen en los ejemplos. Sin embargo, no se estable que los compuestos de la presente invención además se pueden sintetizar por otros vías de síntesis que se puedan crear.

[00382] Se reconocerá fácilmente que ciertos compuestos de acuerdo con la presente invención tienen átomos con conexiones a otros átomos que confieren una estereoquímica particular al compuesto (*por ej.*, centros quirales). Se reconoce que la síntesis de los compuestos de acuerdo con la presente invención pueden dar por resultado la creación de mezclas de diferentes estereoisómeros (*es decir*, enantiómeros y

diastereómeros). A menos que se especifique una estereoquímica particular, la recitación de un compuesto intenta abarcar todos los posibles y diferentes estereoisómeros.

[00383] En la técnica se conocen varios métodos para separar las mezclas de diferentes estereoisómeros. Por ejemplo, a una mezcla racémica de un compuesto se puede hacer reaccionar con un agente de resolución ópticamente activo para formar un par de compuestos diastereoisoméricos. Los diastereómeros se pueden separar a fin de recuperar los enantiómeros ópticamente activos. Los complejos disociables también se pueden utilizar para resolver los enantiómeros (*por ej.*, sales diastereoméricas cristalinas). Típicamente, los diastereómeros tienen propiedades físicas lo suficientemente distintas (por ej., puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.) y se pueden separar fácilmente tomando ventaja de estas disimilitudes. Por ejemplo, típicamente los diastereómeros se pueden separar por cromatografía o por técnicas de separación/resolución en base a las diferencias en solubilidad. Una descripción más detallada de las técnicas que se pueden utilizar para resolver los estereoisómeros de los compuestos a partir de su mezcla racémica se puede hallar en Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

[00384] Los compuestos de acuerdo con la presente invención también se pueden preparar en forma de una sal de adición de ácido aceptable para uso farmacéutico ácido haciendo reaccionar la forma de base libre del compuesto con un ácido inorgánico u orgánico aceptable para uso farmacéutico. En forma alternativa, un sal de adición de base aceptable para uso farmacéutico de un compuesto se puede preparar haciendo reaccionar la forma de ácido libre del compuesto con una base orgánica o inorgánica aceptable para uso farmacéutico. Los ácidos y bases inorgánicas y orgánicas adecuados para la preparación de las sales aceptables para uso farmacéutico de los compuestos se establecen en la sección definiciones de la presente solicitud. En forma alternativa, las formas de sal de los compuestos se pueden preparar utilizando sales de los materiales de partida o intermediarios.

[00385] Las formas de ácido libre o base libre de los compuestos se pueden preparar a partir de la correspondiente forma de sal de adición de base o sal de adición de ácido. Por ejemplo, un compuesto en una forma de sal de adición de ácido puede convertirse a la correspondiente base libre al tratarlo con una base adecuada (*por ej.*, solución de hidróxido de amonio, hidróxido de sodio, y similares). Un compuesto en una forma de sal de adición de base se puede convertir al correspondiente ácido libre tratándolo con un ácido adecuado (*por ej.*, ácido clorhídrico, etc).

[00386] Los N-óxidos de los compuestos de acuerdo con la presente invención se pueden

preparar mediante métodos conocidos por los expertos en la técnica. Por ejemplo, los *N*-óxidos se pueden preparar tratando una forma no oxidada del compuesto con un agente oxidante (*por ej.*, ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido *meta*-cloroperoxibenzoico, o similares) en un solvente orgánico inerte adecuado (*por ej.*, un hidrocarburo halogenado tal como diclorometano) a aproximadamente 0 °C. En forma alternativa, los N-óxidos de los compuestos se pueden preparar a partir del *N*-óxido de un material de partida apropiado.

[00387] Los compuestos en una forma no oxidada se pueden preparar a partir de *N*-óxidos de los compuestos tratándolos con un agente reductor (*por ej.*, azufre, dióxido sulfúrico, trifenil fosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fósforo, tribromuro, o similar) en un solvente orgánico inerte adecuado (*por ej.*, acetonitrilo, etanol, dioxano acuoso, o similar) a 0ºC hasta 80 °C.

[00388] Los derivados de prodroga de los compuestos se pueden preparar mediante métodos conocidos por los expertos en la técnica (*por ej.*, para otros detalles ver Saulnier *et al.* (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, pág. 1985). Por ejemplo, las prodrogas apropiadas se pueden preparar haciendo reaccionar un compuesto no derivatizado con un agente de carbamilación adecuado (*por ej.*, 1,1-aciloxialquilcarbonocloridrato, *para*-nitrofenil carbonato, o similares).

[00389] Los derivados protegidos de los compuestos se pueden producir mediante métodos conocidos por los expertos en la técnica. Una descripción detallada de las técnicas aplicables a la creación de los grupos protectores y su remoción se puede hallar en T.W. Greene, *Grupos protectores in Organic Synthesis*, 3° edición, John Wiley & Sons, Inc. 1999.

[00390] Los compuestos de acuerdo con la presente invención se pueden preparar en forma conveniente, o formarse durante el proceso de la invención, en forma de solvatos (*por ej.*, hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar en forma conveniente por recristalización a partir de una mezcla solvente acuosa/orgánica, utilizando solventes orgánicos tales como dioxina, tetrahidrofurano o metanol.

[00391] Los compuestos de acuerdo con la presente invención además se pueden preparar como sus estereoisómeros individuales haciendo reaccionar una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diastereoméricos, separando los diastereómeros y recuperando el enantiómero ópticamente puro. Mientras que la resolución de los enantiómeros se puede llevar a cabo utilizando derivados diastereoméricos covalentes de los compuestos, se prefieren los complejos disociables (*por ej.*, sales diastereoméricas cristalinas). Los

diastereómeros tienen distintas propiedades físicas (*por ej.*, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.) y se pueden separar fácilmente tomando ventaja de estas disimilitudes. Los diastereómeros se pueden separar por cromatografía, o, con preferencia, por técnicas de separación/resolución basado en las diferencias en solubilidad. El enantiómero ópticamente puro se recupera, junto con el agente de resolución, mediante cualquier medio práctico que no daría racemización. Una descripción más detallada de las técnicas aplicables a la resolución de los estereoisómeros de los compuestos a partir de su mezcla racémica se puede hallar en Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

[00392] Como se utiliza en la presente los símbolos y convenciones utilizados en estos procesos, esquemas y ejemplos son consistentes con los utilizados en la literatura científica contemporánea, por ejemplo, the Journal of the American Chemical Society o the Journal of Biological Chemistry. Las abreviaturas de una o tres letras estándares se utilizan en general para designar los residuos aminoácidos, los cuales se presume están en la configuración L a menos que se observe de otro modo. A menos que se indique lo contrario, todos los materiales de partida se obtuvieron de proveedores comerciales y se utilizaron sin purificación posterior. Específicamente, las siguientes abreviaturas se pueden utilizar en los ejemplos y a lo largo de la memoria descriptiva.

µL (microlitros)	Ac (acetilo)
atm (atmósfera)	ATP (Adenosina Trifosfatasa)
BOC (ter-butiloxicarbonilo)	BOP (cloruro bis(2-oxo-3-oxazolidinil)fosfínico)
BSA (albúmina de suero bovino)	CBZ (benciloxicarbonilo)
CDI (1,1-carbonildiimidazol)	DCC (diciclohexilcarbodiimida)
DCE (dicloroetano)	DCM (diclorometano)
DMAP (4-dimetilaminopiridina)	DME (1,2-dimetoxietano)
DMF (N,N-dimetilformamida)	DMPU (N,N'-dimetilpropileneurea)
DMSO (dimetilsulfóxido)	EDCI (clorhidrato etilcarbodiimida)
EDTA (ácido etilendiaminatetraacético)	Et (etilo)
Et_2O (dietil éter)	EtOAc (acetato de etilo)
FMOC (9-fluorenilmetoxicarbonilo)	g (gramos)
h (horas)	HOAc o AcOH (ácido acético)
HOBT (1-hidroxibenzotriazol)	HOSu (N-hidroxisuccinimida)

HPLC (cromatografía líquida de alta resolución)	Hz (Hertz)
i.v. (intravenosa)	IBCF (cloroformiato de isobutilo)
i-PrOH (isopropanol)	L (litros)
M (molar)	mCPBA (ácido meta-cloroperbenzoico)
Me (metilo)	MeOH (metanol)
mg (miligramos)	MHz (megahertz)
min (minutos)	ml (mililitros)
mM (milimolar)	mmol (milimoles)
mol (moles)	MOPS (ácido morfolinpropansulfónico)
pf (punto de fusión)	NaOAc (acetato de sodio)
OMe (metoxi)	psi (libras por pulgada cuadrada)
RP (fase inversa)	RT (temperatura ambiente)
SPA (Ensayo de proximidad de centelleo)	TBAF (fluoruro de tetra-n-butilamonio)
TBS (t-butildimetilsililo)	tBu (ter-butilo)
TEA (trietilamina)	TFA (ácido trifluoroacético)
TFAA (anhídrido trifluoroacético)	THF (tetrahidrofurano)
TIPS (triisopropilsililo)	TLC (cromatografía de capa delgada)
TMS (trimetilsililo)	TMSE (2-(trimetilsilil)etilo)
Tr (tiempo de retención)	

[00393] Todas las referencias a éter o Et_2O son dietil éter; y salmuera se refiere a una solución acuosa saturada de NaCl. A menos que se indique lo contrario, todas las temperaturas se expresan en °C (grado centígrado). Todas las reacciones se llevan a cabo bajo un atmósfera inerte a temperatura ambiente a menos que se indique lo contrario.

[00394] Se registraron espectros de ^1H RMN en un Bruker Avance 400. Los cambios químicos se expresan en partes por millón (ppm). Las constantes de acoplamiento son en unidades de Hertz (Hz). Los patrones de división describen multiplicidades aparentes y están diseñados como s (singulete), d (doblete), t (triplete), q (cuarteto), m (multiplete), br (ancho).

[00395] Los espectros de masa de baja resolución (EM) y los datos de pureza del compuesto se adquirieron en sistema Waters ZQ LC/MS single quadrupol equipado con fuente de ionización por electroaspersión (ESI), detector UV (220 y 254 nm), y detector de dispersión de luz evaporativa (ELSD). La cromatografía de capa delgada se realizó sobre

placas de gel de sílice E. Merck de 0,25 mm (60F-254), se visualizó con luz UV, solución al 5% de ácido etanólico fosfomolíbdico, Ninhydrin o p-anisaldehído. La cromatografía de columna flash se realizó sobre gel de sílice (malla 230-400, Merck).

[00396] Los materiales de partida y los reactivos utilizados en la preparación de estos compuestos están disponibles de proveedores comerciales tales como Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), o se pueden preparar mediante métodos bien conocidos por los expertos en la técnica, siguiendo los procedimientos que se describen en referencias estándar tales como Fieser and Fieser's *Reactives for Organic Synthesis*, vols. 1-17, John Wiley y Sons, New York, NY, 1991; *Rodd's Chemistry of Carbon Compounds*, vols. 1-5 y supps., Elsevier Science Publishers, 1989; Organic Reactions, vols. 1-40, John Wiley y Sons, New York, NY, 1991; March J.: *Advanced Organic Chemistry*, 4th ed., John Wiley and Sons, New York, NY; y Larock: *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989.

[00397] Las divulgaciones completas de todos los documentos citados a través de esta solicitud se incorporan a la presente como referencia.

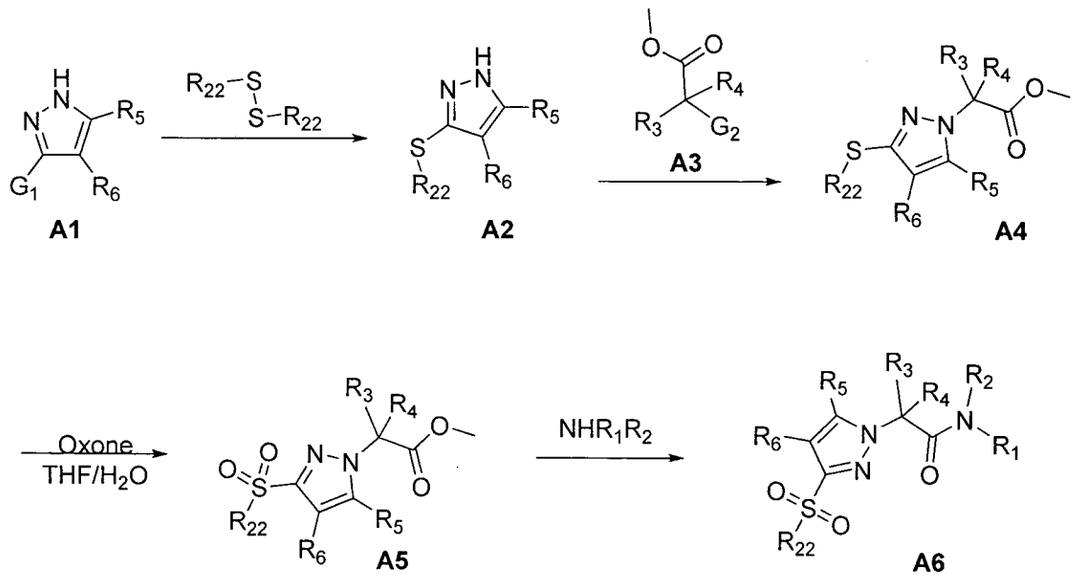
Esquemas de síntesis para los compuestos de la presente invención

[00398] Los compuestos de acuerdo con la presente invención se pueden sintetizar de acuerdo con los esquemas de reacción que se muestran a continuación. Expertos en la técnica pueden crear otros esquemas de reacción. Debe apreciarse además que una variedad de diferentes solventes, temperaturas y otras condiciones de reacción pueden variar para optimizar los rendimientos de las reacciones.

[00399] En las reacciones que se describen en adelante puede ser necesario proteger los grupos funcionales reactivos, por ejemplo grupos hidroxi, amino, imino, tio o carboxi, donde estos se deVern en el producto final, para evitar su participación no deseada en las reacciones. Los grupos protectores convencionales se pueden utilizar de acuerdo con la práctica estándar, por ejemplos ver T.W. Greene y P. G. M. Wuts en "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

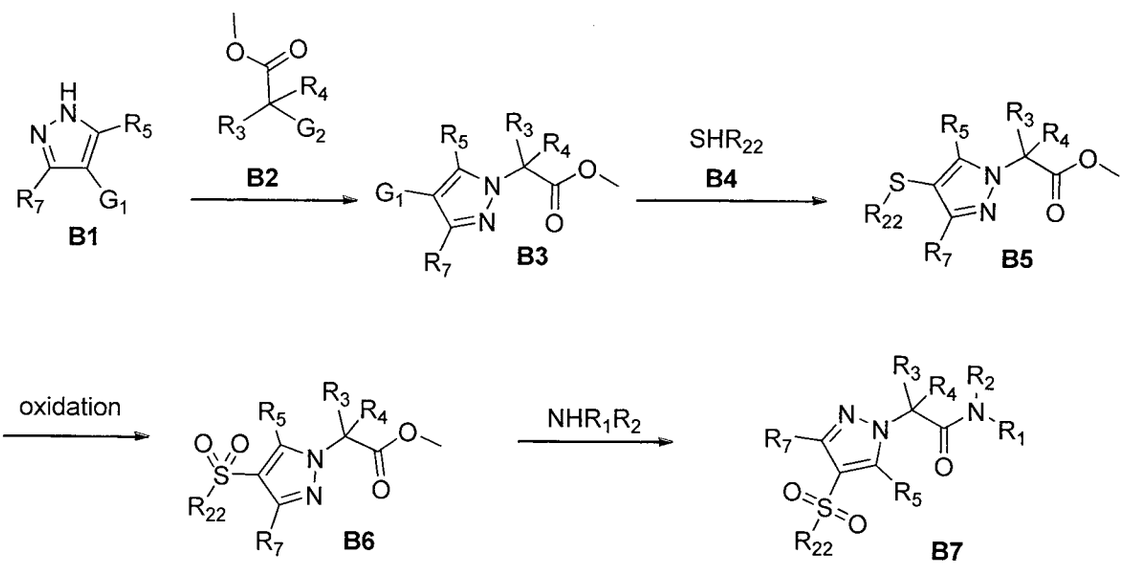
[00400] Las vías de síntesis generales para producir los compuestos de la presente invención se muestran a continuación.

Esquema A



[00401] Con referencia al **Esquema A**, un halo-pirazol (A1, donde G_1 es un grupo saliente (*por ej.*, halo tal como bromo)) y un disulfuro se tratan con NiBr y Zn en presencia de 2,2'-bipiridina para dar intermediarios A2. El tratamiento posterior de A2 con base y reactivo A3 (donde G_2 es un grupo saliente (*por ej.*, halo tal como bromo)) da intermediarios A4. La oxidación de la funcionalidad azufre de A4 con Oxone® da análogos A5 los cuales se tratan a continuación con varias moléculas que contienen amina para dar amidas A6.

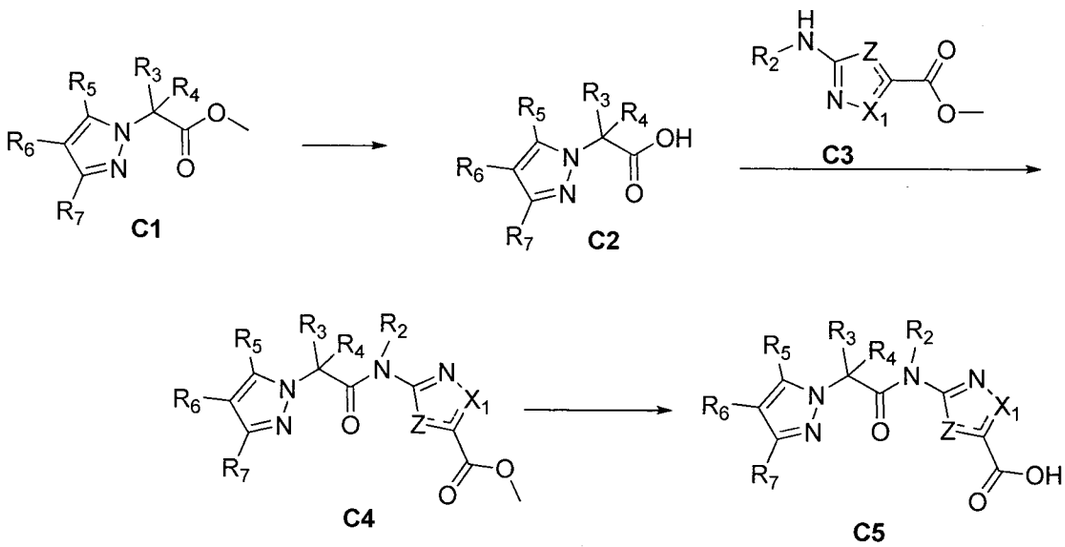
Esquema B



[00402] Con referencia al **Esquema B**, un halo-pirazol (B1, donde G_1 es un grupo saliente (*por ej.*, halo tal como bromo)) se trata con base y reactivo B2 (donde G_2 es un grupo

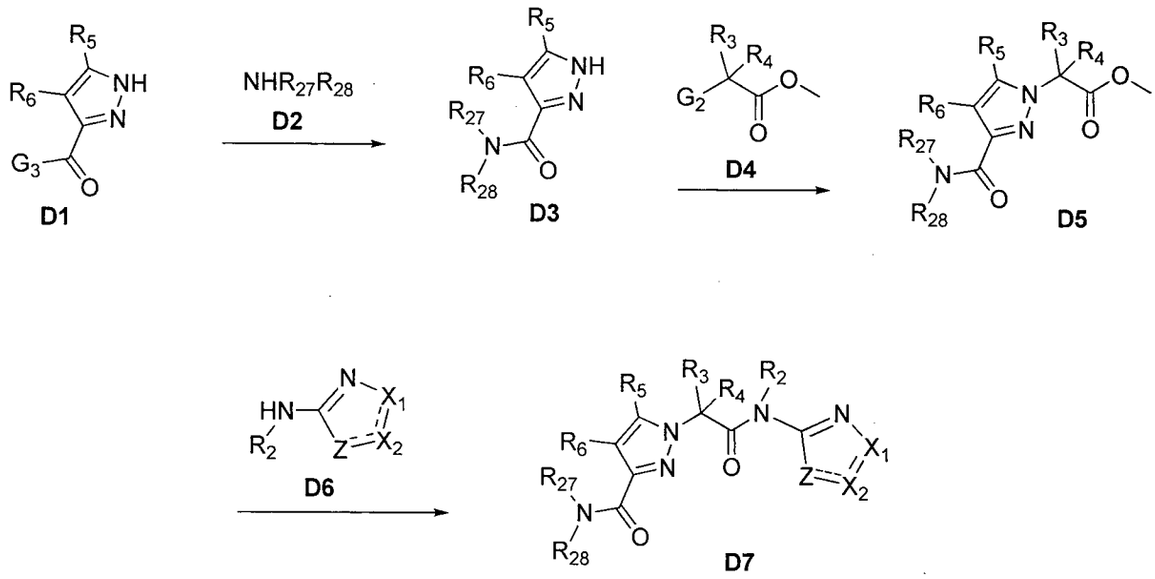
saliente (*por ej.*, halo tal como bromo)) para dar intermediarios B3. El tratamiento posterior de este material con varios mercaptanos en presencia de tris(dibencilacetona)dipaladio y 4,5-bis(difenilfosfino)-9,9-dimetilxanteno da B5. La oxidación de la funcionalidad azufre de B5 da análogos B6 los cuales se tratan con varias moléculas que contienen amina para dar amidas B7.

Esquema C



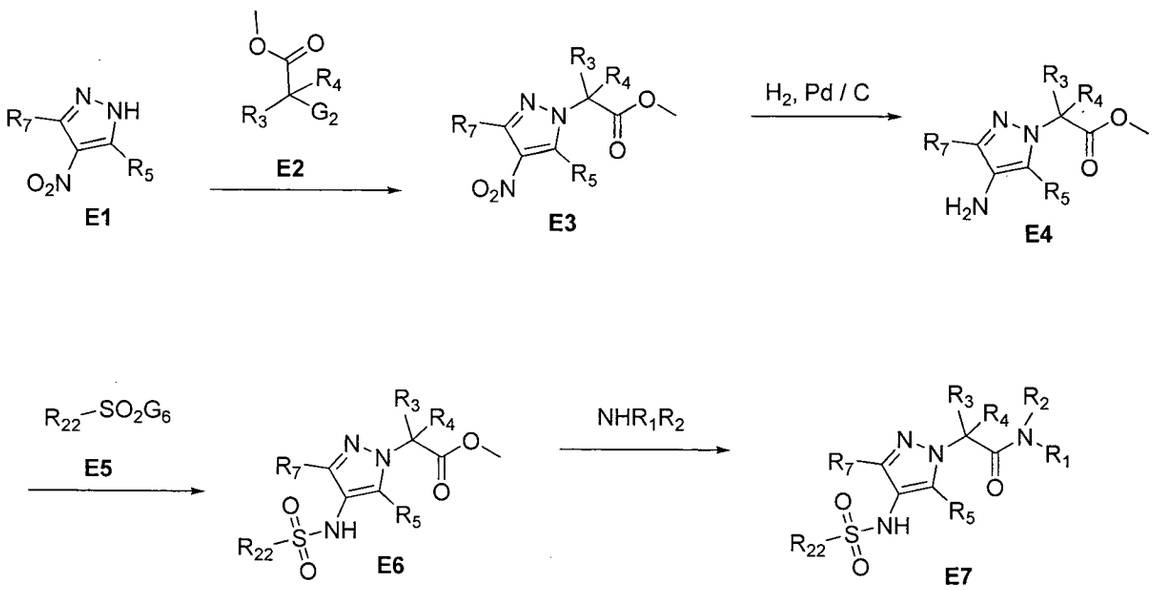
[00403] Con referencia al **Esquema C**, el éster C1 el cual puede ser generado, por ejemplo, de acuerdo con el Esquema B es saponificado al ácido C2 y acoplado con un amino heterociclo C3 para obtener el intermediario C4. Este intermediario al cabo de la saponificación da el compuesto blanco C5.

Esquema D



[00404] Con referencia al **Esquema D**, el intermediario D3 se puede obtener mediante el tratamiento de un cloruro de pirazol-3-carbonilo sustituido (D1, donde G_3 es un grupo saliente (*por ej.*, halo tal como cloro)) con una amina D2 en presencia de una base. La alquilación seguida del acoplamiento con el amino heterociclo D6 puede realizarse utilizando un procedimiento análogo al del Esquema A para obtener el compuesto blanco D7.

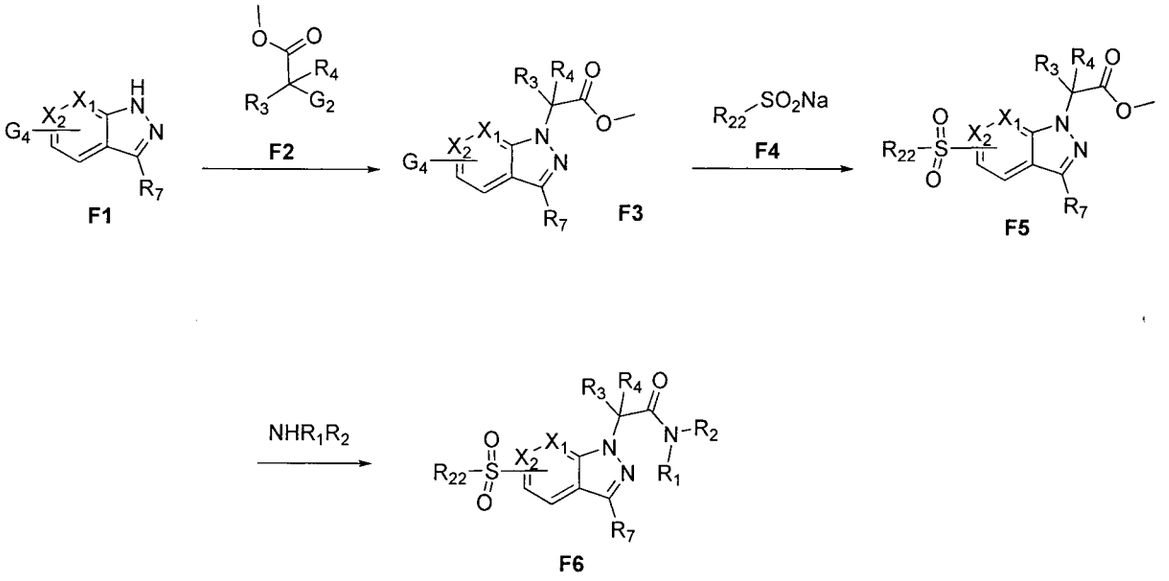
Esquema E



[00405] Con referencia al **Esquema E**, un nitro pirazol E1 se trata con una base y reactivo

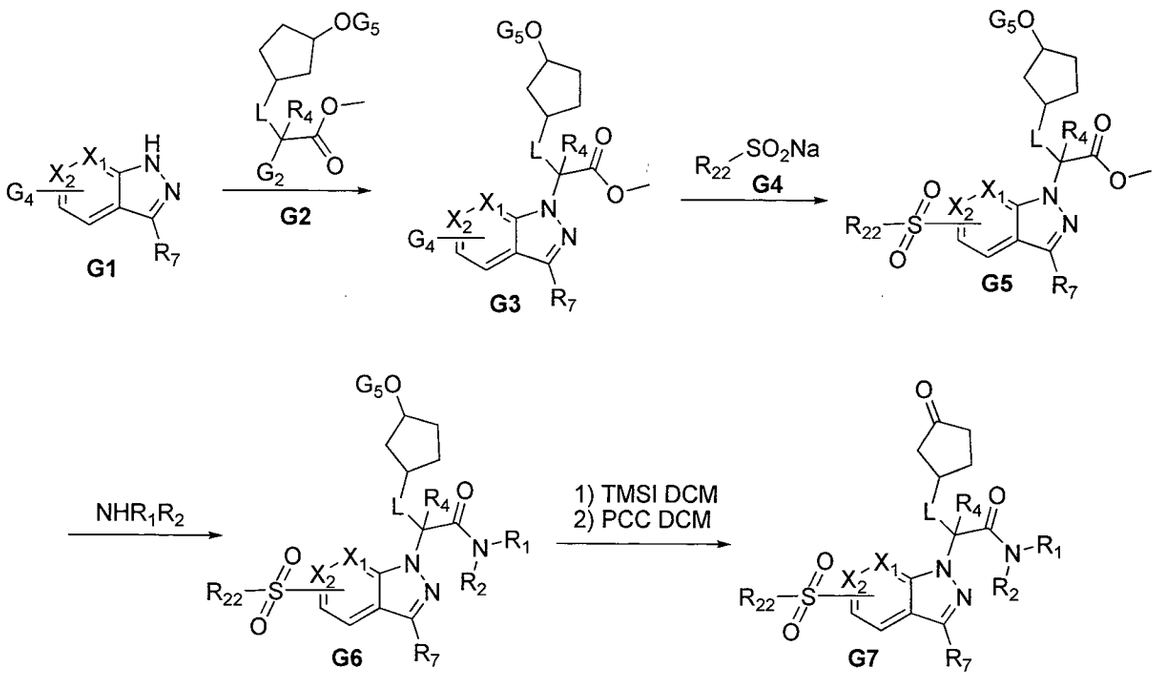
E2 (donde G_2 es un grupo saliente (*por ej.*, halo tal como bromo)) para dar el intermediario E3. La reducción del grupo seguido del tratamiento con un electrófilo E5 (donde G_6 es un grupo saliente (*por ej.*, halo tal como cloro)) en presencia de una base da el intermediario E6. El acoplamiento con una amina da el compuesto blanco E7.

Esquema F



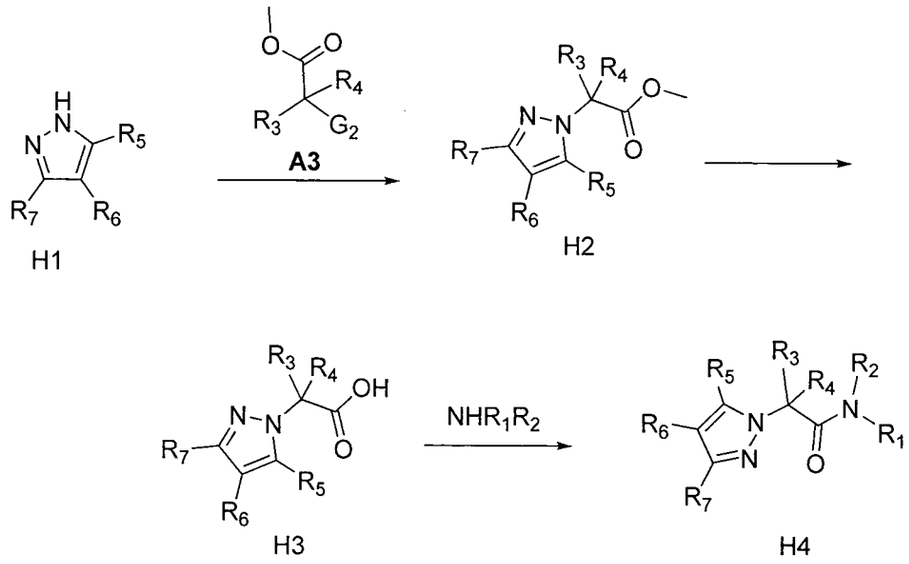
[00406] Con referencia al **Esquema F**, un indazol sustituido (F1, donde G_4 es un grupo saliente (*por ej.*, halo tal como bromo)) se trata con reactivo F2 (donde G_2 es un grupo saliente (*por ej.*, halo tal como bromo)) en presencia de una base para obtener una mezcla de productos alquilados N-1 y N-2 F3 los cuales se pueden separar por cromatografía de columna flash. La introducción del grupo sulfona se puede obtener por acoplamiento en presencia de Pd o Cu para obtener el intermediario F5, el cual a continuación se trata con una amina para obtener el F6 blanco deseado.

Esquema G



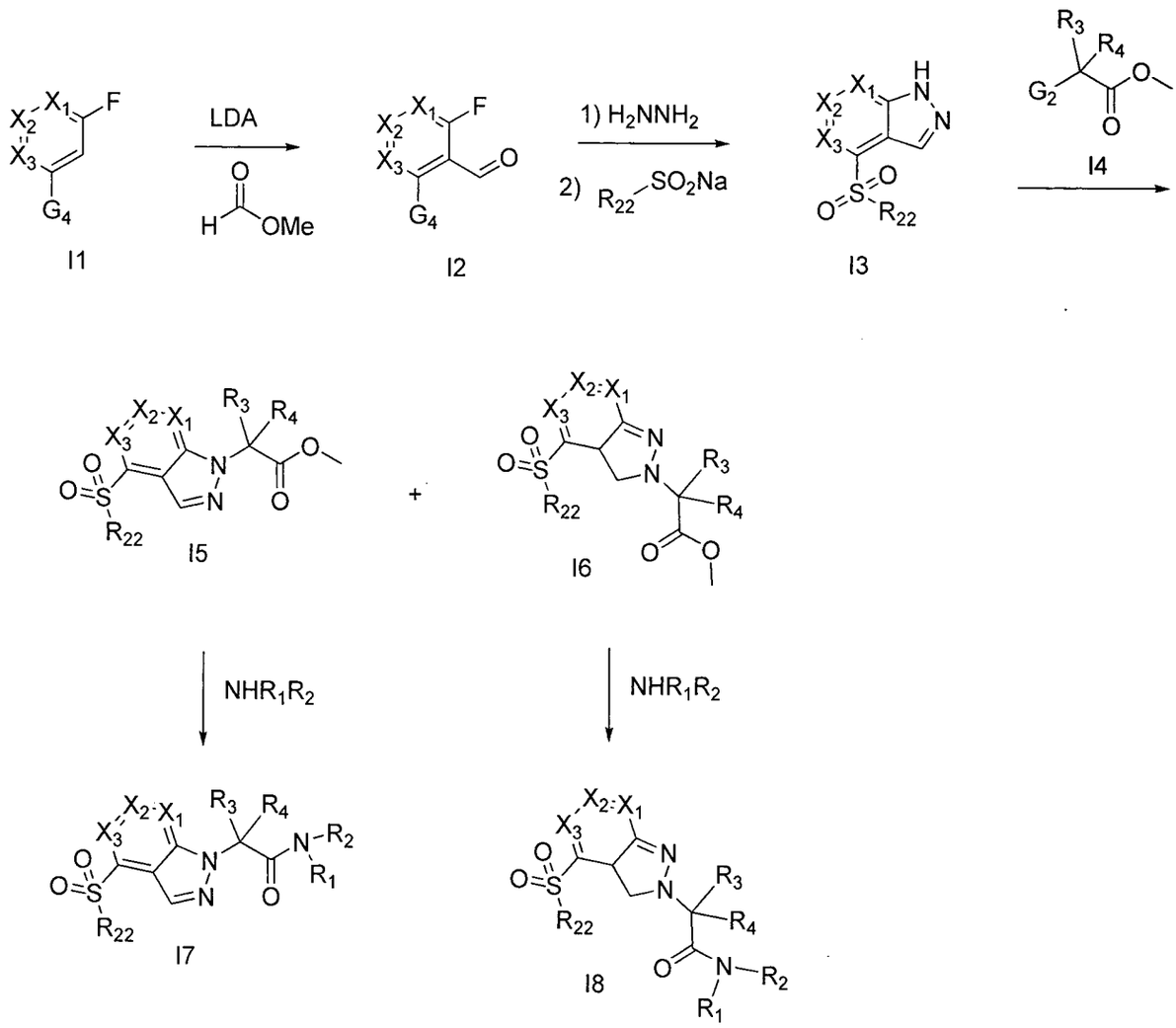
[00407] Con referencia al **Esquema G**, un indazol sustituido (G1, donde G_4 es un grupo saliente (*por ej.*, halo tal como bromo)) se trata con un haluro de alquilo (G2, donde G_2 es un grupo saliente (*por ej.*, halo tal como bromo) y G_5 es un grupo protector (*por ej.*, bencilo)) en presencia de una base para obtener una mezcla de productos alquilados N-1 y N-2 (G3) los cuales se pueden separar por cromatografía de columna flash. La introducción del grupo sulfona se puede obtener por el acoplamiento en presencia de Pd o Cu para obtener el intermediario G5 el cual se trata a continuación con una amina para obtener el intermediario (G6). La desprotección del grupo bencilo seguido de la oxidación del alcohol da el blanco deseado (G7).

Esquema H



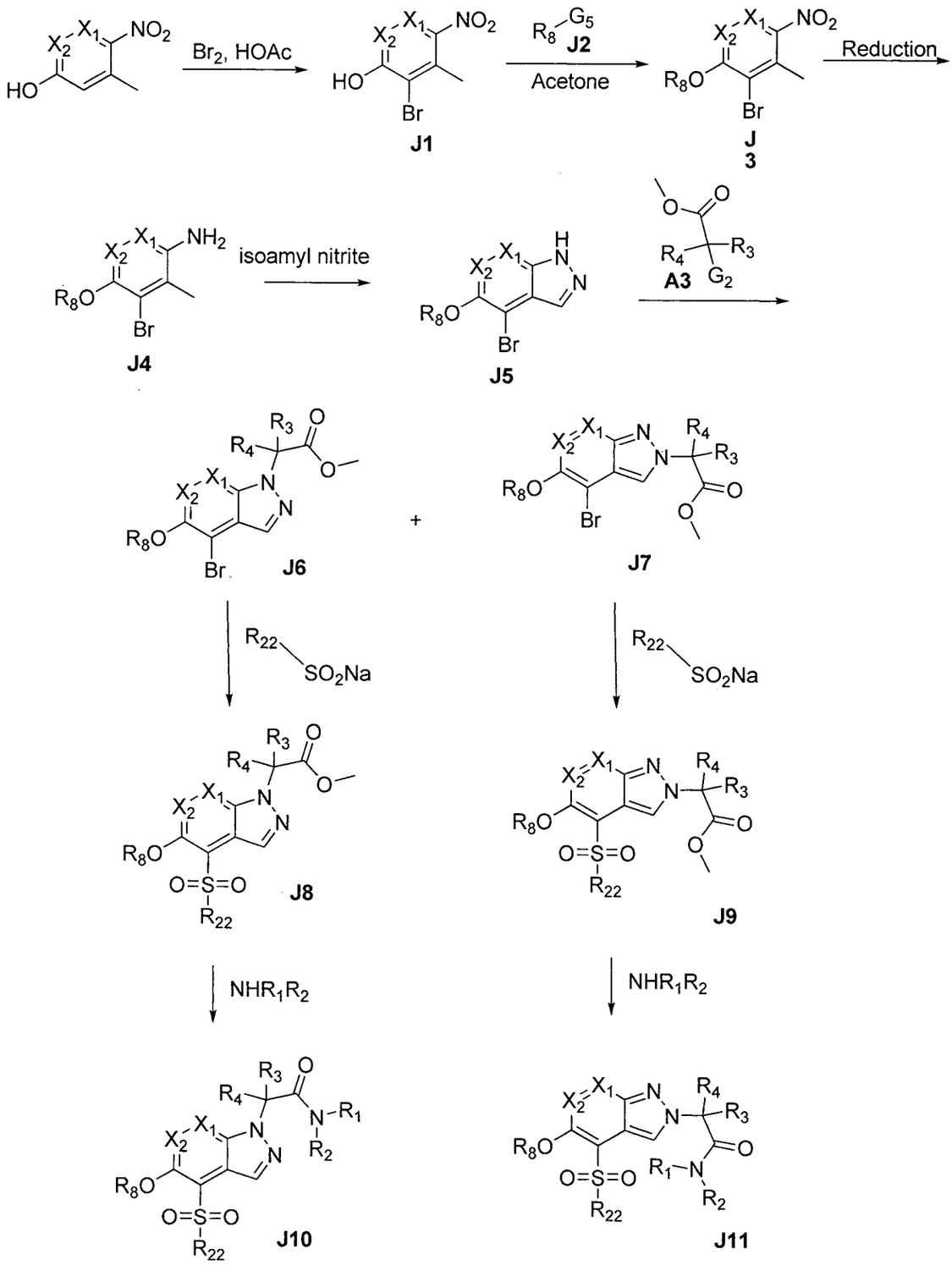
[00408] Con referencia al **Esquema H**, un pirazol sustituido H1, se trata con reactivo A3 (donde G_2 es un grupo saliente (*por ej.*, halo tal como bromo)) en presencia de una base para obtener una mezcla de productos alquilados H2 los cuales se pueden separar por cromatografía de columna. La hidrólisis del éster a H3, seguido del acoplamiento con una amina da el compuesto blanco H4.

Esquema I



[00409] Con referencia al **Esquema I**, la litiación orto de I1, donde G_4 es un grupo saliente (*por ej.*, halo tal como fluoro), seguido de la introducción del orto aldehído al fluoruro da I2. El tratamiento con hidrazina da la hidrazona la cual cicliza a un intermediario indazol al cabo del calentamiento. La introducción del grupo sulfona se puede obtener ya sea por desplazamiento con un sulfinato o por el acoplamiento en presencia de Pd o Cu para obtener el intermediario I3. El indazol I3 se trata con reactivo I4 (donde G_2 es un grupo saliente (*por ej.*, halo tal como bromo)) en presencia de una base para obtener una mezcla de productos alquilados N-1 y N-2 I5 y I6, los cuales se pueden separar por cromatografía de columna flash. El tratamiento de I5 y/o I6 con una amina da los blancos deseados I7 y I8, respectivamente.

Esquema J



[00410] Con referencia al Esquema J, la bromination de 3-metil-4-nitrofenol da una mezcla de regioisómeros los cuales se pueden separar por cromatografía de columna. El tratamiento de J1 con un haluro alquilo (J2, donde G5 es un grupo saliente (por ej., halo

tal como bromo)) en presencia de una base da J3. La reducción del grupo nitro da J4 el cual se puede tratar a continuación con isoamilo nitrito en presencia de una base para obtener el indazol sustituido J5. El indazol sustituido J5 se trata con reactivo A3 (donde G_2 es un grupo saliente (*por ej.*, halo tal como bromo)) en presencia de una base para obtener una mezcla de productos alquilados N-1 y N-2, J6 y J7, los cuales se pueden separar por cromatografía de columna flash. La introducción de un grupo sulfona en J6 y/o J7 se puede obtener por el acoplamiento en presencia de Pd o Cu para obtener los intermediarios J8 y J9, respectivamente. J8 y/o J9 pueden ser tratados, a continuación, con una amina para obtener J10 y J11, respectivamente.

[00411] Los componentes quirales se pueden separar y purificar utilizando cualquiera de una variedad de técnicas conocidas por los expertos en la técnica. Por ejemplo, los componentes quirales se pueden purificar utilizando cromatografía de fluido supercrítico (SFC). En una variante particular, los análisis SFC/EM analíticos quirales se llevaron a cabo utilizando un sistema SFC analítico Berger (AutoChem, Newark, DE) el cual consiste de un módulo de control de fluido de bomba dual SFC Berger con una bomba de fluido supercrítico Berger FCM 1100/1200 y una bomba de fluido modificadora FCM 1200, una estufa Berger TCM 2000n, y un automuestreador Alcott 718. El sistema integrado se puede controlar por software BI-SFC Chemstation versión 3,4. La detección se puede realizar con detector Waters ZQ 2000 operado en modo positivo con una interfaz ESI y un rango de barrido de 200-800 Da con 0,5 segundos por barrido. Las separaciones cromatográficas se pueden realizar sobre una columna ChiralPak AD-H, ChiralPak AS-H, ChiralCel OD-H, o ChiralCel OJ-H (5μ4,6 x 250 mm; Chiral Technologies, Inc. West Chester, PA) con 10 a 40% de metanol como el modificador y con o sin acetato de amonio (10 mM). Cualquiera de una variedad de velocidades de flujo se pueden utilizar que incluyen, por ejemplo, 1,5 o 3,5 ml/min con una presión de entrada establecida a 100 bar. Además, se puede utilizar una variedad de condiciones de inyección de muestra que incluyen, por ejemplo, inyecciones de muestra de o bien 5 o 10 uL en metanol a 0,1 mg/ml en concentración.

[00412] En otra variante, las separaciones quirales preparativas se realizan utilizando un sistema de purificación Berger MultiGram II SFC. Por ejemplo, las muestras se pueden cargar sobre una columna ChiralPak AD (21 x 250 mm, 10 μ). En variantes particulares, la velocidad de flujo para separación puede ser 70 ml/min, el volumen de inyección hasta 2 ml, y la presión de entrada establecida a 130 bar. Las inyecciones apiladas se pueden aplicar para aumentar la eficiencia

[00413] En cada uno de los procedimientos o esquemas de reacción anteriores, los

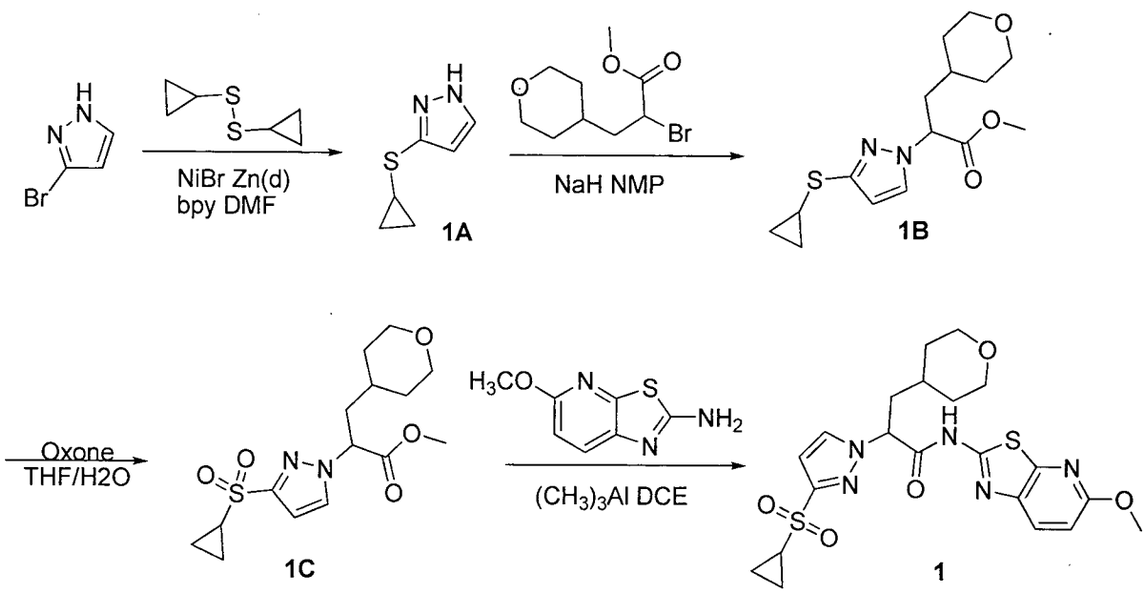
diversos sustituyentes se pueden seleccionar entre los diversos sustituyentes enseñados en la presente.

[00414] Las descripciones de las síntesis de los compuestos particulares de acuerdo con la presente invención que se basan en los esquemas de reacción anteriores se establecen en la presente

Ejemplos de Activadores de glucoquinasa

[00415] La presente invención se ejemplifica además, pero sin limitación, por los siguientes ejemplos que describen la síntesis de compuestos particulares de acuerdo con la invención.

Compuesto 1: 2-(3-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-metoxitiazolo[5,4-b]piridin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida



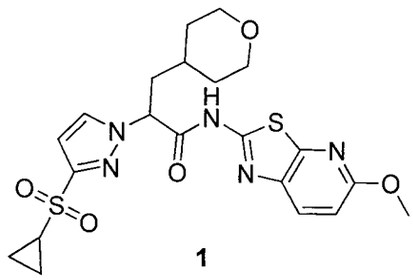
[00416] Se agregaron 3-bromo-1H-pirazol (1,0 g, 6,8 mmol), NiBr (0,148 g, 0,68 mmol), 2,2'-bipiridina (0,106 g, 0,68 mmol), polvo de zinc (0,993 g, 13,6 mmol) y 1,2-diciclopropildisulfano (0,993 g, 6,8 mmol) a una solución de DMF (20 ml) y la mezcla se calentó bajo N_2 durante 18 h a 80°C. El solvente se eliminó de la mezcla de reacción bruta al vacío y la goma de color naranja se trató con MeOH. El ppt resultante se filtró y se descartó. La purificación del filtrado con HPLC en escala preparativa dio el compuesto **1A** en forma de un aceite color marrón claro (367 mg). [M+H] calc. para $C_6H_9N_2S$, 141,04; experimental 141,0. ^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 0,73 (q, *J*=5,05 Hz, 2 H) 1,02 - 1,17 (m, 2 H) 2,26 (ddd, *J*=7,58, 3,66, 3,41 Hz, 1 H) 6,48 (br. s., 1 H) 7,82 (br. s., 1 H).

[00417] Se disolvió 3-(ciclopropiltio)-1H-pirazol (**1A**) (0,083 g, 0,6 mmol) en NMP (2 ml) y la solución se enfrió hasta 0°C. Se agregó NaH (0,060 g, 1,8 mmol) y cuando la reacción bajó se introdujo 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (0,060 g, 1,8 mmol), y la reacción se calentó a 80°C durante 1 h. La reacción se enfrió y se templó con un pequeño volumen de MeOH y la mezcla bruta se purificó utilizando HPLC en escala preparativa. El compuesto **1B** como así también una pequeña cantidad del ácido carboxílico de **1B** se recolectaron. La eliminación del solvente y el tratamiento del ácido con $TMSCH_2N_2$ seguido de la combinación con **1B** dio el compuesto del título en forma de un aceite (81mg). [M+H] calc. para $C_{15}H_{23}N_2O_3S$ (éster **1B**), 311,14; experimental 311,0; [M+H] calc. para $C_{14}H_{21}N_2O_3S$ (ácido **1B**), 297,12; experimental 297,0.

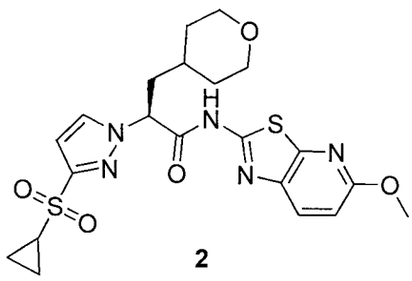
[00418] El compuesto **1B** utilizado directamente del paso precedente se trató con Oxone® (0,147 g, 0,24 mmol) en una solución 1:1 de THF/H_2O (10 ml). Después que la oxidación se consideró completa el solvente se eliminó y el residuo se dividió en porciones entre EtOAc y H_2O. La capa orgánica se separó, se secó y se concentró para dar el compuesto bruto **1C** en forma de un aceite. Este material se purificó utilizando HPLC en escala preparativa y se utilizó directamente en el próximo paso, [M+H] calc. para $C_{15}H_{23}N_2O_5S$, 343,12; experimental 343,3.

[00419] Se agregó 5-Metoxitiazolo[5,4-b]piridin-2-amina (0,048 g, 0,26 mmol) a un frasco para microondas seguido de DCE (2 ml). La mezcla de reacción se enfrió hasta 0°C bajo una atmósfera N2. Se agregó trimetil aluminio (2M en hexanos) (0,13 ml, 0,26 mmol) y cuando la reacción bajó el baño de enfriamiento se eliminó, la solución se agitó a continuación a temperatura ambiente durante 15 min. A esto se agregó una solución de 2-(3-(ciclopropilsulfonil)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanoato de metilo **1C** (0,015 g, 0,04 mmol) en DCE (2ml) y la mezcla de reacción se calentó en un microondas a 110°C durante 1h. La reacción se templó a continuación con HCl 1N y se extrajo 2x con DCM. Las capas orgánicas se reunieron, se secaron sobre Na_2SO_4; el solvente se eliminó y el residuo bruto se purificó por HPLC en escala preparativa para dar el compuesto **1** (46mg). [M+H] calc. para $C_{21}H_{26}N_5O_5S_2$, 492,13; experimental 492,0. ^{1}H RMN (400 MHz, MeOD) d ppm 1,07 (dd, *J*=7,96, 2,15 Hz, 2 H) 1,18 - 1,42 (m, 6 H) 1,52 (d, *J*=9,35 Hz, 1 H) 1,74 (d, *J*=2,02 Hz, 1 H) 2,14 (t, *J*=6,32 Hz, 1 H) 2,32 (t, *J*=10,48 Hz, 1 H) 2,61 - 2,80 (m, 1 H) 3,29 (m, 1 H, bajo señal MeOD) 3,79 - 3,98 (m, 5 H) 5,50 (ddd, *J*=10,80, 5,68, 5,49 Hz, 1 H) 6,81 - 6,90 (m, 2 H) 7,94 (d, *J*=8,84 Hz, 1 H) 8,10 (d, *J*=2,53 Hz, 1 H)

Compuestos 2 y 3: (*S*)-2-(3-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-metoxitiazolo[5,4-b]piridin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida y (*R*)-2-(3-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-metoxitiazolo[5,4-b]piridin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida

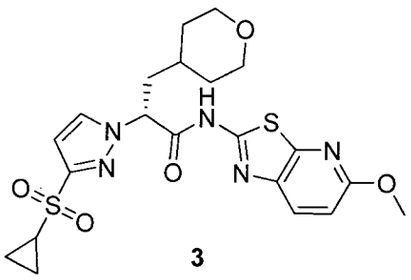


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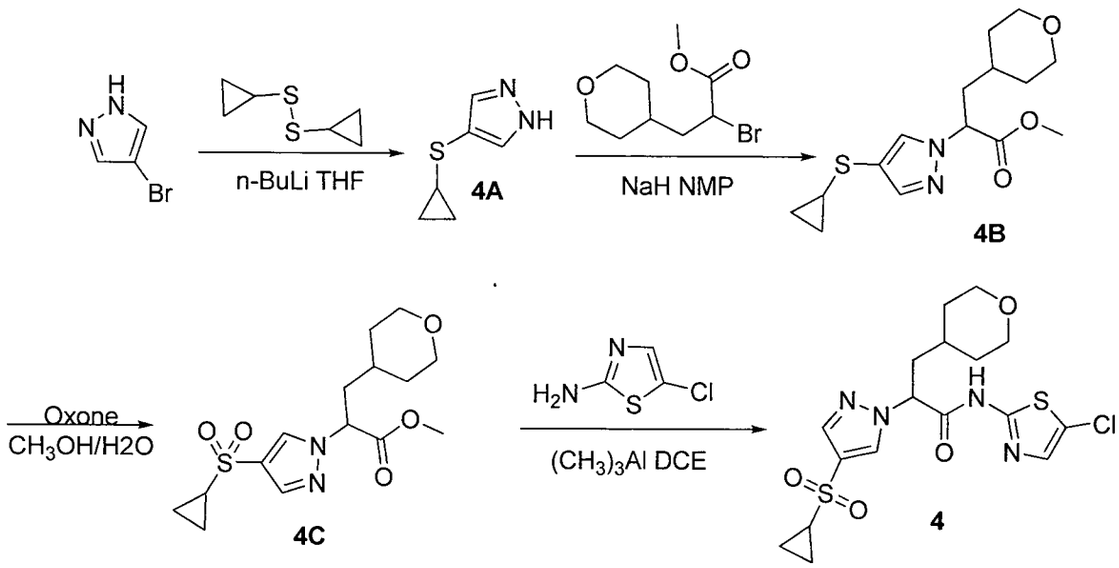
3

[00420] El Compuesto 1 se sometió a separación quiral sobre un instrumento Berger SFC. Para este compuesto particular, se halló que el uso del medio Chiralpak AD-H que eluye con 16% de MeOH para dar los **Compuestos 2** y **3** fue óptimo.

[00421] Compuesto 2: [M+H] calc. para $C_{21}H_{26}N_5O_5S_2$, 492,13; experimental 492,0. ^{1}H RMN (400 MHz, MeOD) δ ppm 1,07 (dd, *J*=7,96, 2,15 Hz, 2 H) 1,18 - 1,42 (m, 6 H) 1,52 (d, *J*=9,35 Hz, 1 H) 1,74 (d, *J*=2,02 Hz, 1 H) 2,14 (t, *J*=6,32 Hz, 1 H) 2,32 (t, *J*=10,48 Hz, 1 H) 2,61 - 2,80 (m, 1 H) 3,29 (m, 1 H, bajo señal de MeOD) 3,79 - 3,98 (m, 5 H) 5,50 (ddd, *J*=10,80, 5,68, 5,49 Hz, 1 H) 6,81 - 6,90 (m, 2 H) 7,94 (d, *J*=8,84 Hz, 1 H) 8,10 (d, *J*=2,53 Hz, 1 H)

[00422] Compuesto 3: [M+H] calc. para $C_{21}H_{26}N_5O_5S_2$, 492,13; experimental 492,0. ^{1}H RMN (400 MHz, MeOD) δ ppm 1,07 (dd, *J*=7,96, 2,15 Hz, 2 H) 1,18 - 1,42 (m, 6 H) 1,52 (d, *J*=9,35 Hz, 1 H) 1,74 (d, *J*=2,02 Hz, 1 H) 2,14 (t, *J*=6,32 Hz, 1 H) 2,32 (t, *J*=10,48 Hz, 1 H) 2,61 - 2,80 (m, 1 H) 3,29 (m, 1 H, bajo señal de MeOD) 3,79 - 3,98 (m, 5 H) 5,50 (ddd, *J*=10,80, 5,68, 5,49 Hz, 1 H) 6,81 - 6,90 (m, 2 H) 7,94 (d, *J*=8,84 Hz, 1 H) 8,10 (d, *J*=2,53 Hz, 1 H)

Compuesto 4: N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida



[00423] Se disolvió 4-bromo-1H-pirazol (4,0 g, 26,9 mmol) en THF (100 ml) y se enfrió hasta 0 °C. Se agregó 1,6 M n-BuLi en THF y la mezcla de reacción se agitó durante 1 h a temperatura ambiente. La reacción se enfrió a continuación hasta 0°C y se agregó 1,2-diciclopropildisulfano (3,9 g, 26,9 mmol); la reacción se agitó durante 1h a 0°C y se templó con NH4Cl sat y se extrajo con EtOAc. El producto bruto se obtuvo en forma de un aceite y se utilizó directamente en el próximo paso. [M+H] calc. para $C_6H_9N_2S$, 141,04; experimental 141,9.

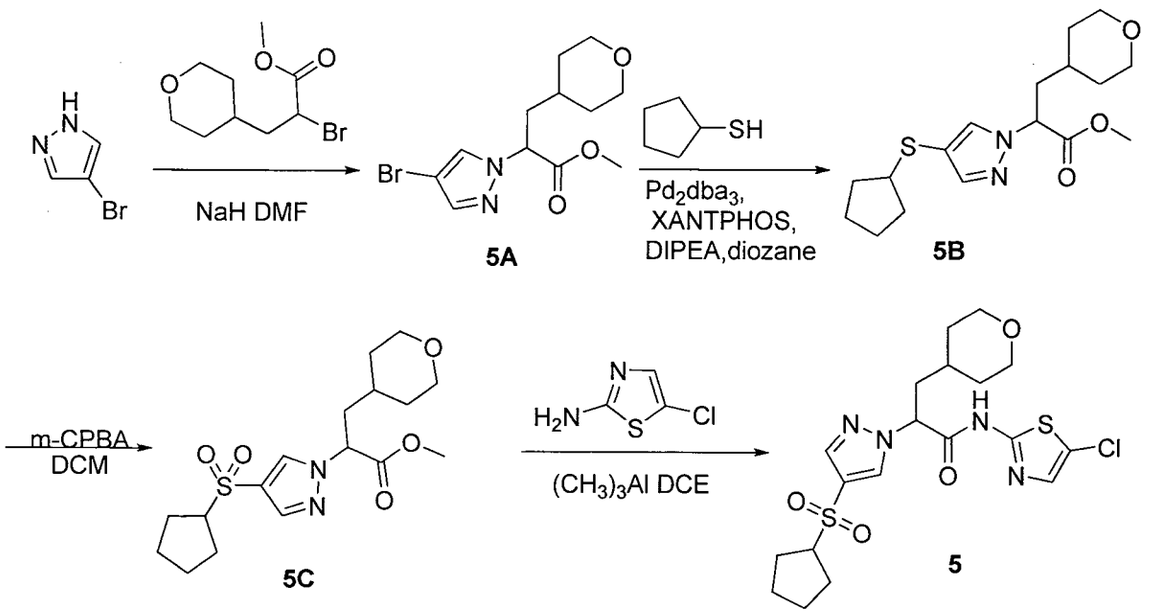
[00424] Se disolvió 4-(ciclopropiltio)-1H-pirazol (**4A**) (1,0 g, 7,14 mmol) en NMP (5 ml) y la solución se enfrió hasta 0 °C. Se agregó NaH (0,263 g, 7,9 mmol) y cuando la reacción bajó se introdujo 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (1,1 g, 7,9 mmol), y la reacción se calentó a 80 °C durante 1 h. La reacción se enfrió y se templó con un pequeño volumen de MeOH y la mezcla bruta se purificó utilizando HPLC en escala preparativa. El compuesto **4B** como así también una pequeña cantidad del ácido carboxílico de **4B** se recolectaron. La eliminación del solvente y el tratamiento del ácido con $TMSCH_2N_2$ seguido de la combinación con **4B** dio el compuesto del título en forma de un aceite (0,68 g). [M+H] calc. para $C_{15}H_{23}N_2O_3S$ (éster **4B**), 311,14; experimental 311,2; [M+H] calc. para $C_{14}H_{21}N_2O_3S$ (ácido **4B**), 297,12; experimental 297,1.

[00425] El compuesto **4B** (0,68 g, 1,9 mmol) se trató con Oxone® (2,4 g, 3,8 mmol) en una solución 1:1 de MeOH/H_2O (20 ml). Después que la oxidación se consideró completa el solvente se eliminó y el residuo se dividió en porciones entre EtOAc y H_2O. La capa orgánica se separó, se secó y se concentró para dar el compuesto bruto **4C** en forma de un aceite (0,729 g). Este material se purificó utilizando HPLC en escala preparativa y se

utilizó directamente en el próximo paso, [M+H] calc. para $C_{15}H_{23}N_2O_5S$, 343,12; experimental 343,0.

[00426] 5-clorotiazol-2-amina (0,519 g, 3,03 mmol) se agregó a un frasco para microondas seguido de DCE (3 ml). La mezcla de reacción se enfrió hasta 0ºC bajo una atmósfera N2. Trimetil aluminio (2M en hexanos) (2,6 mmol) se agregó y cuando la reacción bajó el baño de enfriamiento se eliminó, la solución se agitó a continuación a temperatura ambiente durante 15 min. A esto se agregó una solución de 2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanoato de metilo **4C** (0,173 g, 0,51 mmol) en DCE (2ml) y la mezcla de reacción se calentó en un microondas a 110ºC durante 1h. La reacción se templó a continuación con HCl 1N y se extrajo 2x con DCM. Las capas orgánicas se reunieron, se secaron sobre Na_2SO_4 y el solvente se eliminó. Este residuo bruto se purificó por HPLC en escala preparativa para dar el compuesto **4** (0,21g). [M+H] calc. para $C_{17}H2_2ClN_4O_4S_2$, 445,07; experimental 445,2. ^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 0,93 - 1,75 (m, 9 H) 2,19 (br. s., 2 H) 2,55 (br. s., 1 H) 3,31 (br. s., 2 H) 3,94 (br. s., 2 H) 5,10 (br. s., 1 H) 7,32 (s, 1 H) 8,01 (d, *J*=9,35 Hz, 2 H) 10,35 (bs, 1 H)

Compuesto 5: N-(5-clorotiazol-2-il)-2-(4-(ciclopentilsulfonil)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida



[00427] Se suspendió hidruro de sodio (63 mg, 2,47 mmol) en DMF (5 ml), y se enfrió hasta 0°C. Una solución de 4-bromo-1H-pirazol (300 mg, 2,06 mmol) en DMF(5 ml) se agregó gota a gota. Después de agitar durante 20 min a 0°C, se agregó 2-bromo-3-

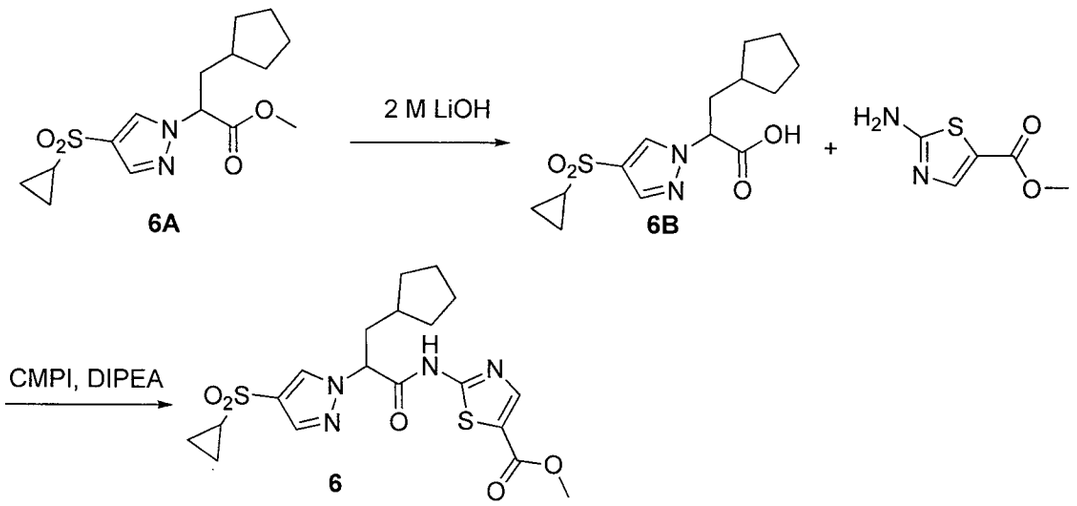
(tetrahidro-2H-piran-4-il)propanoato de metilo (620 mg, 2,47 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La reacción se templó con cloruro de amonio sat. y se extrajo en acetato de etilo. La capa orgánica se lavó con agua, se secó sobre $MgSO_4$, se concentró a alto vacío para dar el compuesto bruto **5A** (492 mg). [M+H] calc. para $C_{12}H_{17}BrN_2O_3$ 318,18; experimental 318.

[00428] El compuesto **5A** (492 mg, 1,56 mmol) se disolvió en dioxano (5 ml). Se agregó ciclopentilmercaptano (159 mg, 1,56 mmol), seguido de diisopropiletilamina (0,54 ml, 3,12 mmol) tris(dibencilacetona)dipaladio (71 mg, 0,078 mmol) y 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (90 mg, 0,156 mmol). La mezcla de reacción se calentó a 100°C en frasco cerrado durante toda la noche. Después de enfriar hasta temperatura ambiente, la solución se vertió en agua, se extrajo con acetato de etilo, se lavó con agua, se secó sobre $MgSO_4$, se concentró a alto vacío hasta el compuesto bruto **5B** (695 mg). [M+H] calc. para $C_{17}H_{26}N_2O_3S$ 339,46; experimental 339.

[00429] El compuesto **5B** (695 mg, 2,06 mmol) se disolvió en diclorometano (20 ml) y se enfrió hasta 0°C. Se agregó ácido m-cloroperoxibenzoico (1,84 g, 8,22 mmol). Después de agitar 3 horas a temperatura ambiente, la solución de reacción se diluyó con diclorometano, se lavó con NaOH 1 N, agua, se secó sobre $MgSO_4$, se concentró al vacío para dar el compuesto bruto **5C** (593 mg). [M+H] calc. para $C_{17}H_{26}N_2O_5S$ 371,46; experimental 371.

[00430] El compuesto **5** se sintetizó de acuerdo con el procedimiento que se describió con relación al **Compuesto 4.** [M+H] calc. para C19H25FN4O4S2 457,56,01; experimental 457. ^{1}H RMN (400 MHz, CLOROFORM-d) δ ppm 1,34 (m, 3H) 1,50 (m, 1H) 1,65 (m, 3H) 1,77 (m, 2H) 2,02 (m, 4H) 2,16 (m, 1H), 2,24 (m, 1H) 3,29 (m, 2H) 3,50 (m, 1H) 3,94 (t, J = 16, 16 Hz, 2H) 5,13 (m, 1H) 7,08 (d, J = 4 Hz, 1H) 7,98 (s, 1H) 8,06 (s, 1H)

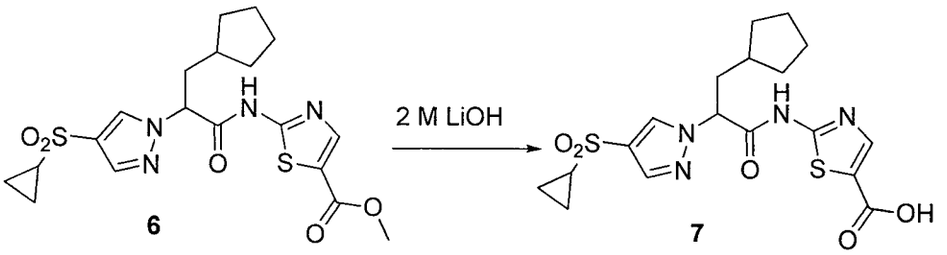
Compuesto 6: 2-(3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)propanamido)tiazol-5-carboxilato de metilo



[00431] El compuesto **6A** (1,663 g, 5,1 mmol), el cual se generó de acuerdo con el procedimiento que se describió con relación al **Compuesto 1**, se disolvió en dioxano (15 ml). 2 M LiOH (5,1 ml, 10,2 mmol) se agregó y la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. La solución de reacción se concentró, se vertió en agua, se acidificó con 20% de HCl, se extrajo con acetato de etilo, se secó sobre Na_2SO_4, se concentró al vació hasta el compuesto bruto **6B** (1,494 g). [M+H] calc. para $C_{14}H_{20}N_2O_4S$ 313,38; experimental 313.

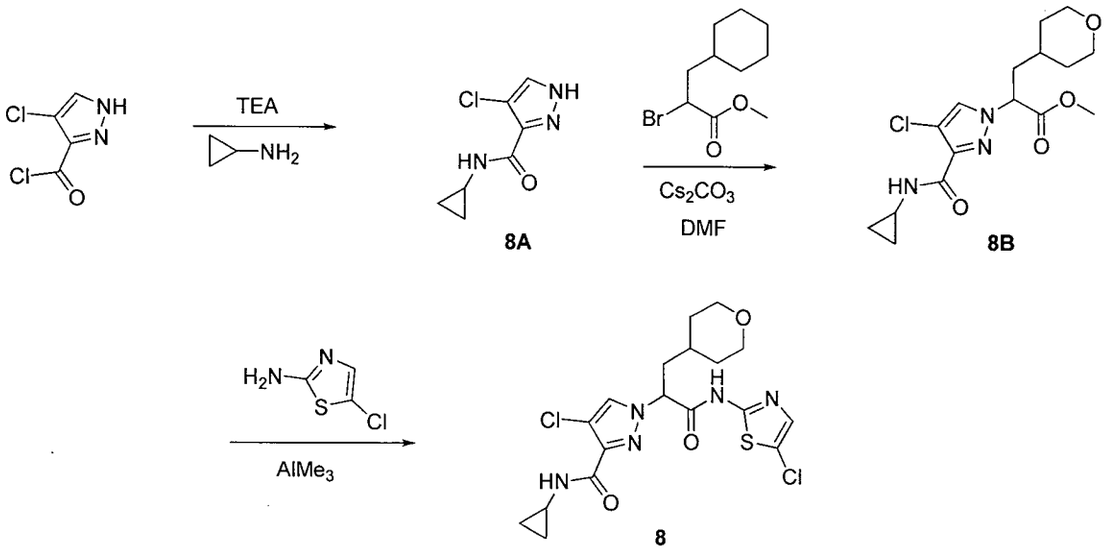
[00432] El compuesto **6B** (200 mg, 0,64 mmol) se disolvió en NMP (5 ml). Se agregó 2-aminotioazol-5-carboxilato de metilo (184 mg, 1,282 mmol), seguido de yoduro de 2-cloro-1-metilpiridinilo (360 mg, 1,41 mmol), diisopropiletilamina (0,25 ml, 1,41 mmol). La mezcla de reacción se calentó a 90°C en frasco cerrado durante toda la noche. Después de enfriar hasta temperatura ambiente, la solución de reacción se vertió en agua, se extrajo con acetato de etilo, se concentró. El residuo se purificó con HPLC para dar el compuesto **6** (85 mg). [M+H] calc. para $C_{19}H_{24}N_4O_5S_2$ 453,55; experimental 453. ^{1}H RMN (400 MHz, MeOD). δ ppm 1,23 (m, 6H) 1,60 (m, 6H) 1,82 (m, 1H) 2,20 (m, 1H) 2,34 (m, 1H) 2,75 (m, 1H), 3,86 (s, 3H) 5,34 (m, 1H) 7,90 (s, 1H) 8,10 (s, 1H) 8,47 (s, 1H)

Compuesto 7: ácido 2-(3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)propanamido)tiazol-5-carboxílico



[00433] El compuesto **6** (67 mg, 0,149 mmol) se disolvió en dioxano (3 ml) y se agregó una solución de 2 M LiOH (0,15 ml, 0,3 mmol). Después de agitar a temperatura ambiente durante toda la noche, se agregó agua (10 ml) y la mezcla de reacción se acidificó con 20% de HCl seguido de extracción con acetato de etilo. La capa orgánica se separó, se secó y se concentró. Este material se purificó utilizando HPLC prep. para dar el compuesto **7** (36,3 mg). [M+H] calc. para δ ppm 1,09 (m, 3H) 1,23 (m, 3H) 1,52 (m, 2H) 1,65 (m, 4H) 1,82 (m, 1H) 2,19 (m, 1H), 2,34 (m, 1H) 2,75 (m, 1H) 5,35 (m, 1H) 7,90 (s, 1H) 8,06 (s, 1H) 8,48 (s, 1H).

Compuesto 8: 4-cloro-1-(1-(5-clorotiazol-2-ilamino)-1-oxo-3-(tetrahidro-2H-piran-4-il)propan-2-il)-N-ciclopropil-1H-pirazol-3-carboxamida



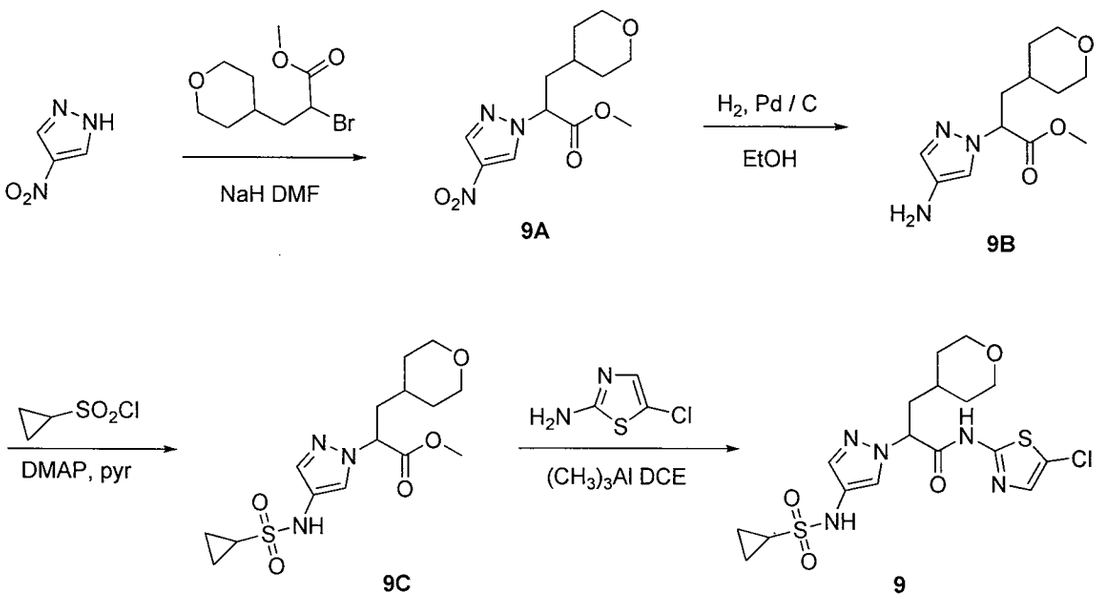
[00434] A cloruro de 4-cloro-1H-pirazol-3-carbonilo (0,5 g, 3,03 mmol) en diclorometano (10 ml) a 0°C se agregó TEA (0,46 ml, 3,33 mmol) seguido de la adición gota a gota de ciclopropilamina (0,419 ml, 6,06 mmol). La mezcla de reacción se dejó entibiar hasta temperatura ambiente y se agitó durante toda la noche. La mezcla de reacción se concentró al vacío, se extrajo en acetato de etilo y se lavó con bicarbonato sat. y solución salina. La capa orgánica se secó sobre Na_2SO_4, se concentró para obtener 0,55 g de **8A**

en forma de un aceite y se utilizó como estaba en el próximo paso. [M+H] calc. para $C_7H_8ClN_3O$, 186,61; experimental 186,6

[00435] Al compuesto **8A** (0,20 g, 1,08 mmol) en DMF (6 ml) se agregó Cs_2CO_3 (0,373g, 1,14 mmol) y 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (0,271 g, 1,08 mmol) en 2 ml de DMF. La mezcla de reacción se agitó durante toda la noche a temperatura ambiente, se extrajo en acetato de etilo y se lavó con solución salina sat. La capa orgánica se secó sobre Na_2SO_4 y se concentró hasta un aceite. Este material se purificó por columna flash de gel de sílice (75% acetato de etilo en hexanos) para obtener 0,3 g de compuesto **8B**. [M+H] calc. para $C_{16}H_{22}ClN_3O_4$, 356,82; experimental 356,80

[00436] **El compuesto 8** se sintetizó utilizando 2-(4-cloro-3-(ciclopropilcarbamoílo)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (**8B**) como material de partida utilizando el procedimiento análogo que se describe con relación al **Compuesto 1**. [M+H] calc. para $C_{18}H_{21}Cl_2N_5O_3S$, 459,36; experimental 459,30. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0,52 - 0,60 (m, 2 H) 0,61 - 0,71 (m, 2 H) 1,13 - 1,38 (m, 3 H) 1,44 - 1,65 (m, 2 H) 1,89 - 2,05 (m, 1 H) 2,26 - 2,38 (m, 1 H) 2,76 (td, *J*=7,33, 4,04 Hz, 1 H) 3,19 (q, *J*=11,79 Hz, 2 H) 3,71 - 3,90 (m, 2 H) 5,35 (dd, *J*=10,99, 4,42 Hz, 1 H) 7,58 (s, 1 H) 8,18 (d, *J*=4,29 Hz, 1 H) 8,37 (s, 1 H) 13,01 (s, 1 H)

Compuesto 9: N-(5-clorotiazol-2-il)-2-(4-(ciclopropansulfonamido)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida



[00437] **El compuesto 9A** se sintetizó utilizando 4-nitro-1H-pirazol y 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo como material de partida utilizando el procedimiento análogo que se describe con relación al **Compuesto 1**.

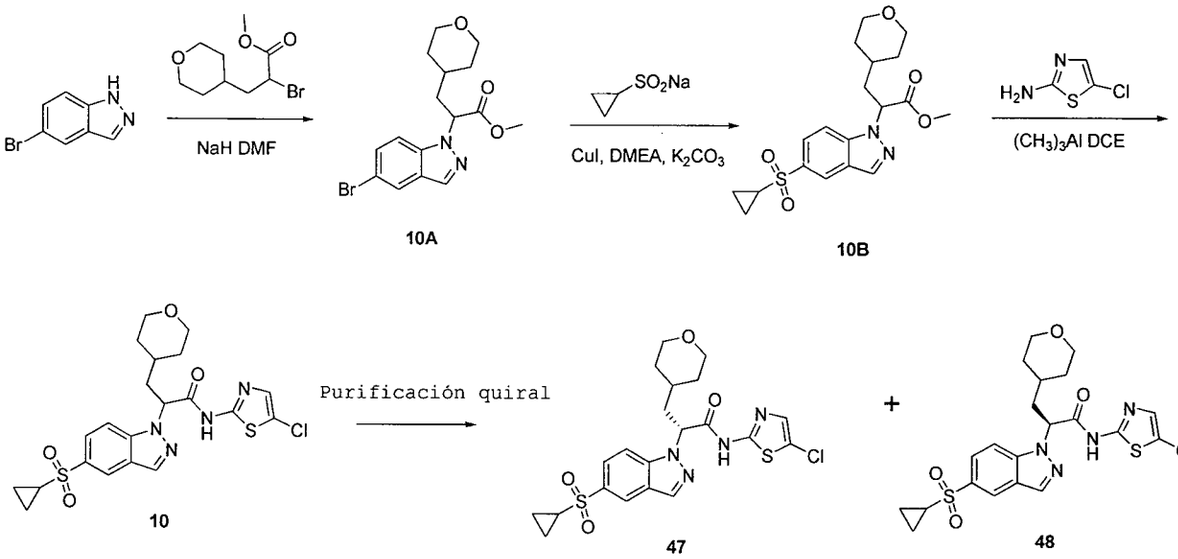
[00438] El Compuesto **9A** (0,37 g) se disolvió en EtOH (15 ml). Se agregó Una cantidad

catalítica de Pd-C. La suspensión se purgó con gas H_2 3 veces, y a continuación se agitó a temperatura ambiente bajo H_2 durante toda la noche. La suspensión se filtró y el filtrado se concentró al vacío para dar **9B** (0,121 g). [M+H] calc. para $C_{12}H_{19}N_3O_3$, 254,3, experimental, 254,3

[00439] A la amina **9B** (0,120 g) en 10 ml de DCM a 0°C se agregó piridina (0,038 ml), DMAP (0,057 g), seguido de la adición gota a gota de cloruro de metan sulfonilo (0,052 ml). La mezcla de reacción se dejó entibiar hasta temperatura ambiente y se agitó durante toda la noche. La mezcla de reacción se lavó con agua y salmuera, se secó sobre Na_2SO_4, y se concentró al vacío para obtener el intermediario **9C** en forma de un aceite. [M+H] calc. para $C_{15}H_{23}N_3O_5S$, 358,4 experimental, 358,4.

[00440] El compuesto **9** se sintetizó utilizando 2-(4-(ciclopropansulfonamido)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (**9C**) como material de partida utilizando el procedimiento análogo que se describe con relación al **Compuesto 1**. [M+H] calc. para $C_{17}H_{22}ClN_5O_4S_2$ 460,97, experimental 461,0; ^{1}H RMN (400 MHz, DMSO-d_6) □ ppm 0,80 - 0,87 (m, 2 H) 0,88 - 0,96 (m, 2 H) 1,14 - 1,31 (m, 3 H) 1,46 (d, *J*=10,36 Hz, 1 H) 1,59 (d, *J*=9,35 Hz, 1 H) 1,92 - 2,02 (m, 1 H) 2,12 - 2,23 (m, 1 H) 2,54 - 2,57 (m, 1 H) 3,09 - 3,21 (m, 3 H) 3,74 - 3,86 (m, 2 H) 5,30 (dd, *J*=10,10, 5,31 Hz, 1 H) 7,36 (s, 1 H) 7,57 (s, 1 H) 7,82 (s, 1 H) 9,22 (s, 1 H) 12,87 (s, 1 H)

Compuesto 10: N-(5-clorotiazol-2-il)-2-(5-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida



10A 10B 10 47 48

[00441] **El compuesto 10A** se sintetizó utilizando 5-bromo-1H-indazol y metilo 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato como material de partida utilizando el procedimiento

análogo que se describe con relación al **Compuesto 1**. Una mezcla (~ 4:1) del producto alquilado N-1 vs. N-2 se obtuvo. La purificación utilizando cromatografía de columna flash (4:1, hexano:acetato de etilo) dio el compuesto **10A**.

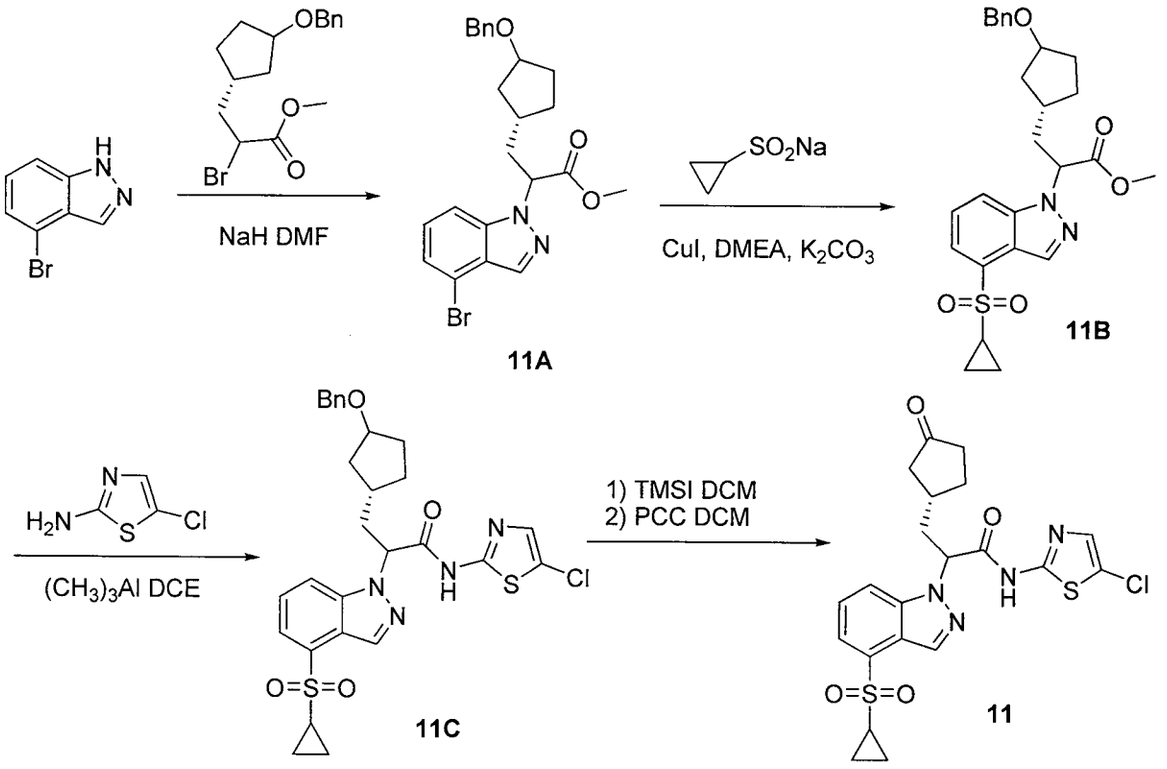
[00442] A 2-(5-bromo-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (0,22 g) en 10 ml de DMSO, se agregó ciclopropansulfinato de sodio (0,23g), yoduro de cobre (0,011g), dimetiletilendiamina (0,013 ml) y K_2CO_3 (0,167 g). La reacción se calentó a 100°C durante toda la noche. La mezcla de reacción se extrajo en acetato de etilo, se lavó con agua y salmuera, se secó sobre Na_2SO_4, y se concentró al vacío para obtener el intermediario **10B** en forma de un aceite. [M+H] calc. para $C_{19}H_{24}N_2O_5S$, 393,47 experimental, 393,5

[00443] **El compuesto 10** se sintetizó utilizando 2-(5-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (**10B**) como material de partida utilizando el procedimiento análogo que se describe con relación al **Compuesto 1**. [M+H] calc. para $C_{21}H_{23}ClN_4O_4S_2$ 496,01, experimental 496,1. ^{1}H RMN (400 MHz, CLOROFORM-*d*) □ ppm 1,01 - 1,11 (m, 2 H) 1,18 - 1,29 (m, 1 H) 1,31 - 1,52 (m, 5 H) 1,59 - 1,71 (m, 1 H) 2,31 (ddd, *J*=14,02, 8,72, 4,80 Hz, 1 H) 2,45 - 2,59 (m, 2 H) 3,20 (m, *J*=19,48, 11,67, 11,67, 2,15 Hz, 2 H) 3,84 - 3,97 (m, 2 H) 5,51 (dd, *J*=10,36, 4,80 Hz, 1 H) 7,26 (s, 1 H) 7,61 (d, *J*=8,84 Hz, 1 H) 7,94 (dd, *J*=8,84, 1,52 Hz, 1 H) 8,35 (s, 1 H) 8,44 (s, 1 H)

[00444] **El compuesto 10** se sometió a separación quiral sobre un instrumento Berger SFC utilizando medio Chiralpak AD-H que eluye con 40% MeOH para dar los compuestos **47** y **48**.

[00445] **Compuesto 70** se obtuvo utilizando un procedimiento análogo con el isómero N-2 de un indazol relacionado con el compuesto **10B**.

Compuesto 11: N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(R)-3-oxociclopentil)propanamida



[00446] **El compuesto 11A** se sintetizó utilizando 4-bromo-1H-indazol y 3-(1R)-3-(benciloxi)ciclopentil)-2-bromopropanoato de metilo como material de partida utilizando el procedimiento análogo que se describe con relación al **Compuesto 1**. Una mezcla del producto alquilado N-1 vs. N-2 se obtuvo. La purificación utilizando cromatografía de columna flash (3:1, hexano:acetato de etilo) dio el compuesto **11A**. [M+H] calc. para $C_{23}H_{26}BrN_2O_3$, 457,1 experimental 457,1.

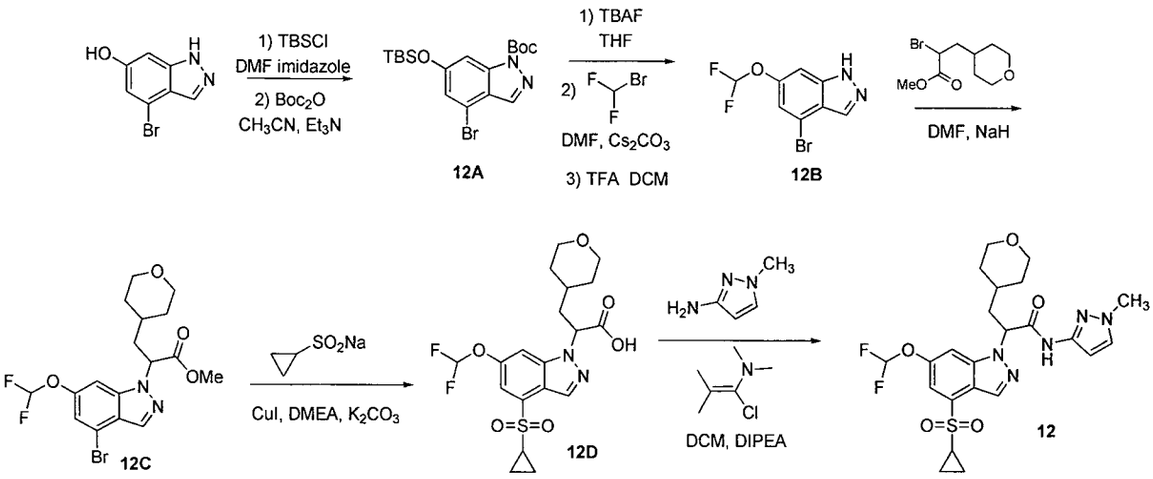
[00447] A 3-(1R)-3-(benciloxi)ciclopentil)-2-(4-bromo-1H-indazol-1-il)propanoato de metilo (0,327 g) en 10 ml de DMSO, se agregó ciclopropansulfinato de sodio (0,57g), yoduro de cobre (0,085g), dimetiletilendiamina (0,096 ml). La reacción se calentó a 150°C durante toda la noche. La mezcla de reacción se enfrió y se lavó con agua y salmuera, se secó sobre Na_2SO_4, y se concentró al vacío para dar 11B. [M+H] calc. para $C_{26}H_{31}N_2O_5S$, 483,19 experimental 483,2

[00448] Se agregó 5-clorotiazol-2-amina (0,35 g, 2,04 mmol) a un frasco para microondas seguido de DCE (3 ml). La mezcla de reacción se enfrió hasta 0°C bajo una atmósfera N2. Se agregó trimetil aluminio (2M en hexanos) (2,0 mmol) y cuando la reacción bajó el baño de enfriamiento se eliminó, la solución se agitó a continuación a temperatura ambiente durante 15 min. A esto se agregó una solución de 3-(1R)-3-(benciloxi)ciclopentil)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)propanoato de metilo **11B** (0,165 g, 0,34 mmol) en DCE (2ml) y la mezcla de reacción se calentó en un microondas

a 110ºC durante 1h. La reacción se templó a continuación con HCl 1N y se extrajo 2x con DCM. Las capas orgánicas se reunieron, se secaron sobre Na_2SO_4 y el solvente se eliminó. Este residuo bruto se purificó por HPLC en escala preparativa para dar el compuesto **11C** en forma de un aceite de color amarillo (0,193g). [M+H] calc. para $C_{28}H_{29}ClN_4O_4S_2$, 585,13; experimental 585,2.

[00449] El compuesto 11 se sintetizó tratando el compuesto 11C (0,142g) con un exceso de TMSI a 50°C durante 0,5h. La mezcla de reacción se templó con MeOH, el solvente se eliminó al vacío y el residuo se dividió en porciones entre EtOAc y solución de $NaHCO_3$, los orgánicos se secaron sobre Na_2SO_4 y se concentraron al vacío. El material bruto se redisolvió con posterioridad en DCM y se trató con 20% de clorocromiato de piridinio sobre aluminio básico. Después que se completó la oxidación, la mezcla de reacción se filtró a través de un taco celite y se concentró. La purificación por HPLC en escala preparativa dio el compuesto **11** (0,040g). [M+H] calc. para $C_{21}H_{31}ClN_4O_4S_2$, 493,07; experimental 493,1. ^{1}H RMN (MeOD) δ ppm: 8,48 (s, 1H), 8,07 (dd, J = 8,6, 3,0 Hz, 1H), 7,75 (d, J = 7,1 Hz, 1H), 7,64 (dd, J = 8,6, 7,3 Hz, 1H), 7,30 (s, 1H), 5,59 - 5,73 (m, 1H), 2,73 - 2,85 (m, 1H), 2,52 - 2,70 (m, 1H), 2,24 - 2,42 (m, 1H), 1,76 - 1,87 (m, 2H), 1,57 - 1,75 (m, 3H), 1,42 - 1,56 (m, 1H), 1,18 - 1,35 (m, 3H), 0,98 - 1,11 (m, 2H).

Compuesto 12: 2-(4-(ciclopropilsulfonil)-6-(difluorometoxi)-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida



[00450] El compuesto 12A se sintetizó tratando 4-bromo-1H-indazol-6-ol (1,0 g, 4,7 mmol) con TBSCl (0,78 g, 5,2 mmol) e imidazol (0,35 g, 5,2 mmol) en 5 ml de DMF y agitando la solución a temperatura ambiente durante toda la noche. La mezcla de reacción se elaboró utilizando el protocolo de introducción de grupo protector estándar y el aceite de color rojo naranja resultante cristalizado al asentarse (1,2g). Este material se disolvió en

CH_3CN (10ml) y se trató con Boc_2 (0,88 g, 4,03 mmol), Et_3N (0,48 g, 4,8 mmol) y una cantidad catalítica de DMAP. La reacción se agitó a temperatura ambiente durante toda la noche, se concentró al vacío y se dividió entre DCM y HCl 1N. La capa orgánica se secó sobre $MgSO_4$ y se concentró. La purificación utilizando cromatografía de columna flash dio el material del título en forma de un aceite transparente (519 mg, 33% de rendimiento) [M+H] calc. para $C_{18}H_{28}BrN_2O_3Si$, 427,1 experimental 427,1.

[00451] El compuesto 12B se sintetizó tratando **12A** (0,52 g, 1,2 mmol) en THF (5ml) con 1M TBAF (2,4 mmol) a 0°C durante 15 min. La mezcla de reacción se vertió en NH_4Cl sat y se extrajo con EtOAc. Los orgánicos se secaron sobre Na_2SO_4 y se concentraron al vacío. El material resultante se secó a alto vacío antes del uso en el próximo paso. La transferencia de este compuesto a una botella de presión se obtuvo con 1-2 ml de DMF; seguido de la adición de Cs_2CO_3 (0,39 g, 1,2 mmol). Esta suspensión se enfrió y un exceso de difluorobromometano se condensó en la mezcla de reacción. La botella de presión se cerró, se dejó entibiar hasta temperatura ambiente y se agitó continuamente durante 2d. El calentamiento posterior hasta 50°C durante 1 día dio una mezcla 70/30 del producto y del material de partida, el cual se separó con cromatografía de columna flash. Este material se trató con una mezcla 1:1 de TFA/DFCM a temperatura ambiente durante 1 h. La eliminación del solvente y la división del residuo entre EtOAc y $NaHCO_3$ sat. dio el compuesto del título (0,18g, 57% de rendimiento).

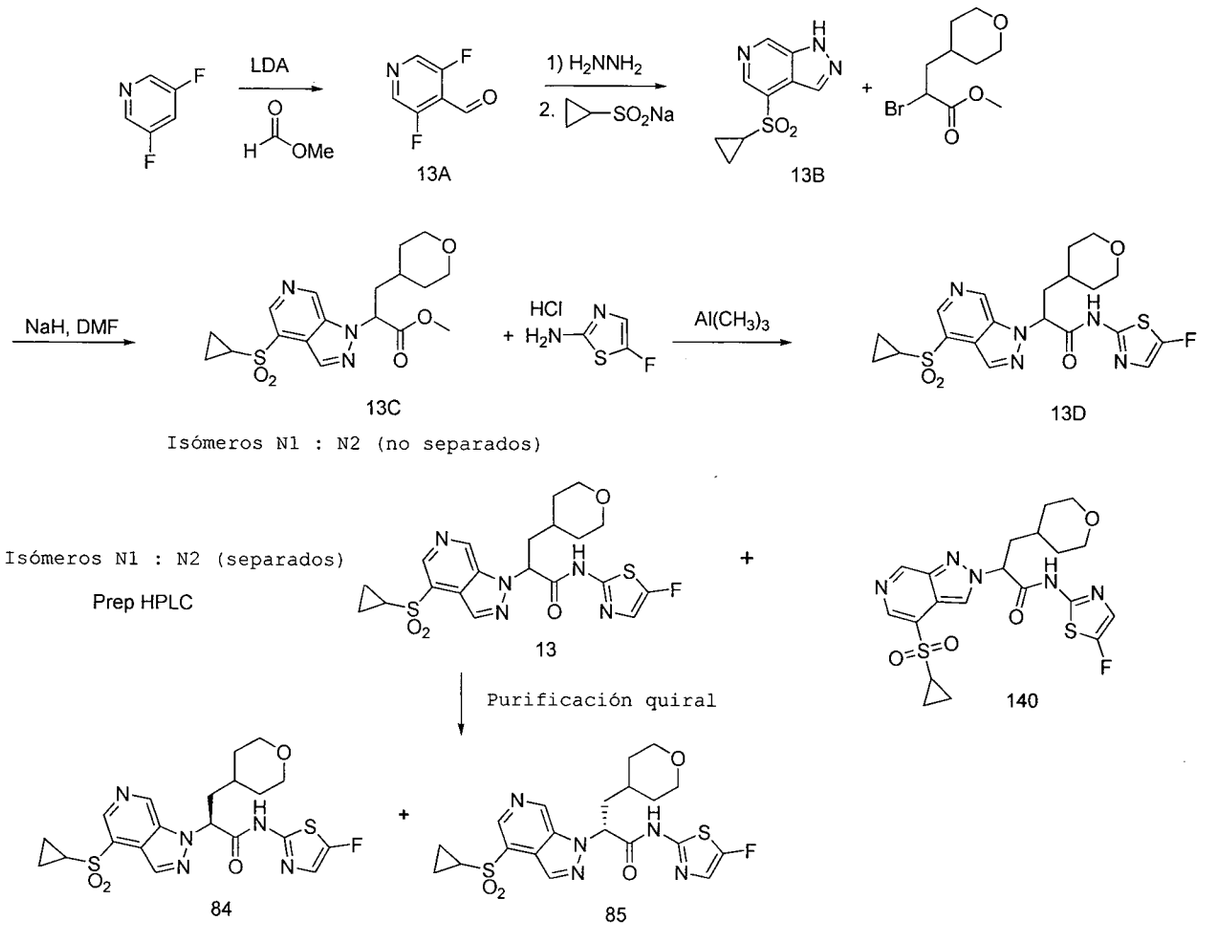
[00452] El compuesto 12C se sintetizó a partir de **12B** (0,18 g, 0,67 mmol) y 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (0,25 g, 1,0 mmol) utilizando un procedimiento análogo que se describe con relación al **Compuesto 1**. El compuesto del título (aceite de color amarillo) se aisló en forma de una mezcla de N1 & N2 bruta (70/30) con el material dominante N1 deseado. Los regioisómeros se separaron con cromatografía de columna flash; [M+H] calc. para $C_{17}H_{20}BrF_2N_2O_4$, 433,1 experimental 433,2.

[00453] El compuesto 12D se sintetizó a partir de **12C** utilizando un procedimiento análogo que se describió con relación al **Compuesto 10**. El material del título se aisló y se purificó utilizando HPLC preparativa; [M+H] calc. para $C_{19}H_{23}F_2N_2O_6S$ 445,1 experimental 445,3.

[00454] El compuesto 12 se sintetizó a partir de **12D** (0,08 g, 0,17 mmol) el cual se disolvió en DCM (5 ml). A esta solución se agregó 1-cloro-N,N,2-trimetilprop-1-en-1-amina (0,04 g, 0,3 mmol) a temperatura ambiente y la mezcla se agitó durante 30 min. Posteriormente se agregó 1-metil-1H-pirazol-3-amina (0,03 g, 0,3 mmol) junto con DIPEA (0,04g, 0,3 mmol). El solvente se eliminó bajo presión reducida y el residuo se dividió entre EtOAc y solución de bicarbonato sat. Los orgánicos se secaron y se purificaron por

cromatografía de columna flash para dar el compuesto **12** (0,044g). [M+H] calc. para $C_{23}H_{28}F_2N_5O_5S$, 524,2; experimental 524,4. ^{1}H RMN (MeOD) δ ppm: 0,94 - 1,13 (m, 2 H) 1,22 - 1,46 (m, 5 H) 1,52 (dd, J=9,47, 1,89 Hz, 1 H) 1,72 (dd, J=9,98, 1,89 Hz, 1 H) 2,05 - 2,29 (m, 1 H) 2,54 (ddd, J=14,15, 10,23, 4,17 Hz, 1 H) 2,84 (tt, J=7,96, 4,80 Hz, 1 H) 3,12 - 3,29 (m, 2 H) 3,65 (s, 1 H) 3,73 - 3,80 (m, 3 H) 3,80 - 3,96 (m, 2 H) 5,63 (dd, J=10,36, 5,31 Hz, 1 H) 6,45 (d, J=2,27 Hz, 1 H) 7,42 (d, J=2,27 Hz, 1 H) 7,54 (d, J=1,77 Hz, 1 H) 7,89 (d, J=2,27 Hz, 1 H) 8,46 (s, 1 H).

Compuesto 13: 2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-c]piridin-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida



[00455] Compuesto 13A: Se enfriaron LDA (68 ml, 478 mmol) y THF (500 ml) hasta 0°C mientras se agitaban bajo nitrógeno y se agregó n-BuLi (192 ml, 478 mmol, 2,5 M en hexanos) gota a gota. Después de 30 min, la mezcla se enfrió hasta -78°C (baño de hielo seco/acetona) y 3,5-difluoropiridina (50g, 434 mmol) disuelta en 500 ml de THF se agregó gota a gota mientras se mantenía la temperatura por debajo de -69°C. Después de 4h, formiato de metilo (54 ml, 868 mmol) disuelto en 135 ml de THF se agregó gota a gota

(adición se completó en 1,25 h). En un frasco separado, se enfrió 1L de $NaHCO_3$ sat. hasta 0°C mientras se agitaba. La mezcla de reacción se agregó a la solución de $NaHCO_3$ mientras se agitaba y la mezcla se dejó entibiar hasta temperatura ambiente. La capa orgánica se separó y la capa acuosa se extrajo con acetato de etilo (4X, 250 ml). Los extractos orgánicos combinados se lavaron con salmuera sat., se secaron sobre Na_2SO_4 y se concentraron para obtener un aceite de color púrpura oscuro. La purificación utilizando cromatografía de columna flash dio 32,5g (52% de rendimiento) del compuesto 13A.

[00456] **Compuesto 13B**: A una solución de 3,5-difluoroisonicotinaldehído (10,15 g , 70,60 mmol) en NMP (50 ml) a 0°C se agregó hidrazina anhídrida (2,3 ml, 70,69 mmol) gota a gota. La solución de reacción se agitó a temperatura ambiente durante 2 hrs. (monitoreada por LC-MS para completar la reacción a hidrazona). La mezcla de reacción se calentó a continuación a 140°C durante toda la noche para la conversión al indazol (monitoreado por LC-MS para completar la reacción). Se agregó a continuación sal de sodio del ácido ciclopropilsulfínico (18,1g, 141,38 mmol) a la mezcla de reacción y se calentó a 180°C durante toda la noche. Cuando la reacción se completó (monitoreado por LC-MS), la mezcla de reacción se concentró utilizando una bomba a alto vacío para eliminar NMP y a continuación se extrajo en acetato de etilo. La capa orgánica se lavó con agua y todo sólido obtenido se filtró a través de celite. Las capas orgánicas combinadas se lavaron con H_2O, se secaron sobre $MgSO_4$, se filtraron, y se concentraron al vacío. El aceite se purificó por cromatografía de columna flash (80% EtOAc en hexanos hasta 100% de EtOAc) para dar 5,492 g (54% de rendimiento) del compuesto 13B. [M+H] calc. para $C_9H_9N_3O_2S$ 224,2; experimental, 224,25.

[00457] **Compuesto 13C:** Se suspendió hidruro de sodio (557 mg, 22,0 mmol) en DMF (5 ml), y se enfrió hasta 0°C. Una solución del **compuesto 13B** (3,77 g, 16,92 mmole) en DMF (15 mL) se agregó gota a gota al mismo. Después de agitar durante 20 min a 0°C, se agregó gota a gota 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (5,52 g, 22,0 mmol) a la mezcla de reacción y se dejó entibiar a temperature ambiente y se agitó durante 2 horas. La mezcla de reacción se templó con cloruro de amonio saturado y se extrajo en acetato de etilo. La capa orgánica se lavó con agua, se secó sobre $MgSO_4$, se filtró, y se concentró a presión reducida para dar el compuesto **13C** (5,94 g; 89% de rendimiento). [M+H] calc. para $C_{18}H_{23}N_3O_5S$ 394,4; experimental, 394,46.

[00458] **Compuesto 13D:** A una suspension de clorhidrato de 5-fluorotiazol-2-amina (9,36 g, 60,5 mmole) en DCE (30 mL) a 0°C bajo una atmósfera N_2 se agregó trimetil aluminio (2M en hexanos) (30,3 mL, 60,5 mmoles) gota a gota. Después de agitar a temperature ambiente durante 30 minutos, una solución del **Compuesto 13C** (5,94 g; 15,12 mmol) en

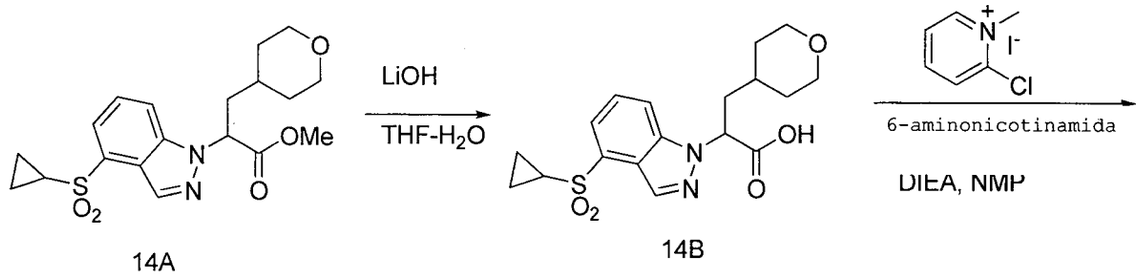
DCE (30 ml) se agregó gota a gota y la mezcla de reacción se calentó a 100°C durante 2 horas. Después de enfriar hasta 0°C, la mezcla de reacción se templó con HCl 1N y se extrajo 2X con DCM. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida para dar el **Compuesto 13D**.

[00459] Los compuestos 13 y **140** se obtuvieron a partir del compuesto 13D en forma de una sal TFA, después de la purificación utilizando HPLC prep. (Waters System: Columna es Phenomenex C18, 5 u, 150X50 mm, fase móvil A: 0,05% TFA en H2O y fase móvil B es 0,035% TFA en acetonitrilo, gradiente de solvente es 40-55% B); [M+H] calc. para $C_{20}H_{22}FN_5O_4S_2$ 480,5; experimental, 480,55.

[00460] El compuesto 13 se obtuvo en forma de una base libre por concentración de las fracciones de HPLC, seguido de extracción en acetato de etilo y lavando con $NaHCO_3$ sat. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida para obtener el **compuesto 13**.

[00461] El compuesto 13 se sometió a separación quiral sobre un instrumento Berger SFC utilizando medio Chiralpak AD-H que eluye con 40% de MeOH para dar los compuestos **84** y **85**.

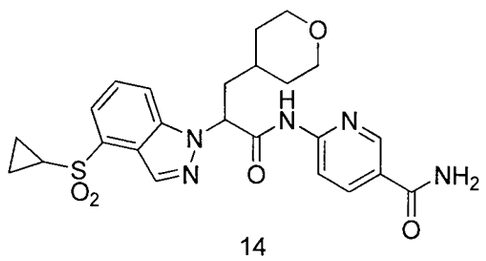
Compuesto 14: 6-(2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamido)nicotinamida



14A

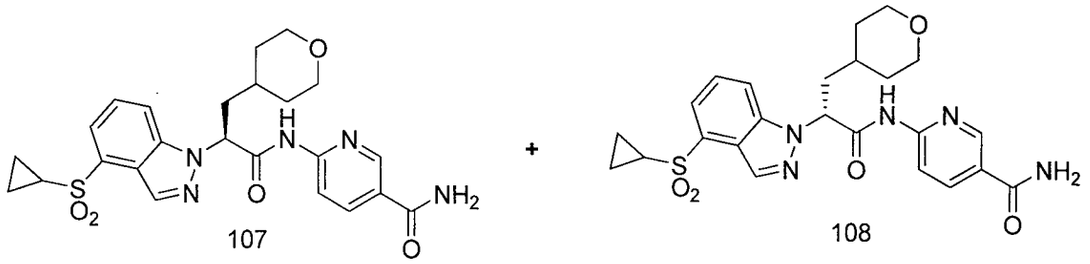
Por preparación ver 10B

14B



14

Separación quiral



107 + 108

[00462] El compuesto 14A se sintetizó utilizando 4-bromo-1H-indazol y 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo como material de partida utilizando el procedimiento análogo que se describe con relación al **Compuesto 10**. Una mezcla (~ 3:1) del producto alquilado N-1 vs. N-2 se obtuvo. La purificación utilizando cromatografía de columna flash (4:1, hexano:acetato de etilo) dio el compuesto **14A**.

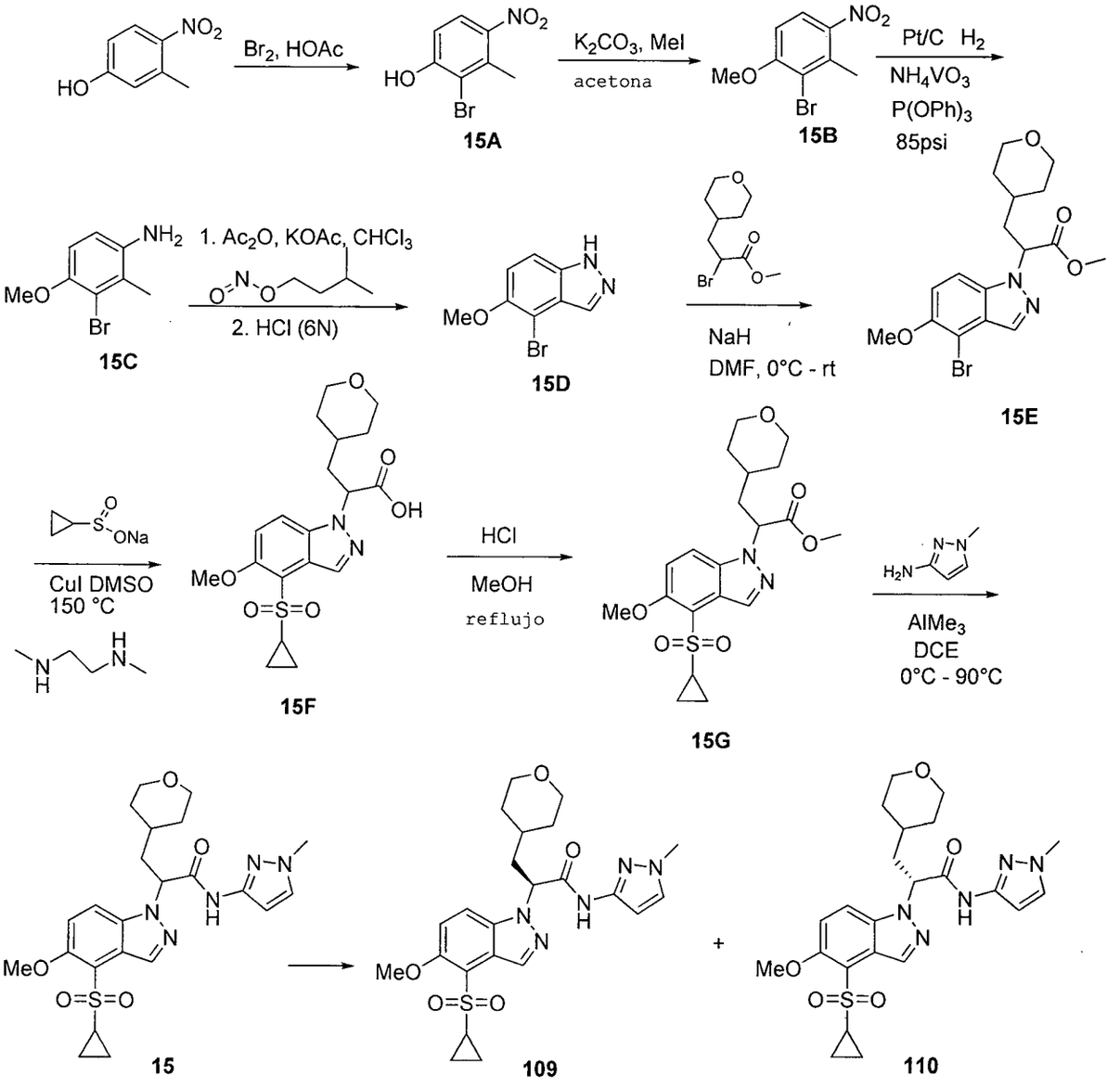
[00463] El compuesto 14B se sintetizó tratando **14A** (0,4 g, 1,0 mmol) en THF-H_2O (5:1, 10ml) con LiOH 1M (3,0 mmol) a 0°C durante 15 min. y la mezcla se agitó durante 18h a temperatura ambiente. La mezcla de reacción se acidificó con HCl 1N y se extrajo con EtOAc. Los orgánicos se secaron sobre Na_2SO_4 y se concentraron al vacío. El material resultante se secó a alto vacío antes del uso en el próximo paso.

[00464] Compuesto 14 se sintetizó a partir del **14B** (0,15 g, 0,39 mmol) el cual se disolvió en NMP (5 ml). A esta solución se agregó 6-aminonicotinamida (0,109 g, 0,79 mmol).

Posteriormente se agregó yoduro de 2-cloro-1-metilpiridinio (0,15 g, 0,58 mmol) junto con DIPEA (0,092ml, 0,53 mmol) a temperatura ambiente y la mezcla se agitó durante 18h a 80°C. La mezcla de reacción se enfrió y se dividió entre EtOAc y solución de NaCl sat. La capa orgánica se secó y se purificó por HPLC prep. (Waters System: Columna es SunFire C18, 5 μ, 30 X 75 mm, fase móvil A: 0,05% TFA en H2O y fase móvil B es 0,035% TFA en acetonitrilo, gradiente de solvente es 30-45% B); para dar el compuesto **14** (158 mg). [M+H] calc. para $C_{24}H_{28}N_5O_5S$, 498,3; experimental 498,6. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0,94 - 1,13 (m, 2 H) 1,13 - 1,43 (m, 5 H) 1,43 - 1,67 (m, 2 H) 2,12 - 2,28 (m, 1 H) 2,50 (ddd, *J*=14,21, 10,42, 5,18 Hz, 1 H) 2,93 - 3,22 (m, 3 H) 3,79 - 3,95 (m, 2 H) 5,89 (dd, *J*=9,47, 4,93 Hz, 1 H) 7,48 (br. s., 1 H) 7,61 - 7,77 (m, 2 H) 7,95 - 8,12 (m, 2 H) 8,12 - 8,28 (m, 2 H) 8,43 (s, 1 H) 8,83 (d, *J*=1,77 Hz, 1 H) 11,32 (s, 1 H).

[00465] El compuesto 14 se sometió a separación quiral sobre un instrumento Berger SFC utilizando medio Chiralpak AD-H que eluye con 40% de MeOH para dar los compuestos **107** y **108**.

Compuesto 15: 2-(4-(ciclopropilsulfonil)-5-metoxi-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida



[00466] Compuesto **15A**: Una solución de bromo (15,69 g, 0,097 mol) en ácido acético (8,88 ml) se agregó gota a gota a una solución de 3-metil-4-nitrofenol (14,8 g, 0,097 mol) en ácido acético (118 ml) durante 45 min, y la mezcla se agitó durante otras 3 horas. Dado que la reacción no se completó como se monitoreó para completar utilizando LC-MS, se agregó 1 ml de bromo en ácido acético (2ml) a la mezcla de reacción, y la mezcla se agitó durante toda la noche. El solvente se eliminó bajo presión reducida y el residuo se suspendió en agua y se extrajo con acetato de etilo. La mezcla se filtró a través de celite. La capa orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4, y se concentró para dar el compuesto bruto **Compuesto 15A** (15 g) y el otro regioisómero (3-

metil-4-nitro-6-bromofenol) en una relación 2:1. El compuesto bruto se tomó para el próximo paso sin purificación.

[00467] Compuesto **15B**: El compuesto bruto **15A** (104g, 0,45mol) en acetona (1000 ml), K_2CO_3 (68g, 0,49mol) y yoduro de metilo (74g, 0,52 mol) se agregaron a temperatura ambiente. La mezcla se reflujó durante 1,5 hora. Dado que la reacción no se completó cuando se monitoreó para terminar por LC-MS, K_2CO_3 (malla 325) (22,6g, 0,16 mol) y se agregó MeI (10ml, 0,16mol) a la mezcla de reacción, y la mezcla se dejó reflujar durante toda la noche. La reacción se monitoreó nuevamente para su terminación por LC-MS. Se agregaron K_2CO_3 adicional (malla 325) (8g, 0,058mol) y MeI (4ml) a la mezcla de reacción, y la mezcla se dejó reflejar durante otra hora. La mezcla de reacción se enfrió a continuación hasta temperatura ambiente, se filtró, y se concentró. El residuo se dividió en porciones entre EtOAc y H_2O. La capa orgánica se separó, se secó y se concentró para dar el compuesto bruto **15B** (152g) en forma de un sólido color marrón.

[00468] Compuesto **15C**: A una solución de compuesto **15B** (76,4g, 0,311mol) en DCM (160ml) se agregó NH_4VO_3 (2,18g, 0,0186mol), $P(OPh)_3$ (0,964g, 0,00311mol) y Pt/C (5%) (15,5g). La mezcla se agitó bajo H_2 a 85 psi durante toda la noche. La mezcla de reacción se filtró a través de celite y se concentró para dar 64,9g del compuesto bruto **15C**. El compuesto bruto **15C** que contiene el otro regioisómero (5-bromo-4-metoxi-2-metilanilina) se separó en esta etapa por cromatografía de columna flash (0-100% acetato de etilo en hexanos) para dar el compuesto **15C** (34,66g).

[00469] Compuesto **15D**: Al compuesto **15C** (32,2g, 0,149mol) en $CHCl_3$ (470ml) se agregó Ac_2O (32,65ml, 0,345mol). La mezcla de reacción se agitó a temperatura ambiente durante 40 min. Se agregaron KOAc (4,47g, 0,0455mol) y nitrito de isoamilo (44,3ml, 0,331mol) a la mezcla de reacción. La mezcla de reacción se reflujó durante toda la noche, se enfrió en un baño de hielo y se neutralizó con 1N NaOH. La capa orgánica se separó de la capa acuosa, se lavó con salmuera y se secó sobre Na_2SO_4 y se concentró. El residuo se colocó en una solución de metanol (296ml) y HCl 6N (90ml). La mezcla de reacción se calentó hasta reflujo durante una hora. Después de enfriar, la mezcla de reacción se concentró. El sólido se neutralizó con una solución de $NaHCO_3$ saturado acuoso, se aisló por filtración, se lavó con agua y se secó para dar el compuesto **15D** (23g)

[00470] Compuesto **15E**: El compuesto **15D** (12g, 0,0529mol) se disolvió en DMF (140 ml) y la solución se enfrió hasta 0 °C. Se agregó NaH (2,65 g, 0,0663mole) y cuando la reacción bajó, se agregó 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (15,9g, 0,0635mole) a la mezcla de reacción. La mezcla de reacción se entibió a continuación hasta temperatura ambiente y se agitó durante toda la noche. Cuando la reacción se

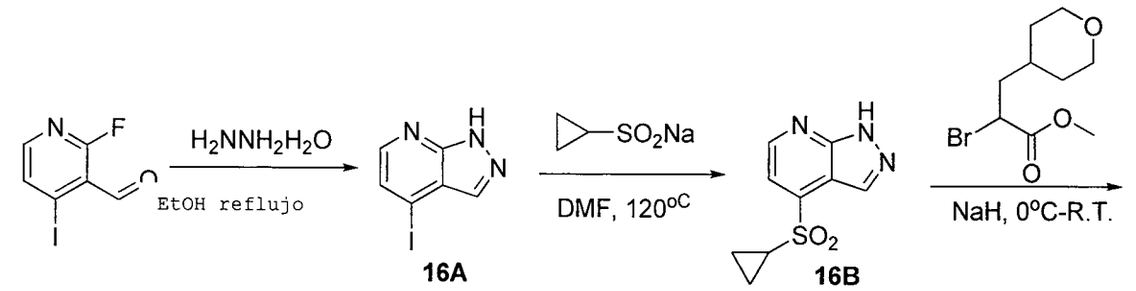
completó como se monitoreado por LC-MS (relación N1:N2 fue 3:1), la mezcla de reacción se enfrió en un baño de hielo, se templó con un pequeño volumen de agua y se extrajo en EtOAc. La capa orgánica se secó sobre Na_2SO_4 , se filtró y se concentró para obtener un aceite el cual se purificó por cromatografía de columna flash para dar el compuesto **15E** (7,54g).

[00471] Compuesto **15G**: Al compuesto **15E** (7g, 0,0177mol) en 48 ml de DMSO se agregó ciclopropansulfinato de sodio (6,93g, 0,0546 mol), yoduro de cobre (3,46 g, 0,0182 mol) y dimetiletilendiamina (1,96 ml, 0,0182 mol). La reacción se calentó a 150°C durante 40 min. La mezcla de reacción se enfrió a continuación en un baño de hielo, se diluyó con EtOAc y se filtró a través de celite. La capa orgánica se secó sobre Na_2SO_4 y se concentró para dar una mezcla del compuesto **15F** y el compuesto **15G**. El residuo se disolvió en MeOH (100ml) y se agregó HCl (6N, 10 ml) al mismo. La mezcla de reacción se calentó hasta reflujo y se agitó durante toda la noche. Después que la mezcla de reacción se enfrió hasta temperatura ambiente, se concentró al vacío, y se extrajo en EtOAc. La capa orgánica se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró para obtener un aceite. El aceite bruto se purificó por cromatografía de columna flash para dar el compuesto **15G** (2,7g).

[00472] Compuesto **15:** A una solución de 1-metil-1H-pirazol-3-amina (2,50g, 25,78mmol) en DCE (25 ml) a 0°C bajo una atmósfera N2 se agregó trimetil aluminio (2M en hexanos) (12,89 ml, 25,8 mmol). Después de 15 min, una solución de compuesto **15G** (2,72g, 6,46 mmol) en DCE (12 ml) se agregó a la mezcla de reacción y la solución se calentó a 90°C durante 2h. La mezcla de reacción se enfrió a continuación en baño de hielo, se templó con HCl 1N y se extrajo 2X con EtOAc. La capa orgánica se secó sobre Na_2SO_4 y el residuo bruto se purificó por cromatografía de columna flash (Hexanos/ EtOAc, 30%-100%) para dar el compuesto **15** (2,7g). [M+H] calc. para $C_{23}H_{29}N_5O_5S$ 488, experimental 488, ^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,72 (s, 1 H), 8,64 (s, 1 H), 7,67 (d, *J*=9,3 Hz, 1 H), 7,30 (d, *J*=9,1 Hz, 1 H), 7,22 (d, *J*=2,5 Hz, 1 H), 6,61 (d, *J*=2,3 Hz, 1 H), 5,27 (dd, *J*=10,6, 4,8 Hz, 1 H), 4,07 (s, 3 H), 3,82 - 3,92 (m, 2 H), 3,75 (s, 3 H), 3,09 - 3,29 (m, 3 H), 2,44 - 2,56 (m, 1 H), 2,28 (d, *J*=5,1 Hz, 1 H), 1,42 - 1,52 (m, 2 H), 1,29 - 1,40 (m, 3 H), 1,21 (d, *J*=6,1 Hz, 2 H), 0,95 - 1,09 ppm (m, 2 H)

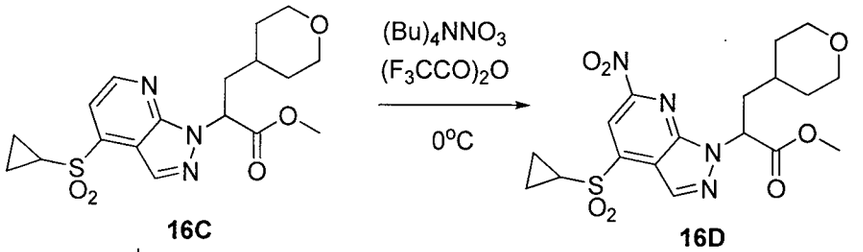
[00473] El compuesto 15 se sometió a separación quiral sobre un instrumento Berger SFC utilizando medio Chiralpak OD-H y que eluye con 25% de isopropanol para dar los compuestos **109 y 110**.

[00474] Compuesto 16: 2-(6-amino-4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida



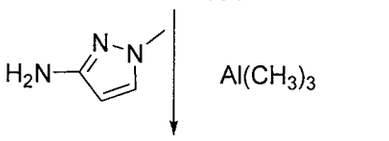
16A

16B

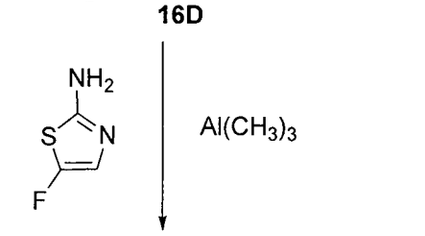


16C

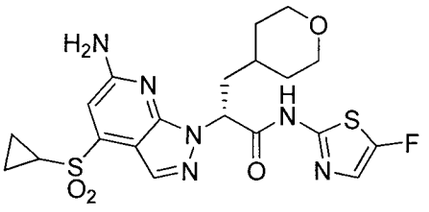
16D



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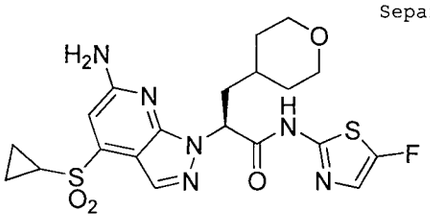


16E



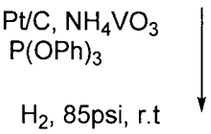
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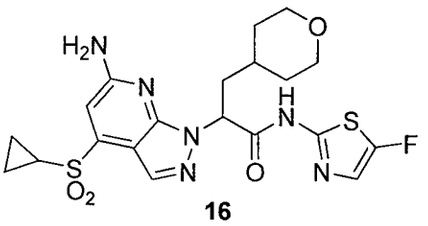
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Separación quiral





16

[00475] Compuesto **16A**: A una solución de 2-fluoro-4-yodonicotinaldehído (3,0 g, 11,95 mmol) en etanol (45 ml) se agregó monohidrato hidrazina (1,12 g, 14,34 mmol) y la mezcla de reacción se calentó a 120°C en un frasco cerrado durante toda la noche. La mezcla de reacción se enfrió hasta temperatura ambiente, y a continuación se concentró bajo presión reducida. El residuo se trató con agua (30 ml) y NaOH 1 N (20 ml) y se extrajo con $CHCl_3$ (40x4 ml). La capa orgánica se separó, se secó sobre $MgSO_4$ y se concentró para dar el compuesto bruto **16A** en forma de un sólido (2,74 g). [M+H] calc. para $C_6H_4IN_3$ 246; experimental 246.

[00476] Compuesto **16B**: A una solución de **16A** (1,00 g, 4,02 mmol) en DMF (12 ml) se agregó ciclopropansulfinato de sodio (1,57 g, 12,2 mmol) y la reacción se calentó a 120°C durante 4 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se concentró y el residuo se trató con agua, seguido de la extracción en acetato de etilo. La capa orgánica se separó, se secó sobre $MgSO_4$ y se concentró bajo presión reducida para dar **16B** bruto (0,98 g). [M+H] calc. para $C_9H_9N_3O_2S$ 224; experimental 224.

[00477] El compuesto **16C** se sintetizó a partir del compuesto **16B** utilizando un procedimiento análogo que se describió con relación al **Compuesto 10** para dar **16C** bruto en forma de un sólido (1,496 g, 86%). [M+H] calc. para $C_{18}H_{23}N_3O_5S$ 394; experimental 394.

[00478] Compuesto **16D**: A una solución de compuesto **16C** (878 mg, 2,23 mmol) en DCM (10 ml) se agregó nitrato de tetrabutilamonio (1,021 g, 3,35 mmol) y la solución se enfrió hasta 0°C. A continuación se agregó anhídrido trifluoroacético (0,47 ml, 3,35 mmol) gota a gota a la mezcla de reacción y se agitó a 0°C durante 1,5 h. Después de lo cual se agregaron otro 1,5 eq. de nitrato de tetrabutilamonio y anhídrido trifluoroacético a la mezcla de reacción a 0°C y se agitó durante 1,5 h. La mezcla de reacción se diluyó con DCM y se lavó con agua. La capa orgánica se separó, se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El residuo obtenido se purificó por HPLC prep. (Waters System: Columna es Phenomenex C18, 5 μ, 150X50 mm, fase móvil A: 0,05% TFA en H2O y fase móvil B es 0,035% TFA en acetonitrilo, gradiente de solvente es 40-55% B); para dar **16D** en forma de un sólido (176 mg, 18%). [M+H] calc. para $C_{18}H_{22}N_4O_7S$ 439; experimental 439.

[00479] El compuesto **16E** se sintetizó a partir del compuesto **16D** utilizando un procedimiento análogo que se describió con relación al **Compuesto 10** para dar **16E** bruto (233 mg). [M+H] calc. para $C_{20}H_{21}FN_6O_6S_2$ 525; experimental 525.

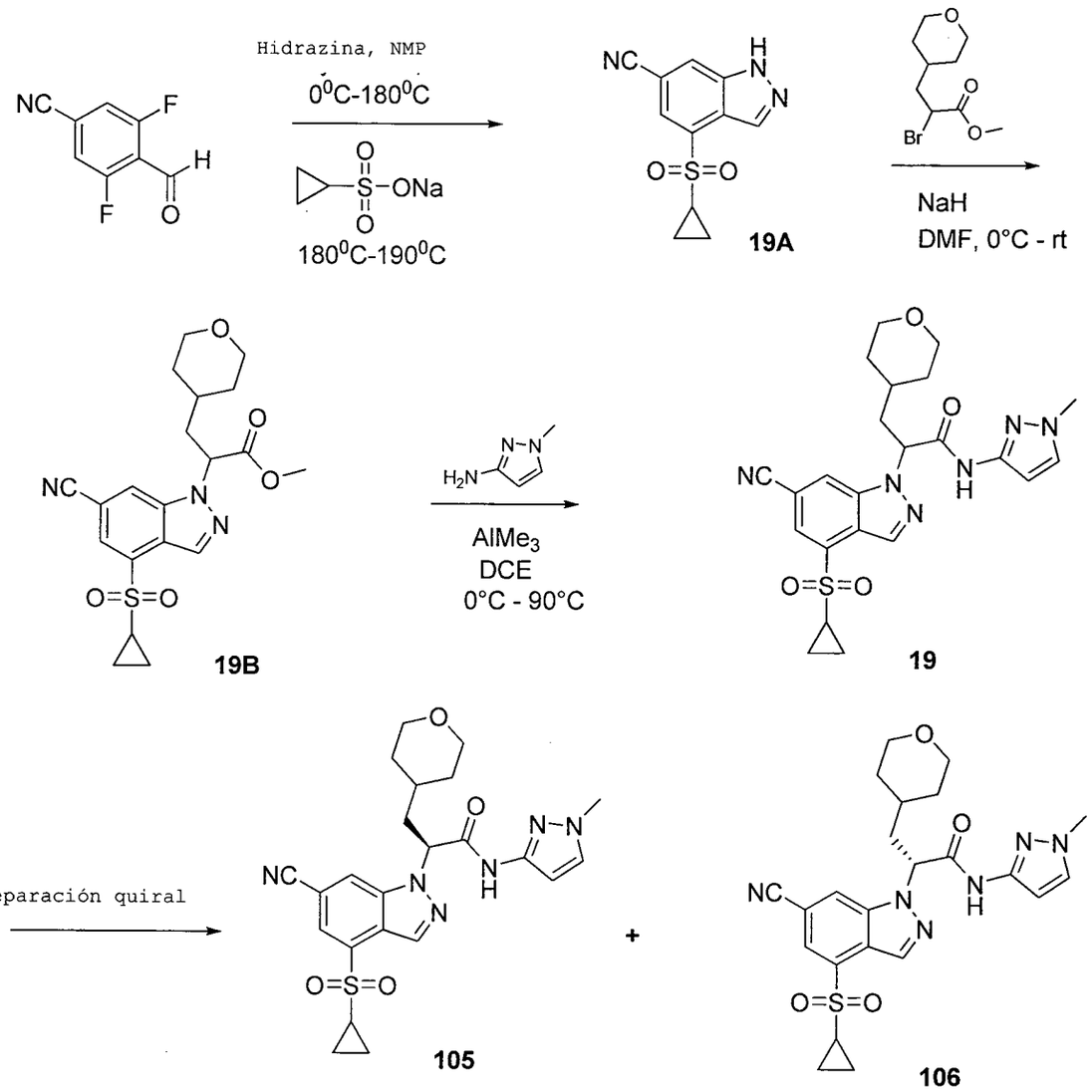
[00480] Compuesto **16**: A un frasco cargado con metavanadato de amonio (5 mg, 0,032 mmol) y trifenilfosfito (2 mg, 0,05 mmol) se agregó una solución del compuesto **16E** (233 mg, 0,54 mmol) en THF (12 ml), seguido de una cantidad catalítica de Pt/C (5%). La

mezcla de reacción se agitó bajo hidrógeno (85 psi) durante 24 horas. La mezcla de reacción se filtró a continuación a través de celite y se concentró bajo presión reducida para obtener un residuo el cual se purificó por HPLC prep. (Waters System: Columna es Phenomenex C18, 5 μ, 150X50 mm, fase móvil A: 0,05% TFA en H2O y fase móvil B es 0,035% de TFA en acetonitrilo, gradiente de solvente es 40-55% B); para dar el compuesto **16** (54 mg). [M+H] calc. para $C_{20}H_{23}FN_6O_4S_2$ 496, experimental 496. ^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 0,99 - 1,07 (m, 9 H) 1,29 - 1,42 (m, 22 H) 1,47 - 1,54 (m, 4 H) 1,71 - 1,78 (m, 4 H) 2,09 - 2,19 (m, 4 H) 2,52 - 2,63 (m, 5 H) 2,90 (tt, *J*=8,08, 4,80 Hz, 5 H) 3,12 - 3,28 (m, 9 H) 3,80 - 3,90 (m, 9 H) 5,86 (dd, *J*=10,99, 4,42 Hz, 5 H) 7,08 (d, *J*=2,53 Hz, 4 H) 8,15 (s, 4 H) 8,32 (s, 4 H).

[00481] El compuesto 16 se sometió a separación quiral sobre un instrumento Berger SFC. Para este compuesto particular se halló que utilizando medio Chiralpak AD-H que eluye con 40% de MeOH dio los compuestos **111** y **112**

[00482] El compuesto 95 se sintetizó a partir del compuesto **16C** utilizando un procedimiento análogo que se describió con relación al **Compuesto 10.** El compuesto bruto se purificó por HPLC prep. (Waters System: Columna es Phenomenex C18, 5 μ, 150X50 mm, fase móvil A: 0,05% TFA en H2O y fase móvil B es 0,035% TFA en acetonitrilo, gradiente de solvente es 40-55% B) para dar el compuesto **95.** [M+H] calc. para $C_{21}H_{27}N_6O_4S$ 459, experimental 459. ^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,08 - 1,18 (m, 2 H) 1,28 - 1,44 (m, 5 H) 1,54 (d, *J*=9,35 Hz, 1 H) 1,74 (dd, *J*=10,11, 1,77 Hz, 1 H) 2,17 - 2,27 (m, 1 H) 2,67 (ddd, *J*=14,21, 10,93, 3,66 Hz, 1 H) 2,89 (tt, *J*=7,86, 4,77 Hz, 1 H) 3,10 - 3,28 (m, 2 H) 3,76 (s, 3 H) 3,85 (dd, *J*=10,74, 4,93 Hz, 2 H) 5,99 (dd, *J*=10,99, 4,67 Hz, 1 H) 6,42 (d, *J*=2,53 Hz, 1 H) 7,42 (d, *J*=2,27 Hz, 1 H) 7,69 (d, *J*=4,80 Hz, 1 H) 8,51 (s, 1 H) 8,81 (d, 1 H)

Compuesto 19: 2-(6-ciano-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il) propanamida



[00483] Compuesto **19A:** A una solución de 3, 5-difluoro-4-formilobenzonitrilo (9,76g, 0,058mol) en N-metil-2-pirrolidinona (100ml) a 0°C se agregó hidrazina anhidra (2,06 g, 0,064 mol) y la mezcla de reacción se agitó a 0°C durante 1h. La solución se dejó entibiar a continuación hasta temperatura ambiente y se agitó durante 2 horas (monitoreado por LC-MS para completar la reacción a hidrazona). La mezcla de reacción se calentó a continuación hasta 180°C durante 4h. La solución se enfrió hasta temperatura ambiente y se agregó ciclopropansulfinato de sodio (9,73 g, 0,076 mol). La mezcla de reacción se calentó a continuación durante toda la noche a 180°C seguido de calentamiento a 190°C durante otras 5h. La mezcla de reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc y se filtró a través de un taco de celite. El filtrado se lavó con solución salina, se secó sobre Na_2SO_4 y se concentró para obtener un residuo el cual se purificó por

cromatografía de columna flash para dar el compuesto **19A** (8,5g). [M+H] calc. para $C_{11}H_9N_3O_2S$ 248, experimental 248

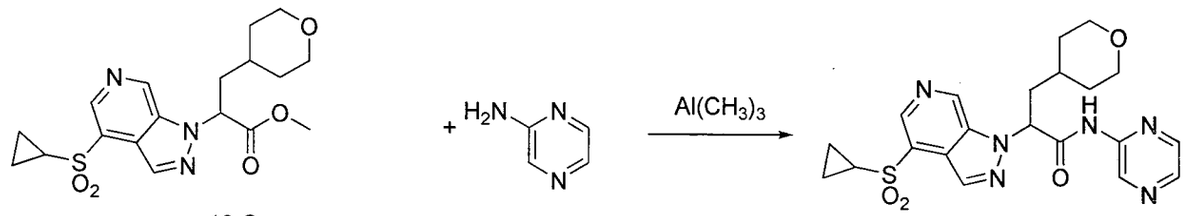
[00484] Compuesto 19B: El compuesto **19A** (4,2 g, 16,99 mmol) se disolvió en DMF (50 ml) y la solución se enfrió hasta 0 °C. Se agregó NaH (0,88 g, 22,08 mmol) y cuando la reacción bajó, se agregó 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (5,54, 22,08 mmol) a la mezcla de reacción. La mezcla de reacción se entibió a continuación hasta temperatura ambiente y se agitó durante toda la noche. Cuando la reacción se completó como se monitoreó por LC-MS (relación N1:N2 fue 3;1), la mezcla de reacción se enfrió en un baño de hielo, se templó con un pequeño volumen de agua y se extrajo en EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para obtener un aceite el cual se purificó por cromatografía de columna flash para dar el isómero N1 como el compuesto **19B (1,8g, 25%)** [M+H] calc. para $C_{20}H_{23}N_3O_5S$ 418, experimental 418

[00485] Compuesto 19: A una solución de 1-metil-1H-pirazol-3-amina (5,21g, 53,7 mmol) en DCE (70 ml) a 0°C bajo una atmósfera N2 se agregó trimetil aluminio (2M en hexanos) (26,8 ml, 53,7 mmol). Después de 15 min, se agregó una solución de compuesto **19B** (5,6g, 13,41 mmol) en DCE (15 ml) a la mezcla de reacción y la solución se calentó durante toda la noche a 90°C. La mezcla de reacción se enfrió a continuación en baño de hielo, se templó con HCl 1N y se extrajo 2X con EtOAc. La capa orgánica se secó sobre Na_2SO_4 y el residuo bruto se purificó por cromatografía de columna flash (Hexanos/ EtOAc, 40%- 100%) para dar el compuesto **19** en forma de una base libre (4,47g, 69%). [M+H] calc. para $C_{23}H_{26}N_6O_4S$ 483, experimental 483. ^{1}H RMN (400 MHz, CLOROFORM-d) δ 8,60 - 8,71 (m, 2H), 8,24 (s, 1H), 7,96 (d, *J* = 1,01 Hz, 1H), 7,22 - 7,28 (m, 1H), 6,62 (d, *J* = 2,27 Hz, 1H), 5,45 (dd, *J* = 5,56, 9,85 Hz, 1H), 3,84 - 3,98 (m, 2H), 3,77 (s, 3H), 3,13 - 3,32 (m, 2H), 2,55 - 2,67 (m, 1H), 2,44 - 2,55 (m, 1H), 2,35 (dd, *J* = 7,71, 13,77 Hz, 1H), 1,63 (d, *J* = 12,13 Hz, 1H), 1,31 - 1,58 (m, 6H), 1,06 - 1,19 (m, 2H)

[00486] El compuesto 19 además se purificó mediante HPLC prep. (Waters System: Columna es Phenomenex C18, 5 μ, 150X50 mm, fase móvil A: 0,05% TFA en H2O y fase móvil B es 0,035% TFA en acetonitrilo, gradiente de solvente es 40-55% B); para dar el compuesto **19** en forma de una sal TFA.

[00487] El compuesto 19 se sometió a separación quiral sobre un instrumento Berger SFC utilizando medio Chiralpak AD-H que eluye con 20% de IPOH para dar los compuestos **105** y **106**.

Compuesto 20: 2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-c]piridin-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida



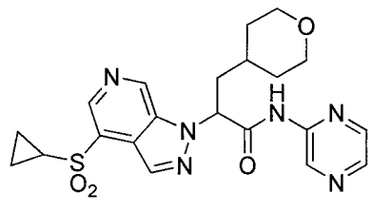
13 C

Isómeros N1:N2 (no separados)

20A

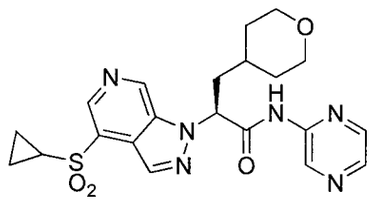
Isómeros N1:N2 (separados)

Prep HPLC



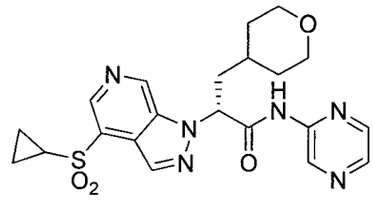
20

Separación quiral



171

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172

[00488] Compuesto 20A: A una solución de amino-pirazina (3,4g, 35,8 mmol) en DCE (40 ml) a 0ºC bajo una atmósfera N2 se agregó trimetil aluminio (2M en hexanos) (17,89 ml, 35,8 mmol). Después de 15 min, se agregó una solución de compuesto **13C** (3,52g, 8,95 mmol) en DCE (20 ml) a la mezcla de reacción y la solución se calentó durante toda la noche a 90ºC. La mezcla de reacción se enfrió a continuación en baño de hielo, se templó con HCl 1N y se extrajo 2X con EtOAc. La capa orgánica se secó sobre Na_2SO_4 y el residuo bruto como compuesto 20A.

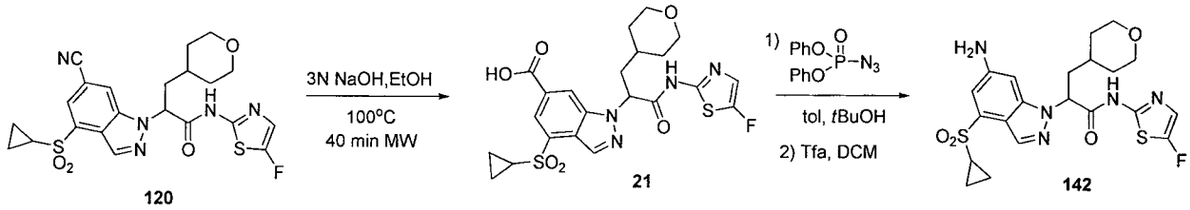
[00489] Compuesto 20 se obtuvo del **compuesto 20A** en forma de una sal TFA después de la purificación utilizando HPLC prep. (Waters System: Columna es Phenomenex C18, 5 μ, 150X50 mm, fase móvil A: 0,05% TFA en H_2O y fase móvil B es 0,035% TFA en acetonitrilo, gradiente de solvente es 40-55% B); [M+H] calc. para $C_{21}H_{24}N_6O_4S$ 457,5; experimental, 457,55 ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,06 - 1,12 (m, 2 H) 1,20 - 1,37 (m, 5 H) 1,50 (d, *J*=11,62 Hz, 1 H) 1,66 (d, *J*=11,12 Hz, 1 H) 2,25 - 2,35 (m, 1 H) 2,52 - 2,58 (m, 1 H) 3,04 - 3,17 (m, 3 H) 3,71 - 3,83 (m, 2 H) 6,06 (dd, *J*=10,11, 5,31 Hz, 1 H) 8,40 (d, *J*=2,53 Hz, 1 H) 8,42 - 8,46 (m, 1 H) 8,55 (s, 1 H) 8,70 (s, 1 H) 9,24 (d, *J*=1,26 Hz,

1 H) 9,68 (s, 1 H).

[00490] El compuesto 20 se obtuvo en forma de una base libre después de la purificación utilizando HPLC prep. (Waters System: Columna es Phenomenex C18, 5 μ, 150X50 mm, fase móvil A: 10mM NH_4HCO_3 en H_2O y fase móvil B es 10mM NH_4HCO_3 en 80% de acetonitrilo, gradiente de solvente es 30-35% B).

[00491] El compuesto 20 se sometió a separación quiral sobre un instrumento Berger SFC utilizando medio Chiralpak AD-H que eluye con 40% de MeOH para dar los compuestos **171** y **172**.

Compuesto 21: ácido 4-(ciclopropilsulfonil)-1-(1-(5-fluorotiazol-2-ilamino)-1-oxo-3-(tetrahidro-2H-piran-4-il)propan-2-il)-1H-indazol-6-carboxílico



120 21 142

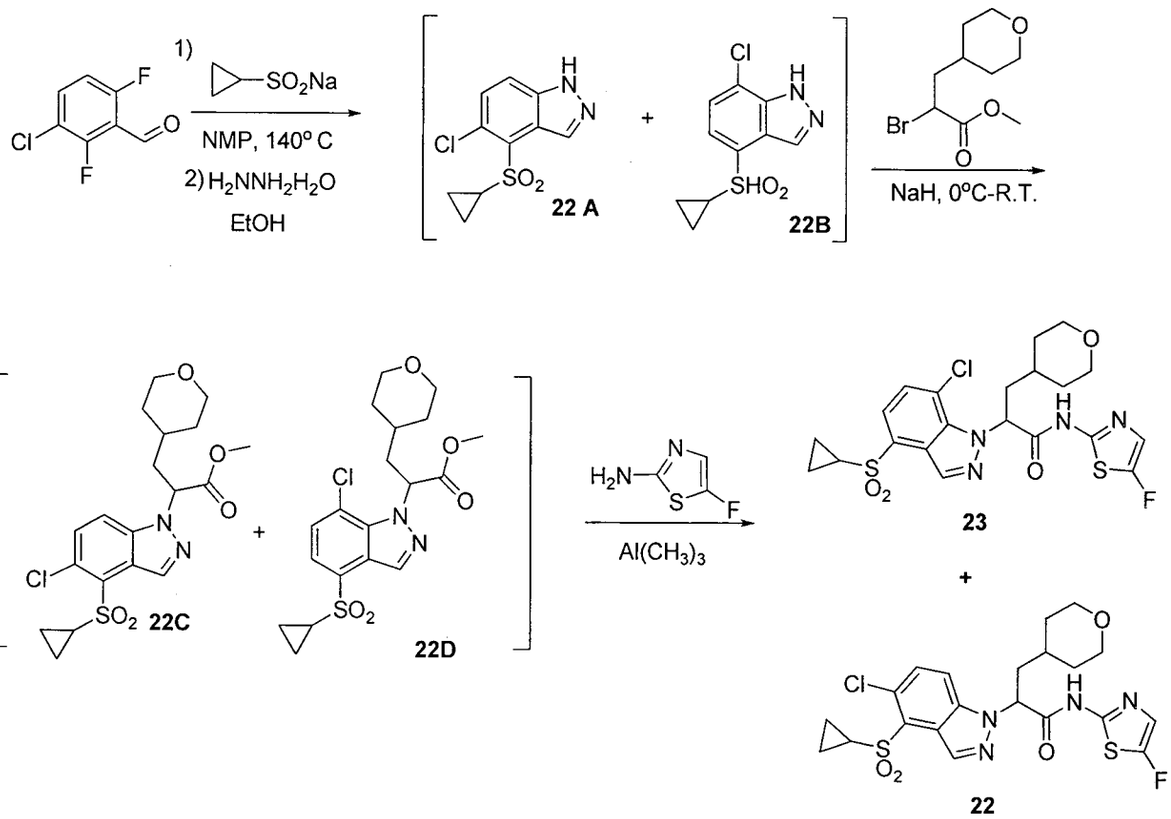
[00492] Una solución de 2-(6-ciano-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida **120** (0,06g, 0,11 mmol) en EtOH (5ml) se agregó a un frasco para microondas seguido de NaOH 3N (1ml) y la mezcla se calentó a 100°C durante 40 min. El solvente se eliminó al vacío y el residuo se dividió entre HCl 1N y EtOAc. La capa orgánica se secó sobre Na_2SO_4 para dar el ácido carboxílico **21** bruto. [M+H] calc. para $C_{22}H_{24}FN_4O_6S_2$ 523,1, experimental 523,3.

[00493] Se combinaron ácido 4-(ciclopropilsulfonil)-1-(1-(5-fluorotiazol-2-ilamino)-1-oxo-3-(tetrahidro-2H-piran-4-il)propan-2-il)-1H-indazol-6-carboxílico **21** (0,1g, 0,19 mmol), difenil fosforazidato (0,05g, 0,19 mmol), trietilamina (0,03g, 0,3 mmol), y tBuOH (0,016g, 0,21 mmol) en tolueno (10 ml) y se reflujaron durante 2h. El solvente se eliminó y el residuo se trató con TFA/ DCM (1/1) durante 15 min. La mezcla se concentró bajo presión reducida y se purificó utilizando HPLC prep. (Waters System: Columna es Phenomenex C18, 5 μ, 150X50 mm, fase móvil A: 0,05% TFA en H_2O y fase móvil B es 0,035% TFA en acetonitrilo) para dar el **compuesto 142** as en forma de un sólido color marrón rojizo (50 mg); [M+H] calc. para $C_{21}H_{25}FN_5O_4S_2$ 494,1, experimental 494,4

Compuesto 22 : 2-(5-cloro-4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanoato de metilo

Compuesto 23: 2-(7-cloro-4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-

il)propanoato de metilo

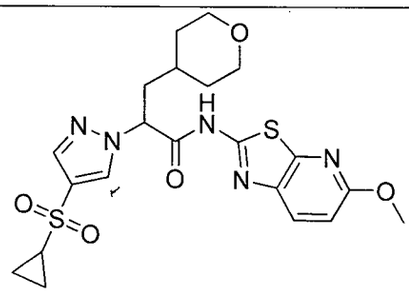


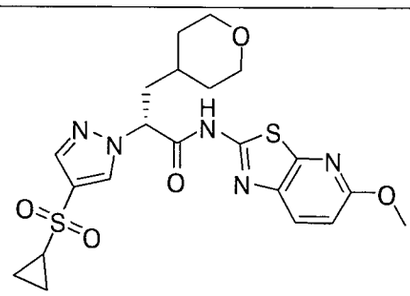
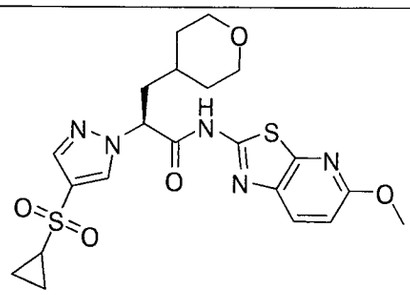
[00494] Se combinaron 3-cloro-2,6-difluorobenzaldehído (0,22 g, 1,23 mmol) y ciclopropansulfinato de sodio (0,19 g, 1,35 mmol) en NMP (3 ml) y se calentó a 140°C durante 0,5h. La mezcla de reacción se diluyó con MeOH y se purificó utilizando HPLC para dar una mezcla de 5-cloro-4-(ciclopropilsulfonil)-1H-indazol **22A** y 7-cloro-4-(ciclopropilsulfonil)-1H-indazol **22 B** en forma de un sólido color blanco (0,14g); [M+H] calc. para $C_{10}H_{10}ClN_2O_2S$ 257,0, experimental 257,1. El análisis ^{1}HRMN confirmó la mezcla de regioisómeros en una relación 1:1 aproximada.

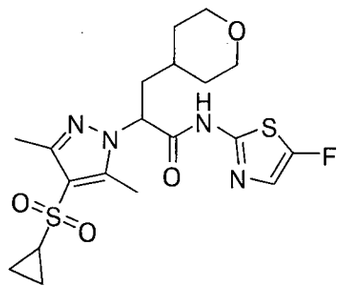
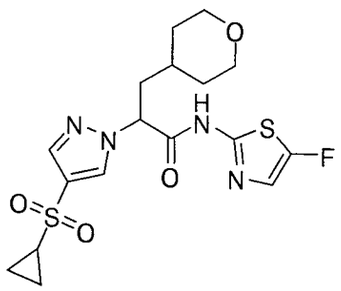
[00495] La mezcla de **22A** y **22 B** (0,14g, 0,54mmol) se disolvió en DMF (4 ml) y la solución se enfrió hasta 0°C. Se agregó NaH (0,02 g, 0,65 mmol) y, cuando la reacción bajó, se agregó 2-bromo-3-(tetrahidro-2H-piran-4-il)propanoato de metilo (0,20, 0,81 mmol) a la mezcla de reacción. La mezcla de reacción se entibió a continuación hasta temperatura ambiente y se agitó durante 1h. La reacción se templó con un pequeño volumen de MeOH y se concentró al vacío. El residuo se dividió en porciones entre EtOAc y HCl 1N. La capa orgánica se secó sobre Na_2SO_4, se filtró y se purificó por cromatografía de columna flash para dar los compuestos **22C y 22D** en forma de un aceite transparente (0,41g); [M+H] calc. para $C_{19}H_{24}ClN_2O_5S$ 427,1, experimental 427,3. La mezcla de isómeros se utilizó como estaba en el próximo paso.

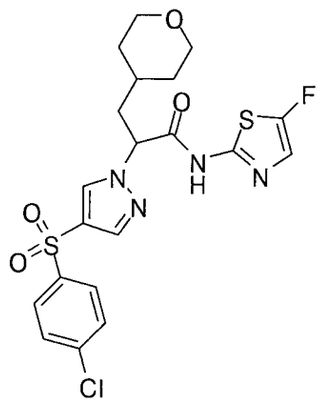
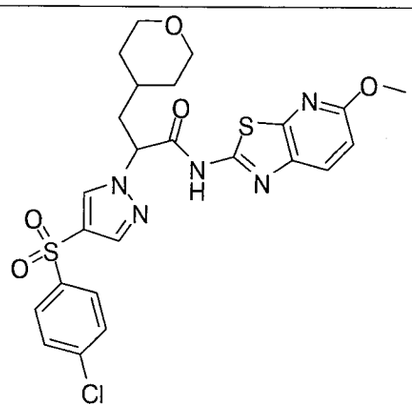
[00496] Compuestos 22 y 23: A una solución de 5-fluorotiazol-2-amina (0,29 g, 1,9 mmol) en DCE (5 ml) a 0ºC bajo una atmósfera N2 se agregó trimetil aluminio (2M en hexanos) (1,9 mmol). Después de 15 min, se agregó una solución de los compuestos **22C y 22D** (0,41g, 0,96 mmol) en DCE (3 ml) a la mezcla de reacción y la solución se calentó en una estufa de microondas a 100ºC durante 1h. La mezcla de reacción se enfrió a continuación en un baño de hielo, se templó con HCl 1N y se extrajo 2X con EtOAc. La capa orgánica se secó sobre Na_2SO_4 y el residuo bruto se purificó por cromatografía de columna flash utilizando (DCM/ MeOH, 0%- 10%) para dar los compuestos **22** y **23** puros. Compuesto **22:** [M+H] calc. para $C_{21}H_{23}ClFN_4O_4S_2$ 513,1, experimental 513,2; ^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 0,96 - 1,14 (m, 2 H) 1,28 - 1,48 (m, 5 H) 1,54 (br. s., 1 H) 1,71 (d, *J*=7,58 Hz, 1 H) 2,32 - 2,60 (m, 3 H) 3,19 - 3,37 (m, 2 H) 3,78 - 4,06 (m, 2 H) 5,42 (dd, *J*=9,22, 6,19 Hz, 1 H) 7,08 (br. s., 1 H) 7,45 - 7,60 (m, 1 H) 7,68 (d, *J*=7,58 Hz, 1 H) 8,60 (s, 1 H). Compuesto **23** [M+H] calc. para $C_{21}H_{23}ClFN_4O_4S_2$ 513,1, experimental 513,2; ^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 0,93 - 1,20 (m, 1 H) 1,30 - 1,60 (m, 5 H) 1,67 (br. s., 3 H) 2,16 - 2,38 (m, 1 H) 2,46 - 2,74 (m, 2 H) 3,17 - 3,44 (m, 2 H) 3,79 - 4,01 (m, 2 H) 6,49 (br. s., 1 H) 7,00 (d, *J*=2,53 Hz, 1 H) 7,60 (dd, *J*=7,83, 4,04 Hz, 1 H) 7,67 - 7,80 (m, 1 H) 8,72 (s, 1 H).

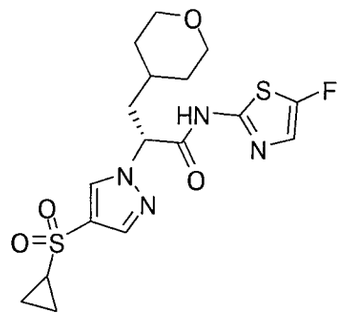
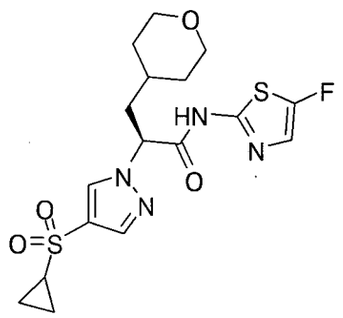
[00497] Además de lo anterior, los esquemas de reacción y sus variantes se pueden utilizar para preparar lo siguiente.

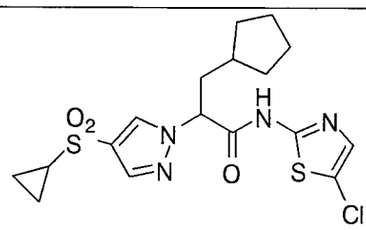
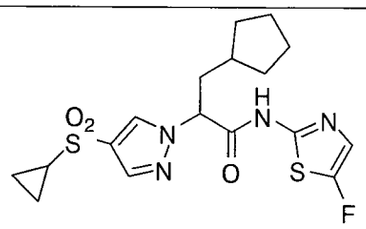
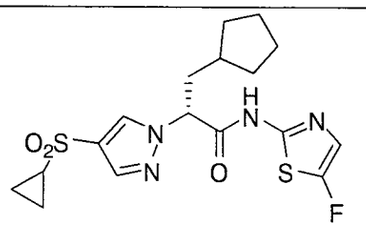
Ej.	Estructura	Método	LCMS	Datos de RMN
24	 2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-metoxitiazolo[5,4-b]piridin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 1	[M+H] calc. para $C_{21}H_{26}N_5O_5S_2$, 492,13; experimental 492,0	^{1}H RMN (400 MHz, MeOD) δ ppm 1,00 - 1,14 (m, 2 H) 1,16 - 1,47 (m, 6 H) 1,66 - 1,84 (m, 2 H) 2,15 (br. s., 1 H) 2,32 (dd, *J*=14,40, 6,82 Hz, 1 H) 2,63 - 2,87 (m, 1 H) 3,77 (s, 3 H) 3,85 - 3,98 (m, 4 H) 5,47 (dd, *J*=10,23, 5,43 Hz, 1 H) 6,84 (d, *J*=8,84 Hz, 1 H) 7,90 - 7,95 (m, 1 H) 8,51 (s, 1 H).

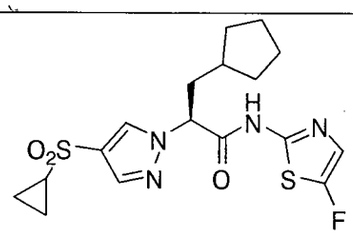
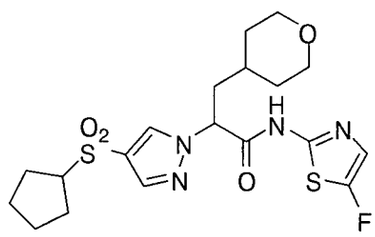
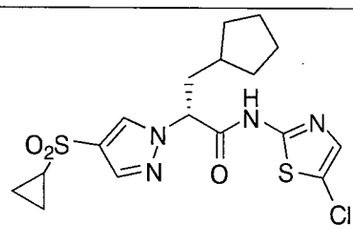
Ej.	Estructura	Método	LCMS	Datos de RMN
25	 (R)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-metoxitiazolo[5,4-b]piridin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comps. 2 y 3	[M+H] calc. para $C_{21}H_{26}N_5O_5S_2$, 492,13; experimental 492,0	^{1}H RMN (400 MHz, MeOD) δ ppm 1,00 - 1,14 (m, 2 H) 1,16 - 1,47 (m, 6 H) 1,66 - 1,84 (m, 2 H) 2,15 (br. s., 1 H) 2,32 (dd, *J*=14,40, 6,82 Hz, 1 H) 2,63 - 2,87 (m, 1 H) 3,77 (s, 3 H) 3,85 - 3,98 (m, 4 H) 5,47 (dd, *J*=10,23, 5,43 Hz, 1 H) 6,84 (d, *J*=8,84 Hz, 1 H) 7,90 - 7,95 (m, 1 H) 8,51 (s, 1 H).
26	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-metoxitiazolo[5,4-b]piridin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comps. 2 y 3	[M+H] calc. para $C_{21}H_{26}N_5O_5S_2$, 492,13; experimental 492,0	^{1}H RMN (400 MHz, MeOD) δ ppm 1,00 - 1,14 (m, 2 H) 1,16 - 1,47 (m, 6 H) 1,66 - 1,84 (m, 2 H) 2,15 (br. s., 1 H) 2,32 (dd, *J*=14,40, 6,82 Hz, 1 H) 2,63 - 2,87 (m, 1 H) 3,77 (s, 3 H) 3,85 - 3,98 (m, 4 H) 5,47 (dd, *J*=10,23, 5,43 Hz, 1 H) 6,84 (d, *J*=8,84 Hz, 1 H) 7,90 - 7,95 (m, 1 H) 8,51 (s, 1 H).

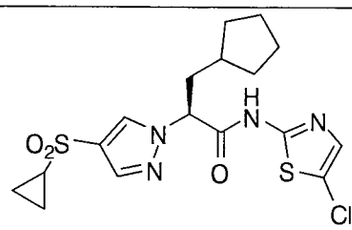
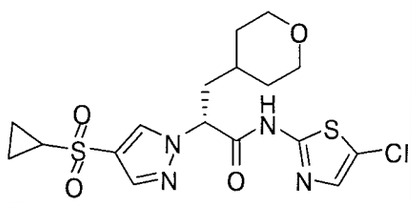
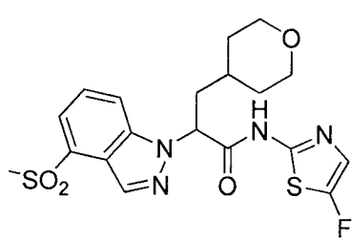
Ej.	Estructura	Método	LCMS	Datos de RMN
27	 2-(4-(ciclopropilsulfonil)-3,5-dimetil-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{19}H_{26}FN_4O_4S_2$, 457,13; experimental 457	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,03 (d, *J*=8,08 Hz, 2 H) 1,21 - 1,45 (m, 5 H) 1,50 - 1,63 (m, 2 H) 2,09 - 2,31 (m, 2 H) 2,48 (d, *J*=3,28 Hz, 1 H) 2,51 (s, 3 H) 2,54 (s, 3 H) 3,33 (d, *J*=9,60 Hz, 2 H) 3,87 - 4,01 (m, 2 H) 4,96 (dd, *J*=9,35, 5,81 Hz, 1 H) 7,06 (d, *J*=2,78 Hz, 1 H)
28	 2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{22}FN_4O_4S_2$, 429,10, experimental 429	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,09 (dq, *J*=7,86, 2,43 Hz, 2 H) 1,27 - 1,46 (m, 5 H) 1,53 (d, *J*=9,35 Hz, 1 H) 1,68 (d, *J*=11,87 Hz, 1 H) 2,23 (d, *J*=14,15 Hz, 1 H) 2,07 - 2,31 (m, 1 H) 2,51 - 2,62 (m, 1 H) 3,33 (dd, *J*=11,37, 2,27 Hz, 2 H) 3,95 (t, *J*=11,87 Hz, 2 H) 5,19 (dd, *J*=9,73, 5,68 Hz, 1 H) 6,40 (br.s., 1H) 7,11 (d, *J*=2,53 Hz, 1 H) 7,94 (s, 1 H) 8,09 (s, 1 H)

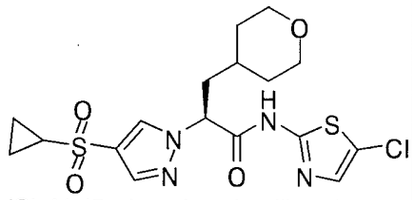
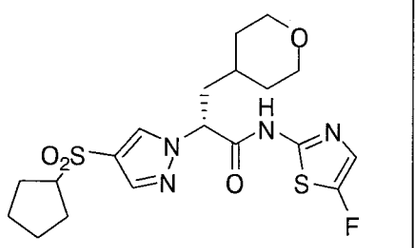
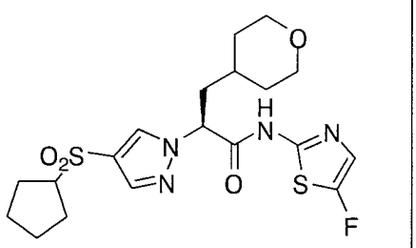
Ej.	Estructura	Método	LCMS	Datos de RMN
29	 2-(4-(4-clorofenilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{20}H_{21}ClFN_4O_4S_2$, 499,06, experimental 499	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,32 (br. s., 2 H) 1,34 (d, *J*=4,29 Hz, 1 H) 1,48 (br. s., 1 H) 1,62 (br. s., 1 H) 2,16 (d, *J*=6,57 Hz, 2 H) 3,23 - 3,34 (m, 2 H) 3,93 (dd, *J*=16,42, 11,87 Hz, 2 H) 5,11 (dd, *J*=9,47, 6,19 Hz, 1 H) 5,50 (br.s., 1H) 7,08 (d, *J*=2,78 Hz, 1 H) 7,51 (d, *J*=8,59 Hz, 2 H) 7,87 - 7,93 (m, 3 H) 8,10 (s, 1 H)
30	 2-(4-(4-clorofenilsulfonil)-1H-pirazol-1-il)-N-(5-metoxitiazolo[5,4-b]piridin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{24}H_{25}ClN_5O_5S_2$, 562,09, experimental 562	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,34 (t, *J*=10,11 Hz, 2 H) 1,36 (br. s., 1 H) 1,50 (br. s., 1 H) 1,65 (br. s., 1 H) 2,24 (d, *J*=4,55 Hz, 1 H) 2,21 (t, *J*=6,06 Hz, 1 H) 3,27 - 3,36 (m, 2 H) 4,00 (s, 3H), 3,87 - 3,98 (m, 2H) 5,17 (dd, *J*=9,35, 6,06 Hz, 1 H) 6,87 (d, *J*=8,84 Hz, 1 H) 7,51 (d, *J*=8,34 Hz, 2 H) 7,86 - 7,93 (m, 3 H) 7,95 (s, 1 H) 8,11 (s, 1 H)

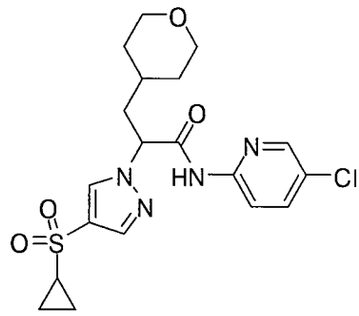
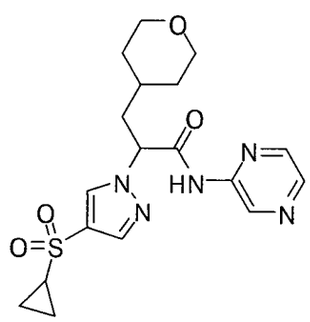
Ej.	Estructura	Método	LCMS	Datos de RMN
31	 (R)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comps. 2 y 3	[M+H] calc. para $C_{17}H_{22}FN_4O_4S_2$, 429,10, experimental 429	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,09 (dq, *J*=7,86, 2,43 Hz, 2 H) 1,27 - 1,46 (m, 5 H) 1,53 (d, *J*=9,35 Hz, 1 H) 1,68 (d, *J*=11,87 Hz, 1 H) 2,23 (d, *J*=14,15 Hz, 1 H) 2,07 - 2,31 (m, 1 H) 2,51 - 2,62 (m, 1 H) 3,33 (dd, *J*=11,37, 2,27 Hz, 2 H) 3,95 (t, *J*=11,87 Hz, 2 H) 5,19 (dd, *J*=9,73, 5,68 Hz, 1 H) 6,40 (br.s., 1H) 7,11 (d, *J*=2,53 Hz, 1 H) 7,94 (s, 1 H) 8,09 (s, 1 H)
32	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comps. 2 y 3	[M+H] calc. para $C_{17}H_{22}FN_4O_4S_2$, 429,10, experimental 429	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,09 (dq, *J*=7,86, 2,43 Hz, 2 H) 1,27 - 1,46 (m, 5 H) 1,53 (d, *J*=9,35 Hz, 1 H) 1,68 (d, *J*=11,87 Hz, 1 H) 2,23 (d, *J*=14,15 Hz, 1 H) 2,07 - 2,31 (m, 1 H) 2,51 - 2,62 (m, 1 H) 3,33 (dd, *J*=11,37, 2,27 Hz, 2 H) 3,95 (t, *J*=11,87 Hz, 2 H) 5,19 (dd, *J*=9,73, 5,68 Hz, 1 H) 6,40 (br.s., 1H) 7,11 (d, *J*=2,53 Hz, 1 H) 7,94 (s, 1 H) 8,09 (s, 1 H)

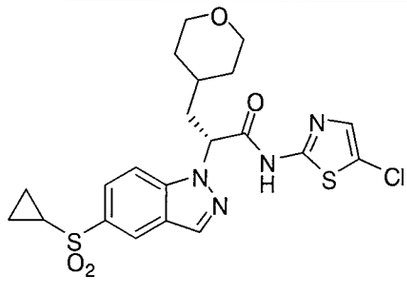
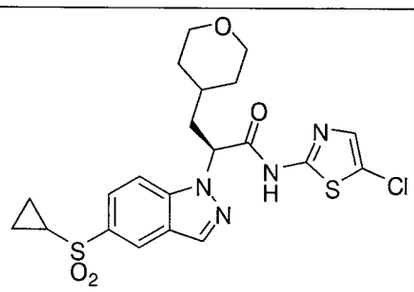
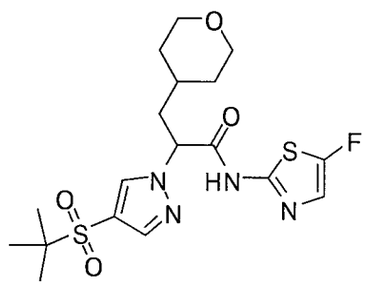
Ej.	Estructura	Método	LCMS	Datos de RMN
33	 N-(5-clorotiazol-2-il)-3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{22}ClN_4O_3S_2$, 429,07, experimental 429	^{1}H RMN (400 MHz, CLOROFORM-d) δ ppm 1,15 (m, 4H) 1,36 (m, 2H) 1,59 (m, 6) 1,79 (m, 1H) 2,29 (m, 2H) 2,56 (m, 1H), 5,03 (m, 1H) 7,35 (s, 1H) 7,99 (s, 1H) 8,06 (m, 1H)
34	 3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{22}FN_4O_3S_2$, 413,50, experimental 413	^{1}H RMN (400 MHz, CLOROFORM-d) δ ppm 1,13 (m, 4H) 1,37 (m, 2H) 1,57 (m, 6H) 1,79 (m, 1H) 2,25 (m, 2H) 2,55 (m, 1H) 5,02 (m, 1H) 7,14 (s, 1H) 7,97 (s, 1H) 8,17 (s, 1H)
35	 (R)-3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{22}FN_4O_3S_2$ 413,50; experimental 413,36	^{1}H RMN (400 MHz, CLOROFORM-d) δ ppm 1,13 (m, 4H) 1,37 (m, 2H) 1,57 (m, 6H) 1,79 (m, 1H) 2,25 (m, 2H) 2,55 (m, 1H) 5,02 (m, 1H) 7,14 (s, 1H) 7,97 (s, 1H) 8,17 (s, 1H)

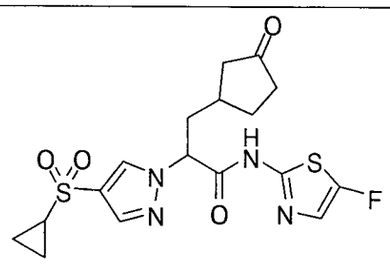
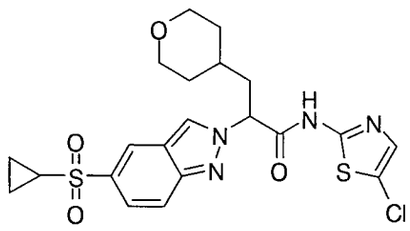
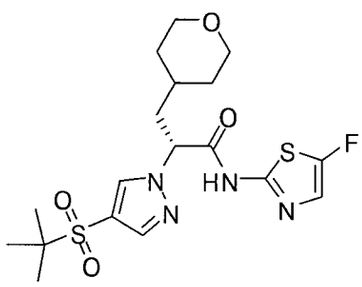
Ej.	Estructura	Método	LCMS	Datos de RMN
36	 (S)-3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{22}FN_4O_3S_2$ 413,50; experimental 413,36	^{1}H RMN (400 MHz, CLOROFORM-d) δ ppm 1,13 (m, 4H) 1,37 (m, 2H) 1,57 (m, 6H) 1,79 (m, 1H) 2,25 (m, 2H) 2,55 (m, 1H) 5,02 (m, 1H) 7,14 (s, 1H) 7,97 (s, 1H) 8,17 (s, 1H)
37	 2-(4-(ciclopentilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 5	[M+H] calc. para $C_{19}H_{26}FN_4O_4S_2$ 457,56, experimental 457	^{1}H RMN (400 MHz, CLOROFORM-d) δ ppm 1,34 (m, 3H) 1,50 (m, 1H) 1,65 (m, 3H) 1,77 (m, 2H) 2,02 (m, 4H) 2,16 (m, 1H), 2,24 (m, 1H) 3,29 (m, 2H) 3,50 (m, 1H) 3,94 (t, J = 16, 16 Hz, 2H) 5,13 (m, 1H) 7,08 (d, J = 4 Hz, 1H) 7,98 (s, 1H) 8,06 (s, 1H)
38	 (R)-N-(5-clorotiazol-2-il)-3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{22}ClN_4O_3S_2$ 429,96, experimental 429,36	^{1}H RMN (400 MHz, CLOROFORM-d) δ ppm 1,15 (m, 4H) 1,36 (m, 2H) 1,59 (m, 6) 1,79 (m, 1H) 2,29 (m, 2H) 2,56 (m, 1H), 5,03 (m, 1H) 7,35 (s, 1H) 7,99 (s, 1H) 8,06 (m, 1H)

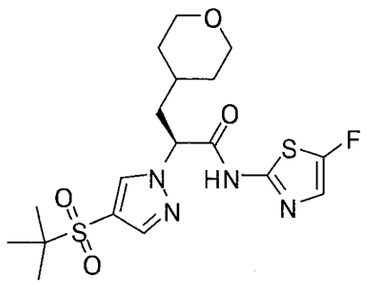
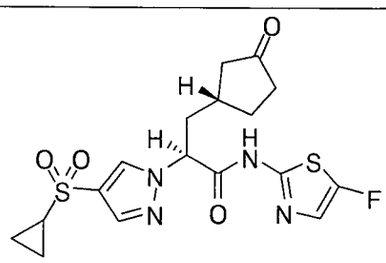
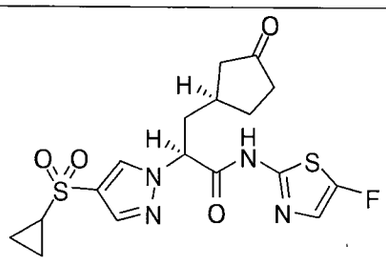
Ej.	Estructura	Método	LCMS	Datos de RMN
39	 (S)-N-(5-clorotiazol-2-il)-3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{22}ClN_4O_3S_2$ 429,96, Experimental 429,3	^{1}H RMN (400 MHz, CLOROFORM-d) δ ppm 1,15 (m, 4H) 1,36 (m, 2H) 1,59 (m, 6) 1,79 (m, 1H) 2,29 (m, 2H) 2,56 (m, 1H), 5,03 (m, 1H) 7,35 (s, 1H) 7,99 (s, 1H) 8,06 (m, 1H)
40	 (R)-N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comps. 2 y 3	[M+H] calc. para $C_{17}H_{22}ClN_4O_4S_2$, 445,07; experimental 445,2.	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 0,93 - 1,75 (m, 9 H) 2,19 (br. s., 2 H) 2,55 (br. s., 1 H) 3,31 (br. s., 2 H) 3,94 (br. s., 2 H) 5,10 (br. s., 1 H) 7,32 (s, 1 H) 8,01 (d, *J*=9,35 Hz, 2 H) 10,35 (bs, 1 H)
41	 N-(5-fluorotiazol-2-il)-2-(4-(metilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* comp. 10	[M+H] calc. para $C_{19}H_{21}FN_4O_4S_2$ 454, experimental 454	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,21 - 1,42 (m, 3 H) 1,42 - 1,49 (m, 1 H) 1,66 - 1,74 (m, 1 H) 2,13 - 2,22 (m, 1 H) 2,49 - 2,58 (m, 1 H) 3,13 - 3,26 (m, 2 H) 3,29 (br. s., 3 H) 3,78 - 3,89 (m, 2 H) 5,65 (dd, *J*=10,61, 4,80 Hz, 1 H) 7,08 (d, *J*=2,53 Hz, 1 H) 7,30 - 7,41 (m, 2 H) 7,67 (d, *J*=8,08 Hz, 1 H) 8,11 (s, 1 H)

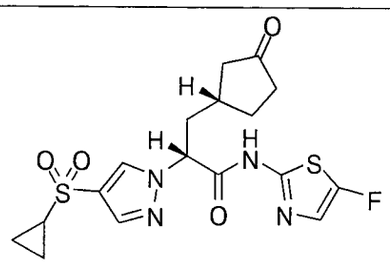
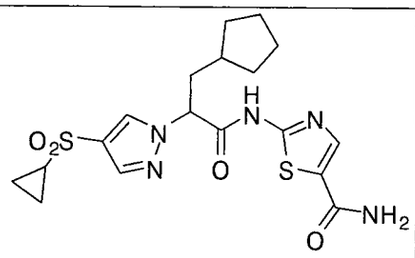
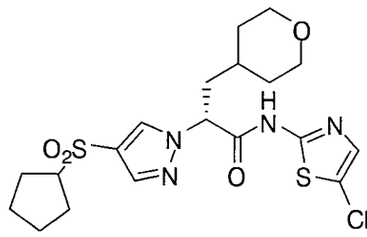
Ej.	Estructura	Método	LCMS	Datos de RMN
42	 (S)-N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comps. 2 y 3	[M+H] calc. para $C_{17}H_{22}ClN_4O_4S_2$, 445,07; experimental 445,2.	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 0,93 - 1,75 (m, 9 H) 2,19 (br. s., 2 H) 2,55 (br. s., 1 H) 3,31 (br. s., 2 H) 3,94 (br. s., 2 H) 5,10 (br. s., 1 H) 7,32 (s, 1 H) 8,01 (d, *J*=9,35 Hz, 2 H) 10,35 (bs, 1 H)
43	 (R)-2-(4-(ciclopentilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 5	[M+H] calc. para $C_{19}H_{26}FN_4O_4S_2$ 457,56, experimental 457	^{1}H RMN (400 MHz, CLOROFORM-d). δ ppm 1,34 (m, 3H) 1,50 (m, 1H) 1,65 (m, 3H) 1,77 (m, 2H) 2,02 (m, 4H) 2,16 (m, 1H), 2,24 (m, 1H) 3,29 (m, 2H) 3,50 (m, 1H) 3,94 (t, J = 16, 16 Hz, 2H) 5,13 (m, 1H) 7,08 (d, J = 4 Hz, 1H) 7,98 (s, 1H) 8,06 (s, 1H)
44	 (S)-2-(4-(ciclopentilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 5	[M+H] calc. para $C_{19}H_{26}FN_4O_4S_2$ 457,56, experimental 457	^{1}H RMN (400 MHz, CLOROFORM-d). δ ppm 1,34 (m, 3H) 1,50 (m, 1H) 1,65 (m, 3H) 1,77 (m, 2H) 2,02 (m, 4H) 2,16 (m, 1H), 2,24 (m, 1H) 3,29 (m, 2H) 3,50 (m, 1H) 3,94 (t, J = 16, 16 Hz, 2H) 5,13 (m, 1H) 7,08 (d, J = 4 Hz, 1H) 7,98 (s, 1H) 8,06 (s, 1H)

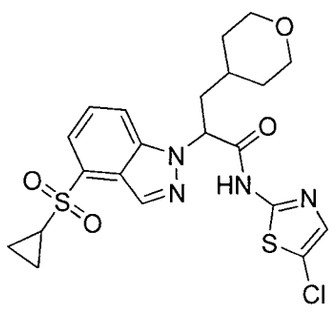
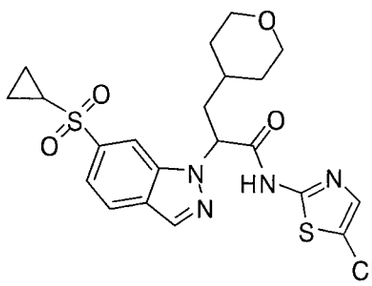
Ej.	Estructura	Método	LCMS	Datos de RMN
45	 N-(5-cloropiridin-2-il)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{19}H_{24}ClN_4O_4S$, 439,11, experimental 439	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,08 (dd, *J*=8,08, 2,02 Hz, 2 H) 1,30 - 1,44 (m, 1 H) 1,36 (dd, *J*=4,42, 2,15 Hz, 4 H) 1,53 (d, *J*=9,09 Hz, 1 H) 1,68 (d, *J*=9,85 Hz, 1 H) 2,19 (t, *J*=6,32 Hz, 1 H) 2,25 (dd, *J*=9,85, 4,04 Hz, 1 H) 2,57 (ddd, *J*=7,96, 4,80, 3,16 Hz, 1 H) 3,31 (td, *J*=11,24, 8,08 Hz, 1 H) 3,25 - 3,37 (m, 1 H) 3,88 - 4,00 (m, 2 H) 5,12 (dd, *J*=9,73, 5,68 Hz, 1 H) 7,74 (dd, *J*=8,84, 2,53 Hz, 1 H) 7,98 (s, 1 H) 8,11 (s, 1 H) 8,20 (d, *J*=8,84 Hz, 1 H) 8,24 (d, *J*=2,27 Hz, 1 H) 9,66 (br. s., 1 H)
46	 2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{18}H_{24}N_5O_4S$, 406,15, experimental 406	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,09 (dd, *J*=7,71, 1,64 Hz, 2 H) 1,29 - 1,47 (m, 5 H) 1,54 (br. s., 1 H) 1,66 (br. s., 1 H) 2,14 - 2,38 (m, 2 H) 2,51 - 2,63 (m, 1 H) 3,23 - 3,42 (m, 2 H) 3,87 - 4,03 (m, 2 H) 5,07 (dd, *J*=9,60, 5,56 Hz, 1 H) 8,03 (d, *J*=6,57 Hz, 2 H) 8,32 (s, 1 H) 8,42 (d, *J*=2,27 Hz, 1 H) 9,27 (br. s., 1 H) 9,50 (s, 1 H)

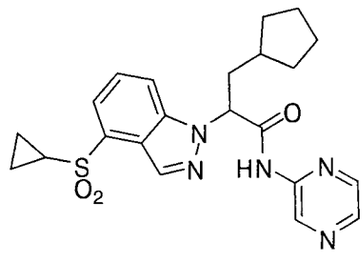
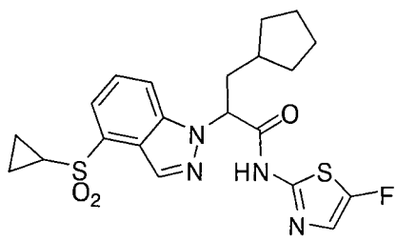
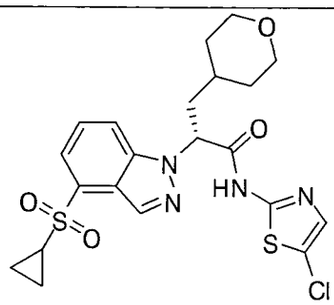
Ej.	Estructura	Método	LCMS	Datos de RMN
47	 (R)-N-(5-clorotiazol-2-il)-2-(5-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}ClN_4O_4S_2$ 496,01, experimental 496,1	
48	 (S)-N-(5-clorotiazol-2-il)-2-(5-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}ClN_4O_4S_2$ 496,01, experimental 496,1	
49	 2-(4-(ter-butilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{18}H_{26}FN_4O_4S_2$, 445,13, experimental 445,3	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,29 - 1,45 (m, 3 H) 1,38 (s, 9 H) 1,51 (d, *J*=2,27 Hz, 1 H) 1,64 (d, *J*=11,62 Hz, 1 H) 2,04 - 2,29 (m, 2 H) 3,14 - 3,35 (m, 2 H) 3,80 - 4,02 (m, 2 H) 5,12 (dd, *J*=9,85, 5,81 Hz, 1 H) 7,12 (d, *J*=2,78 Hz, 1 H) 7,95 (s, 1 H) 8,03 (s, 1 H)

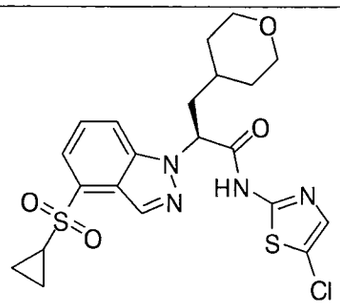
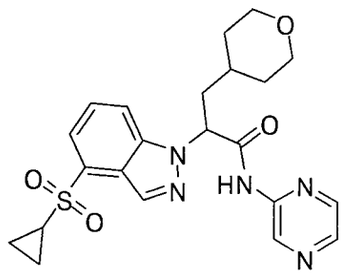
Ej.	Estructura	Método	LCMS	Datos de RMN
50	 2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(3-oxociclopentil)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{20}FN_4O_4S_2$ 427,08, experimental 427,1	
51	 N-(5-clorotiazol-2-il)-2-(5-(ciclopropilsulfonil)-2H-indazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}ClN_4O_4S_2$ 496,01, experimental 496,1	^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,00 - 1,13 (m, 2 H) 1,20 - 1,64 (m, 7 H) 1,76 (d, *J*=12,38 Hz, 1 H) 2,27 - 2,42 (m, 1 H) 2,43 - 2,60 (m, 2 H) 3,30 (t, *J*=10,86 Hz, 2 H) 3,87 - 4,08 (m, 2 H) 5,57 (dd, *J*=9,73, 5,18 Hz, 1 H) 7,32 (br. s., 1 H) 7,70 - 7,82 (m, 1 H) 7,87 (d, *J*=9,09 Hz, 1 H) 8,42 (d, *J*=5,56 Hz, 2 H)
52	 (R)-2-(4-(ter-butilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comps. 2 y 3	[M+H] calc. para $C_{18}H_{26}FN_4O_4S_2$, 445,13, experimental 445,3	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,29 - 1,45 (m, 3 H) 1,38 (s, 9 H) 1,51 (d, *J*=2,27 Hz, 1 H) 1,64 (d, *J*=11,62 Hz, 1 H) 2,04 - 2,29 (m, 2 H) 3,14 - 3,35 (m, 2 H) 3,80 - 4,02 (m, 2 H) 5,12 (dd, *J*=9,85, 5,81 Hz, 1 H) 7,12 (d, *J*=2,78 Hz, 1 H) 7,95 (s, 1 H) 8,03 (s, 1 H)

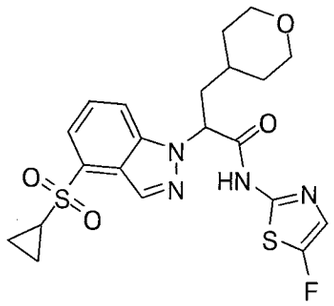
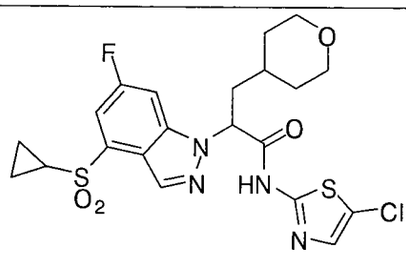
Ej.	Estructura	Método	LCMS	Datos de RMN
53	 (S)-2-(4-(ter-butilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comps. 2 y 3	[M+H] calc. para $C_{18}H_{26}FN_4O_4S_2$, 445,13, experimental 445,3	1H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,29 - 1,45 (m, 3 H) 1,38 (s, 9 H) 1,51 (d, *J*=2,27 Hz, 1 H) 1,64 (d, *J*=11,62 Hz, 1 H) 2,04 - 2,29 (m, 2 H) 3,14 - 3,35 (m, 2 H) 3,80 - 4,02 (m, 2 H) 5,12 (dd, *J*=9,85, 5,81 Hz, 1 H) 7,12 (d, *J*=2,78 Hz, 1 H) 7,95 (s, 1 H) 8,03 (s, 1 H)
54	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(R)-3-oxociclopentil)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{20}FN_4O_4S_2$ 427,08, experimental 427,1	
55	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(S)-3-oxociclopentil)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{20}FN_4O_4S_2$ 427,08, experimental 427,1	

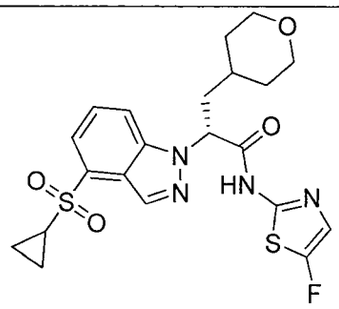
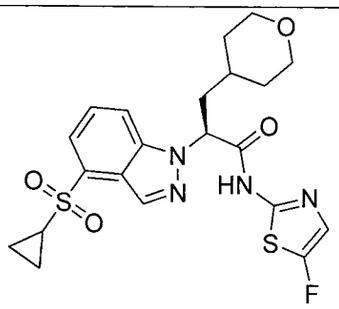
Ej.	Estructura	Método	LCMS	Datos de RMN
56	 (R)-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)-N-(5-fluorotiazol-2-il)-3-(R)-3-oxociclopentil)propanamida	*ver* Comp. 4	[M+H] calc. para $C_{17}H_{20}FN_4O_4S_2$ 427,08, experimental 427,1	
57	 2-(3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-pirazol-1-il)propanamido)tiazol-5-carboxamida	*ver* Comps. 6 y 7	[M+H] calc. para $C_{18}H_{24}N_5O_4S_2$ 438,54, experimental 438	^{1}H RMN (400 MHz, DMSO-d6). δ ppm 1,06 (m, 4H) 1,27 (m, 1H) 1,56 (m, 6H) 2,11 (m, 1H) 2,33 (m, 1H) 2,84 (m, 1H), 3,75 (s, 2H) 5,36 (m, 1H) 7,95 (s, 1H) 8,08 (s, 1H) 8,63 (s, 1H)
58	 (R)-N-(5-clorotiazol-2-il)-2-(4-(ciclopentilsulfonil)-1H-pirazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 5	[M+H] calc. para $C_{19}H_{26}ClN_4O_4S_2$ 474,01, experimental 474	^{1}H RMN (400 MHz, CLOROFORM-d). □ ppm 1,34 (m, 3H) 1,50 (m, 1H) 1,65 (m, 3H) 1,77 (m, 2H) 2,02 (m, 4H) 2,19 (m, 2H), 3,29 (m, 2H) 3,52 (m, 1H) 3,95 (t, J = 12, 12 Hz, 2H) 5,16 (m, 1H) 7,32 (d, J = 4 Hz, 1H) 7,98 (s, 1H) 8,06 (s, 1H)

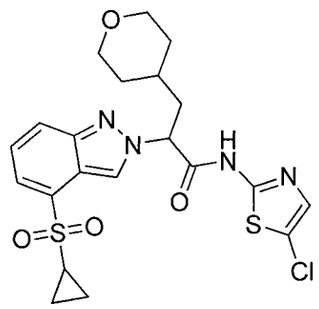
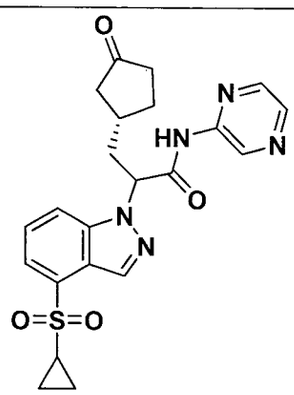
Ej.	Estructura	Método	LCMS	Datos de RMN
59	 N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}ClN_4O_4S_2$ 496,01, experimental 496,1	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,00 - 1,12 (m, 2 H) 1,14 - 1,38 (m, 5 H) 1,45 (br. s., 1 H) 1,60 (br. s., 1 H) 2,26 (d, *J*=6,57 Hz, 1 H) 2,46 (br. s., 1 H) 2,91 - 3,21 (m, 3 H) 3,68 - 3,84 (m, 2 H) 5,87 (dd, *J*=9,98, 4,93 Hz, 1 H) 7,56 (s, 1 H) 7,63 - 7,76 (m, 2 H) 8,18 (d, *J*=8,34 Hz, 1 H) 8,45 (s, 1 H)
60	 N-(5-clorotiazol-2-il)-2-(6-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}ClN_4O_4S_2$ 496,01, experimental 496,1	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,00 - 1,09 (m, 2 H) 1,12 - 1,37 (m, 5 H) 1,45 (d, *J*=8,08 Hz, 1 H) 1,60 (d, *J*=12,13 Hz, 1 H) 2,21 - 2,33 (m, 1 H) 2,35 - 2,47 (m, 1 H) 2,83 - 2,94 (m, 1 H) 3,00 - 3,17 (m, 2 H) 3,70 - 3,85 (m, 2 H) 5,93 (dd, *J*=9,60, 5,31 Hz, 1 H) 7,56 (s, 1 H) 7,64 - 7,72 (m, 1 H) 8,08 (d, *J*=8,59 Hz, 1 H) 8,41 (d, *J*=10,86 Hz, 2 H)

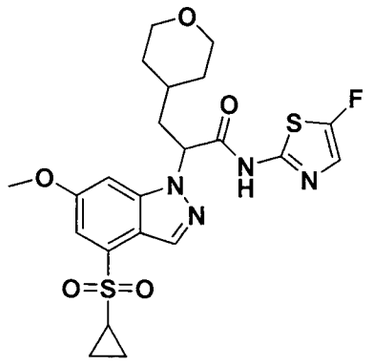
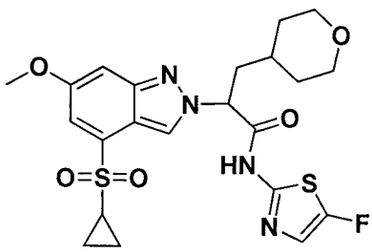
Ej.	Estructura	Método	LCMS	Datos de RMN
61	 3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(pirazin-2-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{26}N_5O_3S$ 440,53; experimental 440	^{1}H RMN (400 MHz, MeOD). δ ppm 1,06 (m, 3H) 1,29 (m, 3H) 1,43 (m, 2H) 1,60 (m, 4H) 1,74 (m, 1H) 2,31 (m, 1H) 2,64 (m, 1H) 2,81 (m, 1H) 5,64 (m, 1H) 7,74 (d, J = 4 Hz, 1H) 8,11 (d, J = 8 Hz, 1H) 8,30 (s, 1H) 8,34 (s, 1H) 8,50 (s, 1H)
62	 3-ciclopentil-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}FN_4O_3S_2$ 463,56; experimental 463	^{1}H RMN (400 MHz, MeOD). δ ppm 1,07 (m, 3H) 1,29 (m, 3H) 1,45 (m, 3H) 1,60 (m, 3H) 1,74 (m, 1H) 2,29 (m, 1H) 2,60 (m, 1H) 2,80 (m, 1H) 5,64 (m, 1H) 7,09 (d, J = 4 Hz, 1H) 7,64 (t, J = 8, 8 Hz, 1H) 7,74 (d, J = 8 Hz, 1H) 8,09 (d, J = 12 Hz, 1H) 8,47 (s, 1H)
63	 (R)-N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}ClN_4O_4S_2$ 496,01, experimental 496,1	

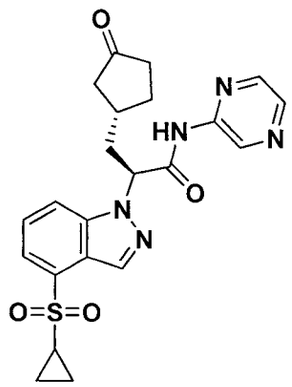
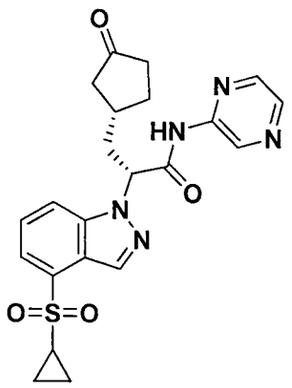
Ej.	Estructura	Método	LCMS	Datos de RMN
64	 (S)-N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}ClN_4O_4S_2$ 496,01, experimental 496,1	
65	 2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{26}N_5O_4S$ 456,53, experimental 456,5	^{1}H RMN (400 MHz, MeOD) δ ppm 0,91 - 1,03 (m, 2 H) 1,16 - 1,35 (m, 5 H) 1,38 - 1,47 (m, 1 H) 1,59 - 1,70 (m, 1 H) 2,10 - 2,21 (m, 1 H) 2,47 - 2,59 (m, 1 H) 2,72 (tt, *J*=7,89, 4,74 Hz, 1 H) 3,05 - 3,18 (m, 2 H) 3,68 - 3,83 (m, 2 H) 5,71 (dd, *J*=10,61, 4,80 Hz, 1 H) 7,51 - 7,59 (m, 1 H) 7,63 - 7,69 (m, 1 H) 8,02 (d, *J*=8,59 Hz, 1 H) 8,24 (d, *J*=15,92 Hz, 2 H) 8,40 (s, 1 H) 9,23 (br. s., 1 H)

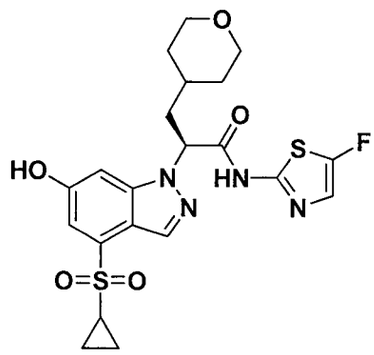
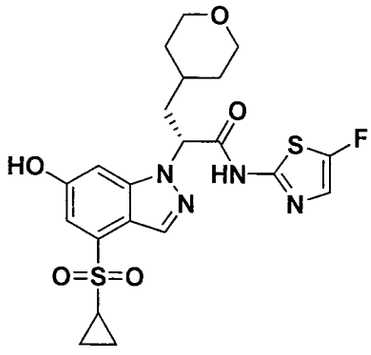
Ej.	Estructura	Método	LCMS	Datos de RMN
66	 2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}FN_4O_4S_2$ 479,56, experimental 479,5	^{1}H RMN (400 MHz, MeOD) δ ppm 0,94 - 1,00 (m, 2 H) 1,17 - 1,32 (m, 5 H) 1,35 - 1,43 (m, 1 H) 1,58 - 1,67 (m, 1 H) 2,08 - 2,18 (m, 1 H) 2,48 (ddd, *J*=14,46, 10,42, 4,42 Hz, 1 H) 2,72 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,04 - 3,17 (m, 2 H) 3,69 - 3,82 (m, 2 H) 5,66 (dd, *J*=10,61, 5,05 Hz, 1 H) 6,99 (d, *J*=2,53 Hz, 1 H) 7,55 (dd, *J*=8,34, 7,33 Hz, 1 H) 7,66 (d, *J*=6,57 Hz, 1 H) 7,97 (d, *J*=8,59 Hz, 1 H) 8,38 (s, 1 H)
67	 N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-6-fluoro-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{23}ClFN_4O_4S_2$ 514,01, experimental 514	^{1}H RMN (400 MHz, MeOD) δ ppm 1,09 (m, 2 H) 1,32 (m, 5 H) 1,47 (m, 1 H) 1,70 (m, 1 H) 2,23 (m, 1 H) 2,56 (m, 1 H) 2,86 (m, 1 H) 3,20 (m, 2 H) 3,85 (m, 2 H) 5,71 (m, 1 H) 7,56 (m, 1 H) 7,87 (m, 1 H) 8,47 (s, 1 H)

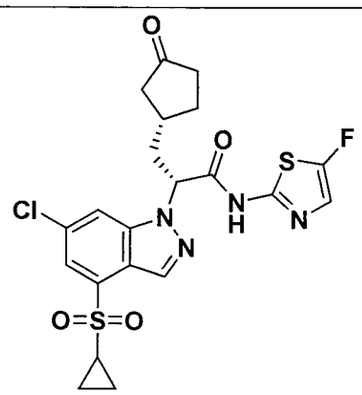
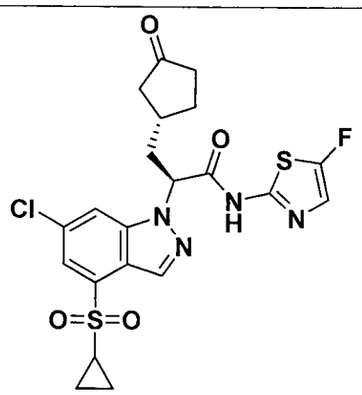
Ej.	Estructura	Método	LCMS	Datos de RMN
68	 (R)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}FN_4O_4S_2$ 479,56, experimental 479,5	
69	 (S)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}FN_4O_4S_2$ 479,56, experimental 479,5	

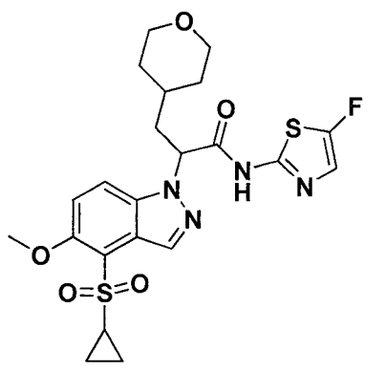
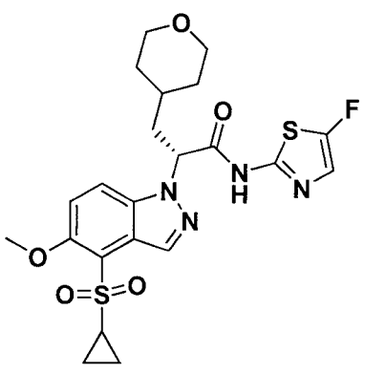
Ej.	Estructura	Método	LCMS	Datos de RMN
70	 N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-2H-indazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}ClN_4O_4S_2$ 496,01, experimental 496,1	^{1}H RMN (400 MHz, MeOD) δ ppm 0,93 - 1,00 (m, 2 H) 1,16 - 1,36 (m, 5 H) 1,39 - 1,47 (m, 1 H) 1,64 - 1,74 (m, 1 H) 2,09 - 2,21 (m, 1 H) 2,40 (ddd, *J*=14,46, 10,17, 4,67 Hz, 1 H) 2,71 - 2,75 (m, 1 H) 3,11 - 3,20 (m, 2 H) 3,70 - 3,84 (m, 2 H) 5,63 (dd, *J*=10,36, 5,31 Hz, 1 H) 7,24 (s, 1 H) 7,41 (dd, *J*=8,59, 7,07 Hz, 1 H) 7,62 (d, *J*=6,32 Hz, 1 H) 7,89 (d, *J*=8,84 Hz, 1 H) 8,67 (d, *J*=1,01 Hz, 1 H)
71	 2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(R)-3-oxociclopentil)-N-(pirazin-2-il)propanamida	*ver* Comp. 11	[M+H] calc. para $C_{22}H_{24}N_5O_4S$ 454,2, experimental 454,0	ver diastereómeros separados para 1H RMN

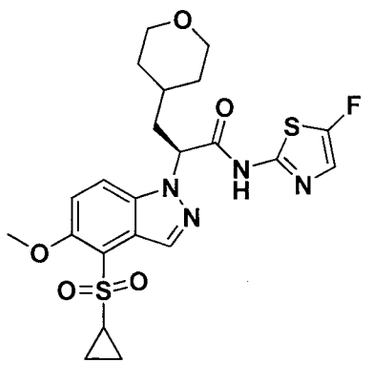
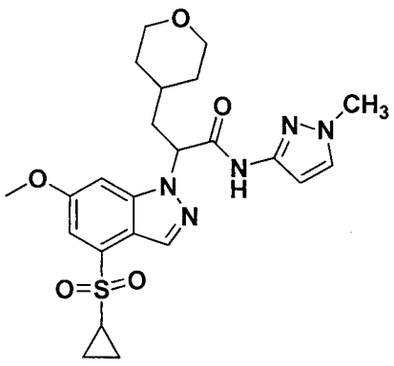
Ej.	Estructura	Método	LCMS	Datos de RMN
72	 2-(4-(ciclopropilsulfonil)-6-metoxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{26}FN_4O_5S_2$ 509, experimental 509	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,52 (s, 1 H), 7,45 (d, *J*=1,8 Hz, 1 H), 7,00 (br. s., 1 H), 6,96 (s, 1 H), 5,30 (s, 1 H), 3,95 (s, 3 H), 3,78 - 3,93 (m, 2 H), 3,13 - 3,30 (m, 2 H), 2,57 - 2,73 (m, 1 H), 2,50 (br. s., 1 H), 2,25 (d, *J*=5,6 Hz, 1 H), 1,59 (d, *J*=12,4 Hz, 1 H), 1,44 - 1,55 (m, 2 H), 1,28 - 1,44 (m, 4 H), 1,01 - 1,16 ppm (m, 2 H)
73	 2-(4-(ciclopropilsulfonil)-6-metoxi-2H-indazol-2-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{26}FN_4O_5S_2$ 509, experimental 509	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,37 (s, 1 H), 7,45 (d, *J*=2,0 Hz, 1 H), 7,27 (d, *J*=2,0 Hz, 1 H), 7,02 (d, *J*=2,8 Hz, 1 H), 5,25 (dd, *J*=10,0, 5,4 Hz, 1 H), 3,95 (s, 3 H), 3,73 - 3,91 (m, 2 H), 3,20 - 3,33 (m, 2 H), 2,49 - 2,58 (m, 1 H), 2,37 - 2,48 (m, 1 H), 2,21 - 2,32 (m, 1 H), 1,69 (d, *J*=12,1 Hz, 1 H), 1,51 (dd, *J*=9,3, 2,0 Hz, 1 H), 1,28 - 1,45 (m, 5 H), 0,99 - 1,08 ppm (m, 2 H)

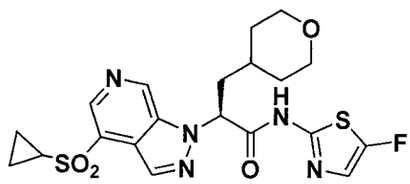
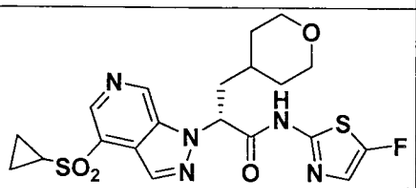
Ej.	Estructura	Método	LCMS	Datos de RMN
74	 (S)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(R)-3-oxociclopentil)-N-(pirazin-2-il)propanamida	*ver* Comp. 11	[M+H] calc. para $C_{22}H_{24}N_5O_4S$ 454,2, experimental 454,0	^{1}H RMN (400 MHz, MeOD) δ ppm 1,01 - 1,14 (m, 2 H) 1,16 - 1,32 (m, 2 H) 1,62 - 1,85 (m, 2 H) 2,00 - 2,13 (m, 3 H) 2,15 - 2,29 (m, 2 H) 2,52 (ddd, *J*=14,08, 7,14, 5,05 Hz, 1 H) 2,65 - 2,86 (m, 2 H) 5,79 (dd, *J*=10,11, 5,05 Hz, 1 H) 7,55 - 7,72 (m, 1 H) 7,76 (d, *J*=6,57 Hz, 1 H) 8,14 (d, *J*=8,59 Hz, 1 H) 8,24 - 8,44 (m, 2 H) 8,51 (s, 1 H) 9,29 - 9,37 (m, 1 H)
75	 (R)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(R)-3-oxociclopentil)-N-(pirazin-2-il)propanamida	*ver* Comp. 11	[M+H] calc. para $C_{22}H_{24}N_5O_4S$ 454,2, experimental 454,0	^{1}H RMN (400 MHz, MeOD) δ ppm 0,92 - 1,13 (m, 2 H) 1,18 - 1,37 (m, 2 H) 1,50 - 1,68 (m, 1 H) 1,89 - 2,13 (m, 4 H) 2,14 - 2,39 (m, 2 H) 2,44 (ddd, *J*=13,96, 8,91, 4,93 Hz, 1 H) 2,70 - 2,92 (m, 2 H) 5,73 (dd, *J*=10,61, 4,80 Hz, 1 H) 7,52 - 7,73 (m, 1 H) 7,75 (d, *J*=6,82 Hz, 1 H) 8,13 (d, *J*=8,59 Hz, 1 H) 8,35 (br. s., 2 H) 8,51 (s, 1 H) 9,33 (br. s., 1 H)

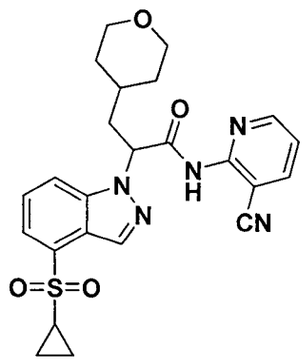
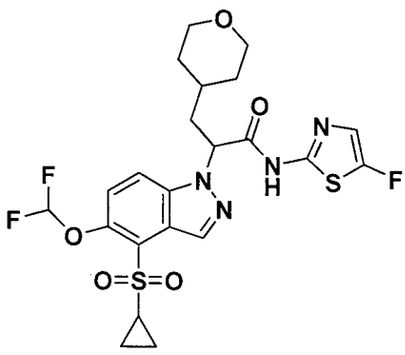
Ej.	Estructura	Método	LCMS	Datos de RMN
76	 (S)-2-(4-(ciclopropilsulfonil)-6-hidroxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}FN_4O_5S_2$ 495, experimental 495	^{1}H RMN (DMSO-d_6 ,400MHz): δ = 12,70 (s, 1 H), 10,48 (s, 1 H), 8,23 (s, 1 H), 7,33 - 7,36 (m, 2 H), 7,23 (d, *J*=1,8 Hz, 1 H), 5,62 (d, *J*=4,3 Hz, 1 H), 3,71 - 3,85 (m, 3 H), 3,06 - 3,21 (m, 2 H), 2,24 - 2,41 (m, 1 H), 2,09 - 2,24 (m, 1 H), 1,54 - 1,63 (m, 1 H), 1,48 (br. s., 1 H), 1,28 (br. s., 3 H), 1,16 (br. s., 2 H), 1,06 ppm (dd, *J*=7,8, 2,0 Hz, 2 H)
77	 (R)-2-(4-(ciclopropilsulfonil)-6-hidroxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}FN_4O_5S_2$ 495, experimental 495	^{1}H RMN (DMSO-d_6 ,400MHz): δ = 12,70 (s, 1 H), 10,48 (s, 1 H), 8,23 (s, 1 H), 7,33 - 7,36 (m, 2 H), 7,23 (d, *J*=1,8 Hz, 1 H), 5,62 (d, *J*=4,3 Hz, 1 H), 3,71 - 3,85 (m, 3 H), 3,06 - 3,21 (m, 2 H), 2,24 - 2,41 (m, 1 H), 2,09 - 2,24 (m, 1 H), 1,54 - 1,63 (m, 1 H), 1,48 (br. s., 1 H), 1,28 (br. s., 3 H), 1,16 (br. s., 2 H), 1,06 ppm (dd, *J*=7,8, 2,0 Hz, 2 H)

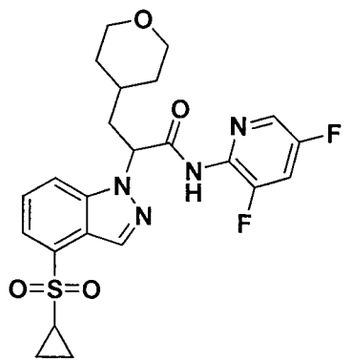
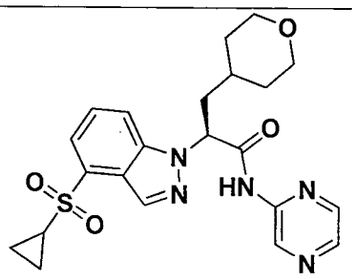
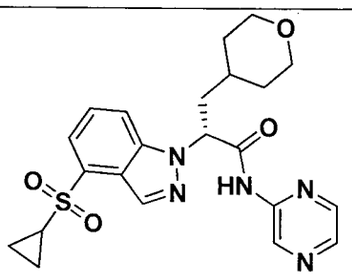
Ej.	Estructura	Método	LCMS	Datos de RMN
78	 (R)-2-(6-cloro-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(R)-3-oxociclopentil)propanamida	*ver* Comp. 11	[M+H] calc. para $C_{21}H_{21}ClFN_4O_4S_2$ 511,1, experimental 511,3	^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,07 - 1,31 (m, 2 H) 1,34 - 1,57 (m, 2 H) 1,57 - 1,84 (m, 3 H) 1,93 - 2,21 (m, 3 H) 2,32 (dd, *J*=18,32, 8,21 Hz, 1 H) 2,47 - 2,70 (m, 2 H) 2,97 - 3,20 (m, 1 H) 5,33 (dd, *J*=9,98, 5,18 Hz, 1 H) 6,93 - 7,13 (m, 1 H) 7,71 - 7,91 (m, 2 H) 8,49 - 8,69 (m, 1 H)
79	 (S)-2-(6-cloro-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(R)-3-oxociclopentil)propanamida	*ver* Comp. 11	[M+H] calc. para $C_{21}H_{21}ClFN_4O_4S_2$ 511,1, experimental 511,3	^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,07 - 1,31 (m, 2 H) 1,39 - 1,69 (m, 4 H) 1,81 - 1,92 (m, 1 H) 1,93 - 2,14 (m, 2 H) 2,18 - 2,38 (m, 2 H) 2,46 (ddd, *J*=14,02, 8,84, 5,18 Hz, 1 H) 2,53 - 2,79 (m, 2 H) 5,27 (dd, *J*=10,48, 4,93 Hz, 1 H) 7,03 (d, *J*=3,03 Hz, 1 H) 7,71 - 7,93 (m, 2 H) 8,63 (s, 1 H)

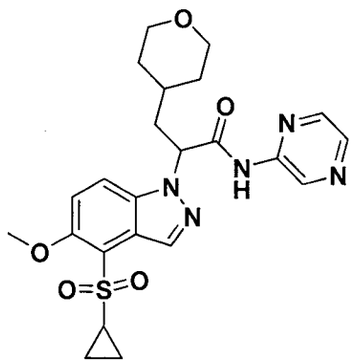
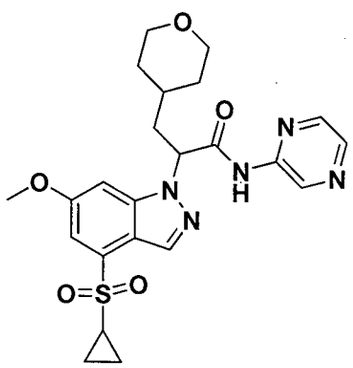
Ej.	Estructura	Método	LCMS	Datos de RMN
80	 2-(4-(ciclopropilsulfonil)-5-metoxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 15	[M+H] calc. para $C_{22}H_{26}FN_4O_5S_2$ 509, experimental 509	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,74 (s, 1 H), 7,67 (d, *J*=9,1 Hz, 1 H), 7,33 (d, *J*=9,3 Hz, 1 H), 7,02 (d, *J*=2,8 Hz, 1 H), 5,37 (dd, *J*=10,6, 4,8 Hz, 1 H), 4,08 (s, 3 H), 3,82 - 3,95 (m, 2 H), 3,05 - 3,29 (m, 3 H), 2,49 (ddd, *J*=14,2, 10,5, 5,1 Hz, 1 H), 2,23 (ddd, *J*=14,0, 8,8, 4,8 Hz, 1 H), 1,53 - 1,66 (m, 1 H), 1,42 - 1,49 (m, 2 H), 1,27 - 1,42 (m, 3 H), 1,21 (dd, *J*=7,5, 3,9 Hz, 1 H), 1,02 ppm (dddd, *J*=16,8, 8,1, 6,5, 4,9 Hz, 2 H)
81	 (R)-2-(4-(ciclopropilsulfonil)-5-metoxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 15	[M+H] calc. para $C_{22}H_{26}FN_4O_5S_2$ 509, experimental 509	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,74 (s, 1 H), 7,67 (d, *J*=9,1 Hz, 1 H), 7,33 (d, *J*=9,3 Hz, 1 H), 7,02 (d, *J*=2,8 Hz, 1 H), 5,37 (dd, *J*=10,6, 4,8 Hz, 1 H), 4,08 (s, 3 H), 3,82 - 3,95 (m, 2 H), 3,05 - 3,29 (m, 3 H), 2,49 (ddd, *J*=14,2, 10,5, 5,1 Hz, 1 H), 2,23 (ddd, *J*=14,0, 8,8, 4,8 Hz, 1 H), 1,53 - 1,66 (m, 1 H), 1,42 - 1,49 (m, 2 H), 1,27 - 1,42 (m, 3 H), 1,21 (dd, *J*=7,5, 3,9 Hz, 1 H), 1,02 ppm (dddd, *J*=16,8, 8,1, 6,5, 4,9 Hz, 2 H)

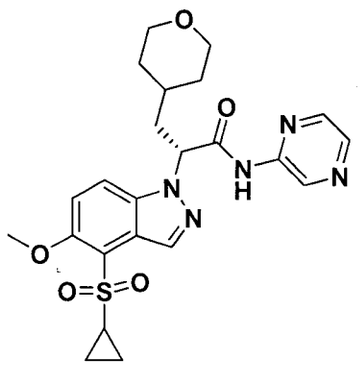
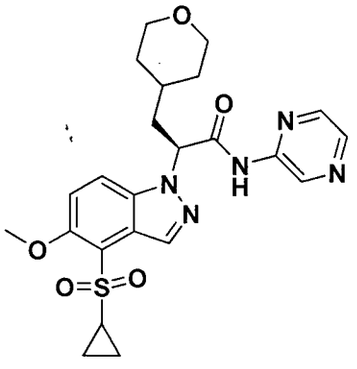
Ej.	Estructura	Método	LCMS	Datos de RMN
82	 (S)-2-(4-(ciclopropilsulfonil)-5-metoxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 15	[M+H] calc. para $C_{22}H_{26}FN_4O_5S_2$ 509, experimental 509	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,74 (s, 1 H), 7,67 (d, *J*=9,1 Hz, 1 H), 7,33 (d, *J*=9,3 Hz, 1 H), 7,02 (d, *J*=2,8 Hz, 1 H), 5,37 (dd, *J*=10,6, 4,8 Hz, 1 H), 4,08 (s, 3 H), 3,82 - 3,95 (m, 2 H), 3,05 - 3,29 (m, 3 H), 2,49 (ddd, *J*=14,2, 10,5, 5,1 Hz, 1 H), 2,23 (ddd, *J*=14,0, 8,8, 4,8 Hz, 1 H), 1,53 - 1,66 (m, 1 H), 1,42 - 1,49 (m, 2 H), 1,27 - 1,42 (m, 3 H), 1,21 (dd, *J*=7,5, 3,9 Hz, 1 H), 1,02 ppm (dddd, *J*=16,8, 8,1, 6,5, 4,9 Hz, 2 H)
83	 2-(4-(ciclopropilsulfonil)-6-metoxi-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{23}H_{30}N_5O_5S$ 488, experimental 488	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 10,28 (s, 1 H), 8,45 (s, 1 H), 7,42 (d, *J*=1,8 Hz, 1 H), 7,33 (d, *J*=2,3 Hz, 1 H), 7,12 - 7,18 (m, 1 H), 6,77 (d, *J*=2,5 Hz, 1 H), 5,40 (dd, *J*=10,1, 5,1 Hz, 1 H), 3,93 (s, 3 H), 3,90 - 4,04 (m, 2 H), 3,85 (s, 3 H), 3,21 - 3,40 (m, 2 H), 2,48 - 2,66 (m, 2 H), 2,22 - 2,34 (m, 1 H), 1,68 (d, *J*=12,4 Hz, 1 H), 1,51 - 1,61 (m, 1 H), 1,28 - 1,50 (m, 5 H), 0,97 - 1,12 ppm (m, 2 H)

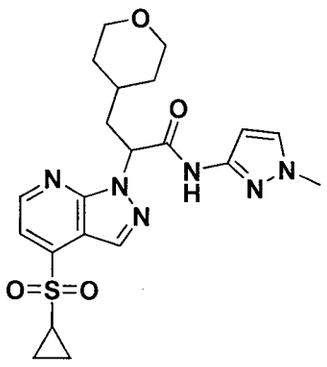
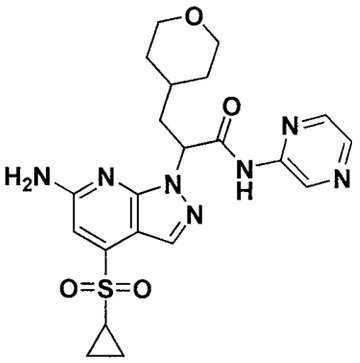
Ej.	Estructura	Método	LCMS	Datos de RMN
84	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-c]piridin-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 13	[M+H] calc. para $C_{20}H_{23}FN_5O_4S_2$ 480, experimental 480	^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,09 - 1,19 (m, 2 H) 1,21 - 1,29 (m, 1 H) 1,31 - 1,55 (m, 5 H) 1,59 - 1,72 (m, 1 H) 2,33 (ddd, *J*=14,15, 8,34, 5,31 Hz, 1 H) 2,42 - 2,56 (m, 1 H) 2,64 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,22 (m, *J*=17,91, 11,64, 11,64, 2,27 Hz, 2 H) 3,90 (ddd, *J*=13,45, 11,43, 2,65 Hz, 2 H) 5,61 (dd, *J*=10,23, 5,43 Hz, 1 H) 7,09 (d, *J*=2,78 Hz, 1 H) 8,65 (s, 1 H) 8,87 (s, 1 H) 9,34 (s, 1 H) 9,99 (br. s., 1 H)
85	 (R)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-c]piridin-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 13	[M+H] calc. para $C_{20}H_{23}FN_5O_4S_2$ 480, experimental 480	

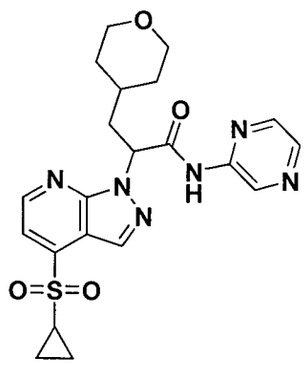
Ej.	Estructura	Método	LCMS	Datos de RMN
86	 N-(3-cianopiridin-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{24}H_{26}N_5O_4S$ 480,3, experimental 480,5	^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 0,89 - 1,05 (m, 2 H) 1,18 - 1,45 (m, 5 H) 1,49 (d, *J*=9,60 Hz, 1 H) 1,53 - 1,65 (m, 1 H) 2,15 - 2,36 (m, 3 H) 2,36 - 2,63 (m, 2 H) 3,07 - 3,28 (m, 2 H) 3,83 (t, *J*=10,74 Hz, 2 H) 5,44 (dd, *J*=9,98, 5,18 Hz, 1 H) 7,55 (dd, *J*=8,72, 7,20 Hz, 1 H) 7,73 (d, *J*=7,58 Hz, 2 H) 7,91 (d, *J*=7,83 Hz, 1 H) 8,62 (s, 1 H), 9,50 (s, 1H)
87	 2-(4-(ciclopropilsulfonil)-5-(difluorometoxi)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 12	[M+H] calc. para $C_{22}H_{24}F_3N_4O_5S_2$ 545, experimental 545	^{1}H RMN (400 MHz, CLOROFORM-*d*) δ ppm 1,02 - 1,13 (m, 2 H) 1,34 - 1,49 (m, 4 H) 1,50 - 1,61 (m, 1 H) 1,65 - 1,76 (m, 1 H) 2,24 - 2,35 (m, 1 H) 2,47 - 2,60 (m, 1 H) 2,66 - 2,77 (m, 2 H) 3,20 - 3,36 (m, 2 H) 3,89 - 3,99 (m, 2 H) 5,46 (dd, *J*=10,86, 4,80 Hz, 1 H) 6,93 (s, 1 H) 7,07 - 7,13 (m, 1 H) 7,29 - 7,60 (m, 1 H) 7,58 - 7,67 (m, 1 H) 8,27 (s, 1 H)

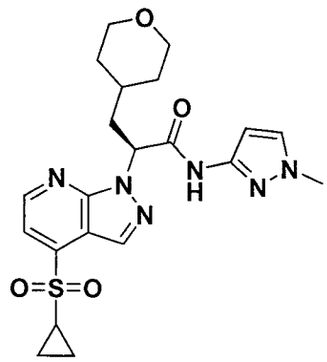
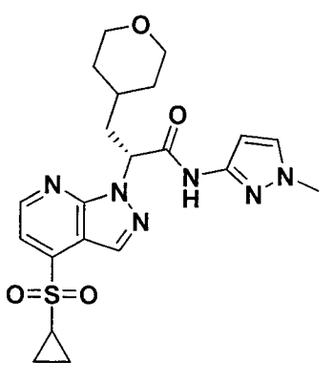
Ej.	Estructura	Método	LCMS	Datos de RMN
88	 2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(3,5-difluoropiridin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{23}H_{25}F2N_4O_4S$ 491,5, experimental 491,6	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0,94 - 1,13 (m, 2 H) 1,13 - 1,37 (m, 4 H) 1,47 - 1,59 (m, 1 H) 1,66 (d, *J*=10,11 Hz, 1 H) 2,25 (d, *J*=7,83 Hz, 1 H) 2,34 - 2,47 (m, 1 H) 2,92 - 3,22 (m, 4 H) 3,71 - 3,86 (m, 2 H) 5,82 (dd, *J*=9,73, 5,43 Hz, 1 H) 7,59 - 7,79 (m, 2 H) 8,02 (ddd, *J*=9,79, 8,40, 2,53 Hz, 1 H) 8,21 (d, *J*=8,34 Hz, 1 H) 8,35 (d, *J*=2,53 Hz, 1 H) 8,39 - 8,51 (m, 1 H) 10,73 (s, 1 H)
89	 (S)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{26}N_5O_4S$ 456,53, experimental 456,5	
90	 (R)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{26}N_5O_4S$ 456,53, experimental 456,5	

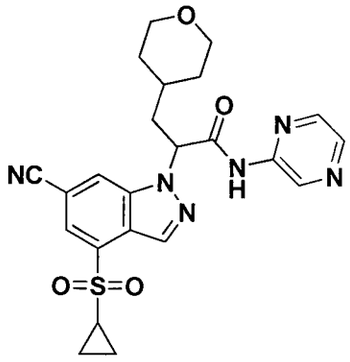
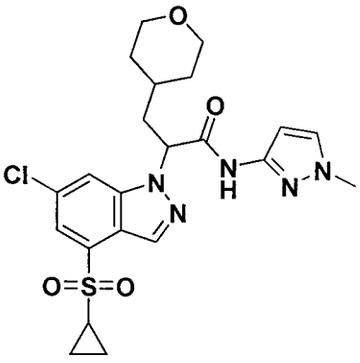
Ej.	Estructura	Método	LCMS	Datos de RMN
91	 2-(4-(ciclopropilsulfonil)-5-metoxi-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 15	[M+H] calc. para $C_{23}H_{28}N_5O_5S$ 486, experimental 486	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,49 (s, 1 H), 9,20 (s, 1 H), 8,79 (s, 1 H), 8,32 (d, *J*=1,5 Hz, 1 H), 8,36 (d, *J*=2,5 Hz, 1 H), 7,71 (d, *J*=9,3 Hz, 1 H), 7,35 (d, *J*=9,3 Hz, 1 H), 5,34 (dd, *J*=10,5, 4,9 Hz, 1 H), 4,08 (s, 3 H), 3,85 - 3,99 (m, 2 H), 3,07 - 3,32 (m, 3 H), 2,54 (d, *J*=3,5 Hz, 1 H), 2,28 (d, *J*=5,3 Hz, 1 H), 1,60 (br. s., 1 H), 1,26 - 1,48 (m, 6 H), 0,92 - 1,12 ppm (m, 2 H)
92	 2-(4-(ciclopropilsulfonil)-6-metoxi-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{23}H_{28}N_5O_5S$ 486, experimental 486	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,50 (s, 1 H), 9,22 (s, 1 H), 8,55 (s, 1 H), 8,33 - 8,41 (m, 1 H), 8,28 (s, 1 H), 7,44 (d, *J*=2,0 Hz, 1 H), 7,03 (d, *J*=1,3 Hz, 1 H), 5,31 (dd, *J*=10,5, 4,9 Hz, 1 H), 3,95 (s, 4 H), 3,87 - 3,97 (m, 1 H), 3,25 - 3,32 (m, 1 H), 3,21 (td, *J*=11,7, 2,5 Hz, 1 H), 2,51 - 2,65 (m, 2 H), 2,25 - 2,35 (m, 1 H), 1,52 - 1,66 (m, 2 H), 1,31 - 1,50 (m, 5 H), 1,02 - 1,13 ppm (m, 2 H)

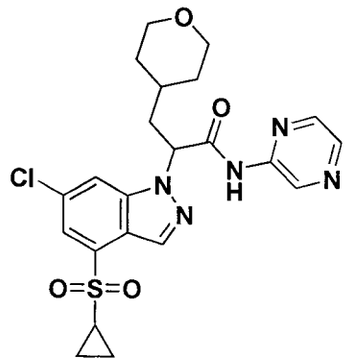
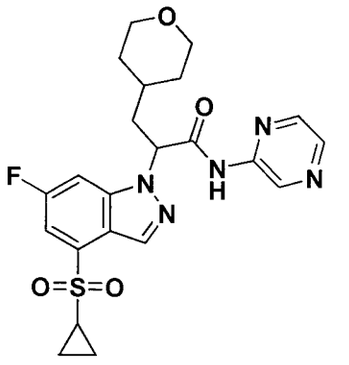
Ej.	Estructura	Método	LCMS	Datos de RMN
93	 (R)-2-(4-(ciclopropilsulfonil)-5-metoxi-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 15	[M+H] calc. para $C_{23}H_{28}N_5O_5S$ 486, experimental 486	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,49 (s, 1 H), 9,20 (s, 1 H), 8,79 (s, 1 H), 8,32 (d, *J*=1,5 Hz, 1 H), 8,36 (d, *J*=2,5 Hz, 1 H), 7,71 (d, *J*=9,3 Hz, 1 H), 7,35 (d, *J*=9,3 Hz, 1 H), 5,34 (dd, *J*=10,5, 4,9 Hz, 1 H), 4,08 (s, 3 H), 3,85 - 3,99 (m, 2 H), 3,07 - 3,32 (m, 3 H), 2,54 (d, *J*=3,5 Hz, 1 H), 2,28 (d, *J*=5,3 Hz, 1 H), 1,60 (br. s., 1 H), 1,26 - 1,48 (m, 6 H), 0,92 - 1,12 ppm (m, 2 H)
94	 (S)-2-(4-(ciclopropilsulfonil)-5-metoxi-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 15	[M+H] calc. para $C_{23}H_{28}N_5O_5S$ 486, experimental 486	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,49 (s, 1 H), 9,20 (s, 1 H), 8,79 (s, 1 H), 8,32 (d, *J*=1,5 Hz, 1 H), 8,36 (d, *J*=2,5 Hz, 1 H), 7,71 (d, *J*=9,3 Hz, 1 H), 7,35 (d, *J*=9,3 Hz, 1 H), 5,34 (dd, *J*=10,5, 4,9 Hz, 1 H), 4,08 (s, 3 H), 3,85 - 3,99 (m, 2 H), 3,07 - 3,32 (m, 3 H), 2,54 (d, *J*=3,5 Hz, 1 H), 2,28 (d, *J*=5,3 Hz, 1 H), 1,60 (br. s., 1 H), 1,26 - 1,48 (m, 6 H), 0,92 - 1,12 ppm (m, 2 H)

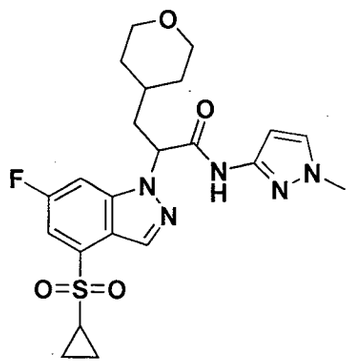
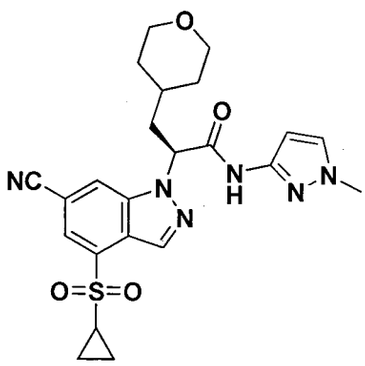
Ej.	Estructura	Método	LCMS	Datos de RMN
95	 2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16	[M+H] calc. para $C_{21}H_{27}N_6O_4S$ 459, experimental 459	^{1}H RMN (4008 ppm 1,08 - 1,18 (m, 2 H) 1,28 - 1,44 (m, 5 H) 1,54 (d, *J*=9,35 Hz, 1 H) 1,74 (dd, *J*=10,11, 1,77 Hz, 1 H) 2,17 - 2,27 (m, 1 H) 2,67 (ddd, *J*=14,21, 10,93, 3,66 Hz, 1 H) 2,89 (tt, *J*=7,86, 4,77 Hz, 1 H) 3,10 - 3,28 (m, 2 H) 3,76 (s, 3 H) 3,85 (dd, *J*=10,74, 4,93 Hz, 2 H) 5,99 (dd, *J*=10,99, 4,67 Hz, 1 H) 6,42 (d, *J*=2,53 Hz, 1 H) 7,42 (d, *J*=2,27 Hz, 1 H) 7,69 (d, *J*=4,80 Hz, 1 H) 8,51 (s, 1 H) 8,81 (d, 1 H)
96	 2-(6-amino-4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16	[M+H] calc. para $C_{21}H_{26}N_7O_4S$ 472, experimental 472	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 0,99 - 1,06 (m, 2 H) 1,29 - 1,44 (m, 5 H) 1,52 (d, *J*=9,35 Hz, 1 H) 1,71 - 1,79 (m, 1 H) 2,13 - 2,22 (m, 1 H) 2,56 - 2,66 (m, 1 H) 2,90 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,12 - 3,29 (m, 2 H) 3,86 (t, *J*=10,74 Hz, 2 H) 5,90 (dd, *J*=10,99, 4,42 Hz, 1 H) 8,17 (s, 1 H) 8,27 - 8,37 (m, 3 H) 9,31 (s, 1 H)

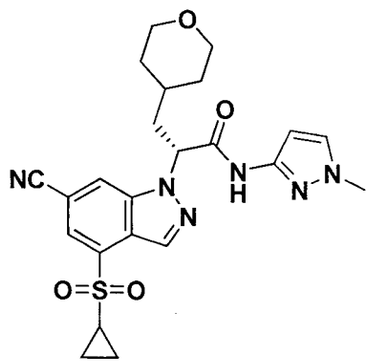
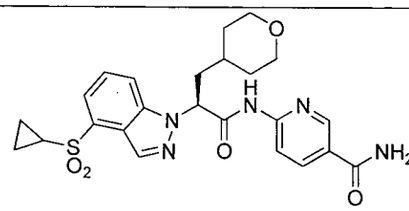
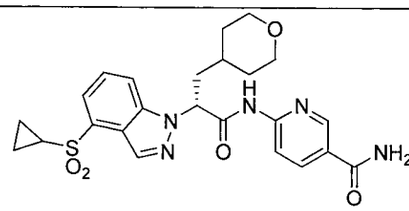
Ej.	Estructura	Método	LCMS	Datos de RMN
97	 2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16 & 95	[M+H] calc. para $C_{21}H_{25}N_6O_4S$ 457, experimental 457	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,09 - 1,20 (m, 2 H) 1,32 - 1,47 (m, 5 H) 1,56 (dd, *J*=9,47, 1,89 Hz, 1 H) 1,76 (dd, *J*=9,73, 1,89 Hz, 1 H) 2,20 - 2,29 (m, 1 H) 2,73 (ddd, *J*=14,15, 11,12, 3,54 Hz, 1 H) 2,91 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,12 - 3,29 (m, 2 H) 3,81 - 3,91 (m, 2 H) 6,10 (dd, *J*=11,12, 4,29 Hz, 1 H) 7,71 (d, *J*=4,55 Hz, 1 H) 8,31 (d, *J*=2,53 Hz, 1 H) 8,36 (dd, *J*=2,53, 1,52 Hz, 1 H) 8,53 (s, 1 H) 8,83 (d, *J*=4,80 Hz, 1 H) 9,29 (s, 1 H)

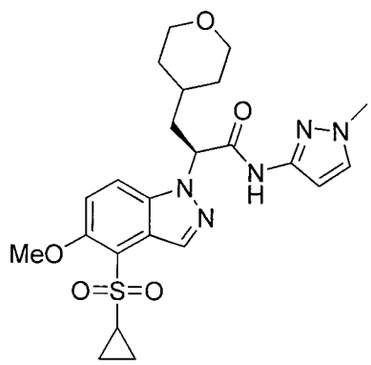
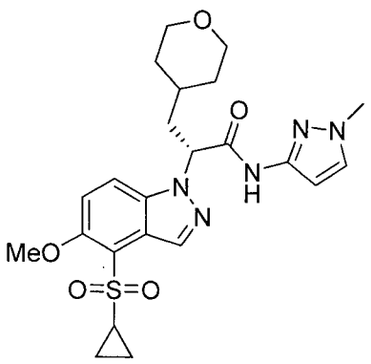
Ej.	Estructura	Método	LCMS	Datos de RMN
98	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16 & 95	[M+H] calc. para $C_{21}H_{27}N_6O_4S$ 459, experimental 459	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,08 - 1,18 (m, 2 H) 1,28 - 1,44 (m, 5 H) 1,54 (d, *J*=9,35 Hz, 1 H) 1,74 (dd, *J*=10,11, 1,77 Hz, 1 H) 2,17 - 2,27 (m, 1 H) 2,67 (ddd, *J*=14,21, 10,93, 3,66 Hz, 1 H) 2,89 (tt, *J*=7,86, 4,77 Hz, 1 H) 3,10 - 3,28 (m, 2 H) 3,76 (s, 3 H) 3,85 (dd, *J*=10,74, 4,93 Hz, 2 H) 5,99 (dd, *J*=10,99, 4,67 Hz, 1 H) 6,42 (d, *J*=2,53 Hz, 1 H) 7,42 (d, *J*=2,27 Hz, 1 H) 7,69 (d, *J*=4,80 Hz, 1 H) 8,51 (s, 1 H) 8,81 (d, 1 H)
99	 (R)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16 & 95	[M+H] calc. para $C_{21}H_{27}N_6O_4S$ 459, experimental 459	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,08 - 1,18 (m, 2 H) 1,28 - 1,44 (m, 5 H) 1,54 (d, *J*=9,35 Hz, 1 H) 1,74 (dd, *J*=10,11, 1,77 Hz, 1 H) 2,17 - 2,27 (m, 1 H) 2,67 (ddd, *J*=14,21, 10,93, 3,66 Hz, 1 H) 2,89 (tt, *J*=7,86, 4,77 Hz, 1 H) 3,10 - 3,28 (m, 2 H) 3,76 (s, 3 H) 3,85 (dd, *J*=10,74, 4,93 Hz, 2 H) 5,99 (dd, *J*=10,99, 4,67 Hz, 1 H) 6,42 (d, *J*=2,53 Hz, 1 H) 7,42 (d, *J*=2,27 Hz, 1 H) 7,69 (d, *J*=4,80 Hz, 1 H) 8,51 (s, 1 H) 8,81 (d, 1 H)

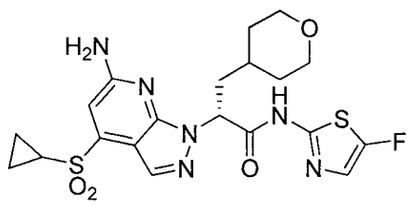
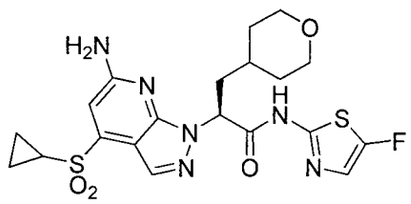
Ej.	Estructura	Método	LCMS	Datos de RMN
100	 2-(6-ciano-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 19	[M+H] calc. para $C_{23}H_{25}N_6O_4S$ 481, experimental 481	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,55 (br. s., 1 H), 9,40 (br. s., 1 H), 8,74 (s, 1 H), 8,45 (br. s., 1 H), 8,37 (br. s., 1 H), 8,22 (s, 1 H), 7,99 (s, 1 H), 5,52 (dd, *J*=9,9, 5,8 Hz, 1 H), 3,90 - 4,09 (m, 2 H), 3,19 - 3,41 (m, 2 H), 2,48 - 2,68 (m, 2 H), 2,39 (dd, *J*=13,8, 7,7 Hz, 1 H), 1,68 (d, *J*=12,1 Hz, 1 H), 1,57 - 1,64 (m, 1 H), 1,34 - 1,54 (m, 5 H), 1,09 - 1,19 ppm (m, 2 H)
101	 2-(6-cloro-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{27}ClN_5O_4S$ 492, experimental 492	^{1}H RMN (400 MHz, CLOROFORM-d) δ 8,57 (s, 2H), 7,67 - 7,82 (m, 2H), 7,23 (d, *J* = 2,53 Hz, 1H), 6,62 (s, 1H), 5,28 (dd, *J* = 5,18, 10,23 Hz, 1H), 3,84 - 3,98 (m, 2H), 3,76 (s, 3H), 3,10 - 3,32 (m, 2H), 2,56 - 2,67 (m, 1H), 2,43 - 2,56 (m, 1H), 2,23 - 2,36 (m, 1H), 1,57 - 1,63 (m, 2H), 1,30 - 1,56 (m, 5H), 1,02 - 1,16 (m, 2H)

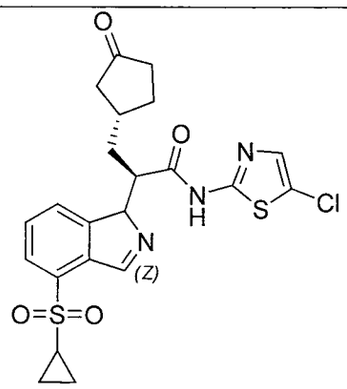
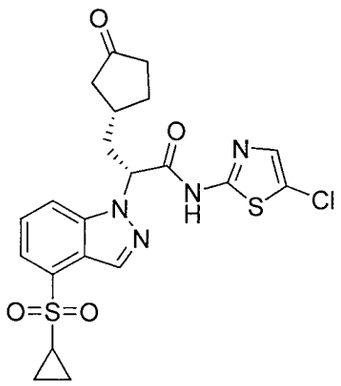
Ej.	Estructura	Método	LCMS	Datos de RMN
102	 2-(6-cloro-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{25}ClN_5O_4S$ 490, experimental 490	^{1}H RMN (400 MHz, CLOROFORM-d) δ 9,47 - 9,50 (m, 1H), 8,93 (s, 1H), 8,64 (s, 1H), 8,36 (d, *J* = 2,53 Hz, 1H), 8,23 (dd, *J* = 1,52, 2,53 Hz, 1H), 7,70 - 7,83 (m, 2H), 5,34 (dd, *J* = 5,31, 10,36 Hz, 1H), 3,80 - 3,97 (m, 2H), 3,14 - 3,35 (m, 2H), 2,47 - 2,67 (m, 2H), 2,27 - 2,38 (m, 1H), 1,53 - 1,65 (m, 2H), 1,31 - 1,52 (m, 5H), 1,04 - 1,16 (m, 2H)
103	 2-(4-(ciclopropilsulfonil)-6-fluoro-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{25}FN_5O_4S$ 474, experimental 474	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,05 - 1,13 (m, 2 H) 1,28 - 1,44 (m, 5 H) 1,52 (dd, *J*=9,47, 1,89 Hz, 1 H) 1,68 - 1,77 (m, 1 H) 2,19 - 2,28 (m, 1 H) 2,55 - 2,65 (m, 1 H) 2,81 - 2,90 (m, 1 H) 3,16 - 3,29 (m, 2 H) 3,80 - 3,92 (m, 2 H) 5,73 (dd, *J*=10,61, 5,05 Hz, 1 H) 7,57 (dd, *J*=8,34, 2,02 Hz, 1 H) 7,89 - 7,94 (m, 1 H) 8,32 (d, *J*=2,53 Hz, 1 H) 8,34 - 8,39 (m, 1 H) 8,48 (s, 1 H) 9,32 (d, 1 H)

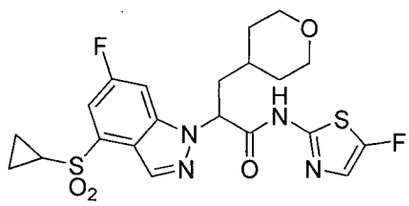
Ej.	Estructura	Método	LCMS	Datos de RMN
104	 2-(4-(ciclopropilsulfonil)-6-fluoro-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{27}FN_5O_4S$ 476, experimental 476	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,05 - 1,13 (m, 2 H) 1,27 - 1,43 (m, 5 H) 1,49 - 1,57 (m, 1 H) 1,72 (dd, *J*=10,23, 1,89 Hz, 1 H) 2,18 - 2,27 (m, 1 H) 2,50 - 2,59 (m, 1 H) 2,81 - 2,89 (m, 1 H) 3,16 - 3,29 (m, 2 H) 3,77 (s, 3 H) 3,81 - 3,91 (m, 2 H) 5,60 (dd, *J*=10,36, 5,31 Hz, 1 H) 6,45 (d, *J*=2,27 Hz, 1 H) 7,43 (d, *J*=2,27 Hz, 1 H) 7,56 (dd, *J*=8,34, 2,02 Hz, 1 H) 7,90 (dd, *J*=9,09, 1,01 Hz, 1 H) 8,46 (s, 1 H)
105	 (S)-2-(6-ciano-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver Ex* Comp. 19	[M+H] calc. para $C_{23}H_{27}N_6O_4S$ 483, experimental 483	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,68 (s, 1 H), 8,45 (s, 1 H), 8,17 (s, 1 H), 7,95 (d, *J*=1,0 Hz, 1 H), 7,24 (d, *J*=2,3 Hz, 1 H), 6,62 (d, *J*=2,3 Hz, 1 H), 5,39 (dd, *J*=9,9, 5,8 Hz, 1 H), 3,91 (t, *J*=11,7 Hz, 2 H), 3,77 (s, 3 H), 3,15 - 3,32 (m, 2 H), 2,56 - 2,66 (m, 1 H), 2,49 (s, 1 H), 2,36 (d, *J*=5,8 Hz, 1 H), 1,62 (m, 1 H), 1,31 - 1,50 (m, 6 H), 1,08 - 1,19 ppm (m, 2 H)

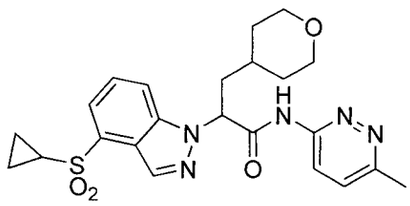
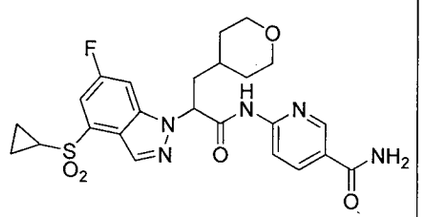
Ej.	Estructura	Método	LCMS	Datos de RMN
106	 (R)-2-(6-ciano-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 19	[M+H] calc. para $C_{23}H_{27}N_6O_4S$ 483, experimental 483	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,68 (s, 1 H), 8,45 (s, 1 H), 8,17 (s, 1 H), 7,95 (d, *J*=1,0 Hz, 1 H), 7,24 (d, *J*=2,3 Hz, 1 H), 6,62 (d, *J*=2,3 Hz, 1 H), 5,39 (dd, *J*=9,9, 5,8 Hz, 1 H), 3,91 (t, *J*=11,7 Hz, 2 H), 3,77 (s, 3 H), 3,15 - 3,32 (m, 2 H), 2,56 - 2,66 (m, 1 H), 2,49 (s, 1 H), 2,36 (d, *J*=5,8 Hz, 1 H), 1,62 (m, 1 H), 1,31 - 1,50 (m, 6 H), 1,08 - 1,19 ppm (m, 2 H)
107	 (S)-6-(2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamido)nicotinamida	*ver* Comp. 14	[M+H] calc. para $C_{24}H_{28}N_5O_5S$ 498,5, experimental 498,5	
108	 (R)-6-(2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamido)nicotinamida	*ver* Comp. 14	[M+H] calc. para $C_{24}H_{28}N_5O_5S$ 498,5, experimental 498,5	

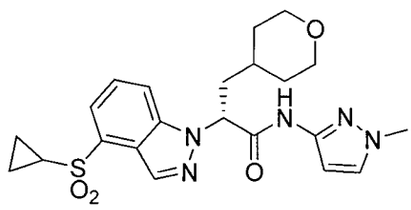
Ej.	Estructura	Método	LCMS	Datos de RMN
109	 (S)-2-(4-(ciclopropilsulfonil)-5-metoxi-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 15	[M+H] calc. para $C_{23}H_{29}N_5O_5S$ 488, experimental 488	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,72 (s, 1 H), 8,64 (s, 1 H), 7,67 (d, *J*=9,3 Hz, 1 H), 7,30 (d, *J*=9,1 Hz, 1 H), 7,22 (d, *J*=2,5 Hz, 1 H), 6,61 (d, *J*=2,3 Hz, 1 H), 5,27 (dd, *J*=10,6, 4,8 Hz, 1 H), 4,07 (s, 3 H), 3,82 - 3,92 (m, 2 H), 3,75 (s, 3 H), 3,09 - 3,29 (m, 3 H), 2,44 - 2,56 (m, 1 H), 2,28 (d, *J*=5,1 Hz, 1 H), 1,42 - 1,52 (m, 2 H), 1,29 - 1,40 (m, 3 H), 1,21 (d, *J*=6,1 Hz, 2 H), 0,95 - 1,09 ppm (m, 2 H)
110	 (R)-2-(4-(ciclopropilsulfonil)-5-metoxi-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 15	[M+H] calc. para $C_{23}H_{29}N_5O_5S$ 488, experimental 488	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,72 (s, 1 H), 8,64 (s, 1 H), 7,67 (d, *J*=9,3 Hz, 1 H), 7,30 (d, *J*=9,1 Hz, 1 H), 7,22 (d, *J*=2,5 Hz, 1 H), 6,61 (d, *J*=2,3 Hz, 1 H), 5,27 (dd, *J*=10,6, 4,8 Hz, 1 H), 4,07 (s, 3 H), 3,82 - 3,92 (m, 2 H), 3,75 (s, 3 H), 3,09 - 3,29 (m, 3 H), 2,44 - 2,56 (m, 1 H), 2,28 (d, *J*=5,1 Hz, 1 H), 1,42 - 1,52 (m, 2 H), 1,29 - 1,40 (m, 3 H), 1,21 (d, *J*=6,1 Hz, 2 H), 0,95 - 1,09 ppm (m, 2 H)

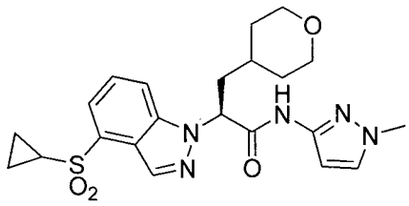
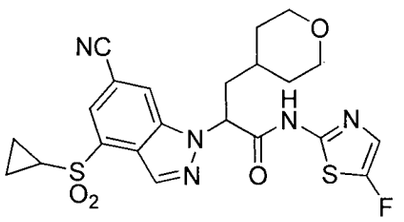
Ej.	Estructura	Método	LCMS	Datos de RMN
111	 (R)-2-(6-amino-4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16	[M+H] calc. para $C_{20}H_{24}FN_6O_4S_2$ 495,5, experimental 495,5	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 0,99 - 1,07 (m, 9 H) 1,29 - 1,42 (m, 22 H) 1,47 - 1,54 (m, 4 H) 1,71 - 1,78 (m, 4 H) 2,09 - 2,19 (m, 4 H) 2,52 - 2,63 (m, 5 H) 2,90 (tt, *J*=8,08, 4,80 Hz, 5 H) 3,12 - 3,28 (m, 9 H) 3,80 - 3,90 (m, 9 H) 5,86 (dd, *J*=10,99, 4,42 Hz, 5 H) 7,08 (d, *J*=2,53 Hz, 4 H) 8,15 (s, 4 H) 8,32 (s, 4 H).
112	 (S)-2-(6-amino-4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16	[M+H] calc. para $C_{20}H_{24}FN_6O_4S_2$ 495,5, experimental 495,5	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 0,99 - 1,07 (m, 9 H) 1,29 - 1,42 (m, 22 H) 1,47 - 1,54 (m, 4 H) 1,71 - 1,78 (m, 4 H) 2,09 - 2,19 (m, 4 H) 2,52 - 2,63 (m, 5 H) 2,90 (tt, *J*=8,08, 4,80 Hz, 5 H) 3,12 - 3,28 (m, 9 H) 3,80 - 3,90 (m, 9 H) 5,86 (dd, *J*=10,99, 4,42 Hz, 5 H) 7,08 (d, *J*=2,53 Hz, 4 H) 8,15 (s, 4 H) 8,32 (s, 4 H).

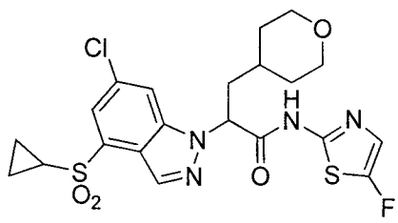
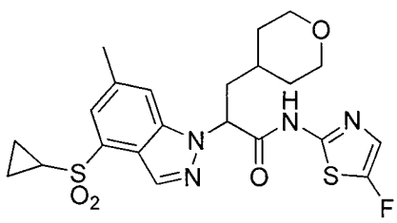
Ej.	Estructura	Método	LCMS	Datos de RMN
113	 (S)-N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(R)-3-oxociclopentil)propanamida	*ver* Comp. 11	[M+H] calc. para $C_{21}H_{22}ClN_4O_4S_2$ 493,1, experimental 493,2	
114	 (R)-N-(5-clorotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(R)-3-oxociclopentil)propanamida	*ver* Comp. 11	[M+H] calc. para $C_{21}H_{22}ClN_4O_4S_2$ 493,1, experimental 493,2	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 0,94 - 1,13 (m, 2 H) 1,18 - 1,38 (m, 3 H) 1,55 - 1,74 (m, 3 H) 1,75 - 2,04 (m, 3 H) 2,21 - 2,41 (m, 1 H) 2,49 - 2,72 (m, 1 H) 2,73 - 2,89 (m, 1 H) 5,56 - 5,80 (m, 1 H) 7,30 (s, 1 H) 7,64 (dd, *J*=8,59, 7,33 Hz, 1 H) 7,75 (d, *J*=7,07 Hz, 1 H) 8,07 (dd, *J*=8,59, 3,03 Hz, 1 H) 8,48 (s, 1 H)

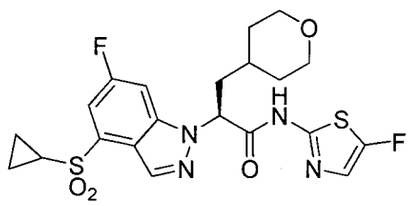
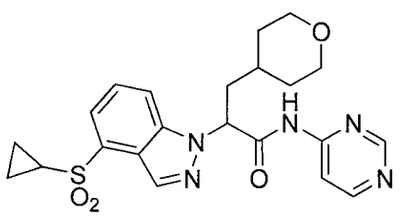
Ej.	Estructura	Método	LCMS	Datos de RMN
115	 2-(4-(ciclopropilsulfonil)-6-fluoro-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{22}F_2N_4O_4S_3$ 498, experimental 498	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,05 - 1,13 (m, 2 H) 1,25 - 1,37 (m, 5 H) 1,45 - 1,53 (m, 1 H) 1,67 - 1,75 (m, 1 H) 2,17 - 2,27 (m, 1 H) 2,55 (ddd, *J*=14,46, 10,42, 4,42 Hz, 1 H) 2,85 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,15 - 3,28 (m, 2 H) 3,79 - 3,91 (m, 2 H) 5,69 (dd, *J*=10,61, 5,05 Hz, 1 H) 7,09 (d, *J*=2,78 Hz, 1 H) 7,57 (dd, *J*=8,34, 2,02 Hz, 1 H) 7,87 (dd, *J*=9,09, 1,01 Hz, 1 H) 8,46 (s, 1 H)

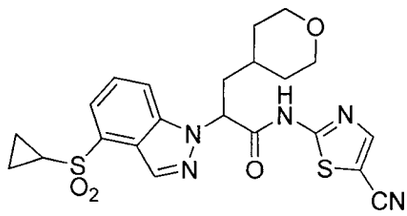
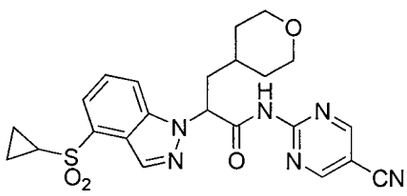
Ej.	Estructura	Método	LCMS	Datos de RMN
116	 2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(6-metilpiridazin-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{23}H_{27}N_5O_4S$ 471, experimental 471	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,02 - 1,09 (m, 2 H) 1,25 - 1,44 (m, 5 H) 1,49 (dd, *J*=9,35, 1,77 Hz, 1 H) 1,72 (d, *J*=12,13 Hz, 1 H) 2,21 - 2,30 (m, 1 H) 2,62 (ddd, *J*=14,15, 10,61, 3,79 Hz, 1 H) 2,72 (s, 3 H) 2,80 (tt, *J*=7,89, 4,74 Hz, 1 H) 3,13 - 3,27 (m, 2 H) 3,79 - 3,91 (m, 2 H) 5,84 (dd, *J*=10,61, 4,80 Hz, 1 H) 7,64 (dd, *J*=8,46, 7,20 Hz, 1 H) 7,75 (d, *J*=6,57 Hz, 1 H) 7,99 (d, *J*=9,35 Hz, 1 H) 8,10 (d, *J*=8,59 Hz, 1 H) 8,48 (s, 1 H) 8,71 (d, 1 H)
117	 6-(2-(4-(ciclopropilsulfonil)-6-fluoro-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamido)nicotinamida	*ver* Comp. 10	[M+H] calc. para $C_{24}H_{26}FN_5O_5S$ 517, experimental 517	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,04 - 1,13 (m, 2 H) 1,17 - 1,38 (m, 5 H) 1,48 - 1,66 (m, 2 H) 2,19 - 2,29 (m, 1 H) 2,40 - 2,48 (m, 1 H) 3,03 - 3,19 (m, 3 H) 3,72 - 3,84 (m, 2 H) 5,81 (dd, *J*=9,73, 5,43 Hz, 1 H) 7,48 (s, 1 H) 7,60 (dd, *J*=8,34, 2,02 Hz, 1 H) 8,05 (s, 1 H) 8,18 - 8,22 (m, 1 H) 8,45 (s, 1 H) 8,83 (d, *J*=1,77 Hz, 1 H) 11,26 (br. s., 1 H)

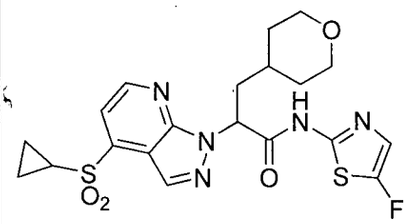
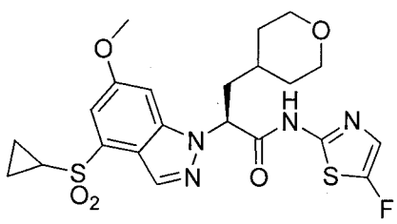
Ej.	Estructura	Método	LCMS	Datos de RMN
118	 (R)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{27}N_5O_4S$ 459, experimental 459	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,02 - 1,09 (m, 2 H) 1,25 - 1,42 (m, 5 H) 1,53 (dd, *J*=9,60, 1,77 Hz, 1 H) 1,72 (dd, *J*=9,98, 1,89 Hz, 1 H) 2,18 - 2,28 (m, 1 H) 2,54 - 2,63 (m, 1 H) 2,81 (s, 1 H) 3,15 - 3,28 (m, 2 H) 3,76 (s, 3 H) 3,81 - 3,90 (m, 2 H) 5,67 (dd, *J*=10,36, 5,31 Hz, 1 H) 6,45 (d, *J*=2,27 Hz, 1 H) 7,43 (d, *J*=2,27 Hz, 1 H) 7,63 (dd, *J*=8,34, 7,33 Hz, 1 H) 7,75 (d, *J*=6,57 Hz, 1 H) 8,09 (d, *J*=8,34 Hz, 1 H) 8,48 (s, 1 H)

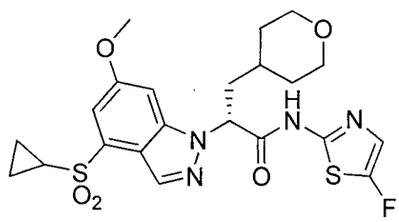
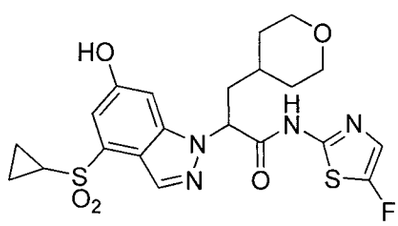
Ej.	Estructura	Método	LCMS	Datos de RMN
119	 (S)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{27}N_5O_4S$ 459, experimental 459	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,02 - 1,09 (m, 2 H) 1,25 - 1,42 (m, 5 H) 1,53 (dd, *J*=9,60, 1,77 Hz, 1 H) 1,72 (dd, *J*=9,98, 1,89 Hz, 1 H) 2,18 - 2,28 (m, 1 H) 2,54 - 2,63 (m, 1 H) 2,81 (s, 1 H) 3,15 - 3,28 (m, 2 H) 3,76 (s, 3 H) 3,81 - 3,90 (m, 2 H) 5,67 (dd, *J*=10,36, 5,31 Hz, 1 H) 6,45 (d, *J*=2,27 Hz, 1 H) 7,43 (d, *J*=2,27 Hz, 1 H) 7,63 (dd, *J*=8,34, 7,33 Hz, 1 H) 7,75 (d, *J*=6,57 Hz, 1 H) 8,09 (d, *J*=8,34 Hz, 1 H) 8,48 (s, 1 H)
120	 2-(6-ciano-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{22}FN_5O_4S_2$ 505, experimental 505	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,07 - 1,14 (m, 2 H) 1,27 - 1,45 (m, 5 H) 1,46 - 1,53 (m, 1 H) 1,68 - 1,76 (m, 1 H) 2,23 - 2,32 (m, 1 H) 2,60 (ddd, *J*=14,46, 10,42, 4,42 Hz, 1 H) 2,89 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,16 - 3,28 (m, 2 H) 3,80 - 3,91 (m, 2 H) 5,83 (dd, *J*=10,61, 5,05 Hz, 1 H) 7,10 (d, *J*=2,78 Hz, 1 H) 7,99 (d, *J*=1,26 Hz, 1 H) 8,59 (s, 1 H) 8,64 (s, 1 H)

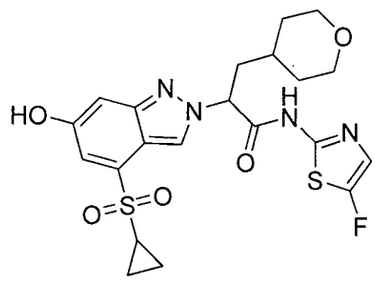
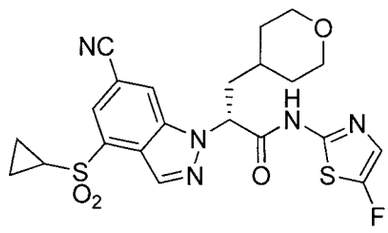
Ej.	Estructura	Método	LCMS	Datos de RMN
121	 2-(6-cloro-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{23}ClFN_4O_4S_2$ 514,0, experimental 514,0	^{1}H RMN (400 MHz, METANOL-d_4) δ 8,55 (s, 1H), 8,34 (s, 1H), 7,92 (s, 1H), 7,00 (d, *J* = 2,78 Hz, 1H), 5,69 (dd, *J* = 5,43, 10,23 Hz, 1H), 3,82 - 3,92 (m, 2H), 3,16 - 3,29 (m, 2H), 2,53 - 2,71 (m, 2H), 2,16 - 2,28 (m, 1H), 1,67 (d, *J* = 12,13 Hz, 1H), 1,48 - 1,58 (m, 1H), 1,28 - 1,46 (m, 5H), 1,04 - 1,16 (m, 2H)
122	 2-(4-(ciclopropilsulfonil)-6-metil-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{26}FN_4O_4S_2$ 493,5, experimental 493,5	^{1}H RMN (400 MHz, METANOL-d_4) δ 8,45 (s, 1H), 8,27 (s, 1H), 7,71 (s, 1H), 7,09 (d, *J* = 2,53 Hz, 1H), 5,68 (dd, *J* = 5,05, 10,61 Hz, 1H), 3,79 - 3,91 (m, 2H), 3,66 (s, 1H), 3,14 - 3,27 (m, 2H), 2,84 - 2,92 (m, 4H), 2,57 (ddd, *J* = 4,29, 10,55, 14,46 Hz, 1H), 2,15 - 2,25 (m, 1H), 1,68 - 1,76 (m, 1H), 1,44 - 1,52 (m, 1H), 1,28 - 1,44 (m, 3H), 1,18 - 1,26 (m, 2H), 1,05 - 1,11 (m, 2H)

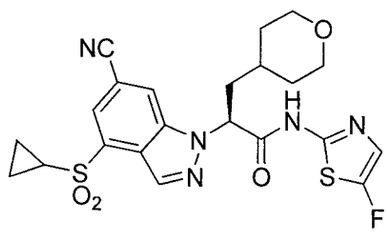
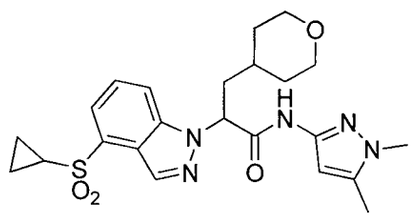
Ej.	Estructura	Método	LCMS	Datos de RMN
123	 (S)-2-(4-(ciclopropilsulfonil)-6-fluoro-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{22}F_2N_4O_4S_2$ 498, experimental 498	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,05 - 1,13 (m, 2 H) 1,26 - 1,37 (m, 5 H) 1,45 - 1,52 (m, 1 H) 1,67 - 1,75 (m, 1 H) 2,17 - 2,27 (m, 1 H) 2,55 (ddd, *J*=14,46, 10,42, 4,42 Hz, 1 H) 2,85 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,15 - 3,28 (m, 2 H) 3,79 - 3,91 (m, 2 H) 5,69 (dd, *J*=10,61, 5,05 Hz, 1 H) 7,09 (d, *J*=2,78 Hz, 1 H) 7,57 (dd, *J*=8,34, 2,02 Hz, 1 H) 7,87 (dd, *J*=9,09, 1,01 Hz, 1 H) 8,46 (s, 1 H)
124	 2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(pirimidin-4-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{25}N_5O_4S$ 457, experimental 457	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,02 - 1,12 (m, 2 H) 1,25 - 1,41 (m, 5 H) 1,41 - 1,53 (m, 1 H) 1,68 - 1,76 (m, 1 H) 2,18 - 2,30 (m, 1 H) 2,59 (m, *J*=14,31, 10,59, 10,59, 3,92 Hz, 1 H) 2,77 - 2,87 (m, 1 H) 3,12 - 3,27 (m, 2 H) 3,78 - 3,91 (m, 2 H) 5,62 - 5,86 (m, 1 H) 7,58 - 7,68 (m, 1 H) 7,70 - 7,79 (m, 1 H) 8,05 - 8,12 (m, 1 H) 8,24 (dd, *J*=6,06, 1,26 Hz, 1 H) 8,49 (s, 1 H) 8,66 (d, *J*=6,06 Hz, 1 H) 8,92 (s, 1 H)

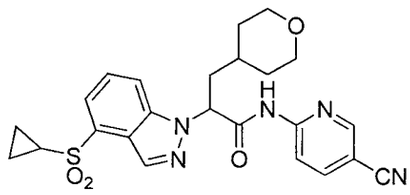
Ej.	Estructura	Método	LCMS	Datos de RMN
125	 N-(5-cianotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{23}N_5O_4S_2$ 487, experimental 487	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,01 - 1,10 (m, 2 H) 1,26 - 1,42 (m, 5 H) 1,50 (dd, *J*=9,35, 2,02 Hz, 1 H) 1,70 - 1,77 (m, 1 H) 2,23 - 2,32 (m, 1 H) 2,58 (ddd, *J*=14,27, 10,61, 3,92 Hz, 1 H) 2,81 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,15 - 3,27 (m, 2 H) 3,79 - 3,90 (m, 2 H) 5,77 (dd, *J*=10,61, 4,80 Hz, 1 H) 7,62 (dd, *J*=8,46, 7,20 Hz, 1 H) 7,74 (d, *J*=6,57 Hz, 1 H) 8,03 - 8,07 (m, 2 H) 8,46 (s, 1 H)
126	 N-(5-cianopirimidin-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{23}H_{24}N_6O_4S$ 482, experimental 482	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,02 - 1,11 (m, 2 H) 1,26 - 1,41 (m, 5 H) 1,42 - 1,52 (m, 1 H) 1,70 - 1,79 (m, 1 H) 2,18 - 2,30 (m, 1 H) 2,53 - 2,65 (m, 1 H) 2,77 - 2,87 (m, 1 H) 3,12 - 3,27 (m, 2 H) 3,79 - 3,91 (m, 2 H) 5,65 (dd, *J*=11,37, 4,29 Hz, 1 H) 7,63 (dt, *J*=8,59, 6,95 Hz, 1 H) 7,74 (dd, *J*=6,57, 5,05 Hz, 1 H) 7,99 - 8,10 (m, 1 H) 8,45 (d, *J*=12,88 Hz, 1 H) 8,54 (s, 1 H) 8,95 (s, 1 H)

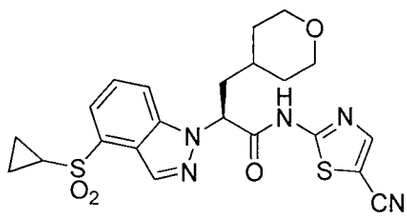
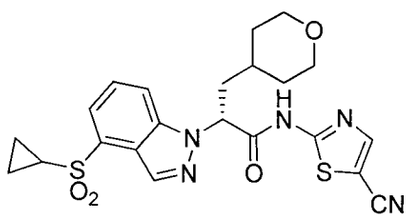
Ej.	Estructura	Método	LCMS	Datos de RMN
127	 2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16 & 95	[M+H] calc. para $C_{20}H_{22}FN_5O_4S_2$ 481, experimental 481	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,10 - 1,20 (m, 2 H) 1,30 - 1,43 (m, 5 H) 1,50 - 1,57 (m, 1 H) 1,76 (dd, *J*=10,23, 1,89 Hz, 1 H) 2,16 - 2,26 (m, 1 H) 2,67 (ddd, *J*=14,27, 10,99, 3,79 Hz, 1 H) 2,90 (tt, *J*=7,93, 4,71 Hz, 1 H) 3,11 - 3,28 (m, 2 H) 3,81 - 3,90 (m, 2 H) 6,05 (dd, *J*=11,12, 4,29 Hz, 1 H) 7,08 (d, *J*=2,53 Hz, 1 H) 7,71 (d, *J*=4,80 Hz, 1 H) 8,51 (s, 1 H) 8,82 (d, 1 H)
128	 (S)-2-(4-(ciclopropilsulfonil)-6-metoxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{26}FN_4O_5S_2$ 509, experimental 509	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,52 (s, 1 H), 7,45 (d, *J*=1,8 Hz, 1 H), 7,00 (br. s., 1 H), 6,96 (s, 1 H), 5,30 (s, 1 H), 3,95 (s, 3 H), 3,78 - 3,93 (m, 2 H), 3,13 - 3,30 (m, 2 H), 2,57 - 2,73 (m, 1 H), 2,50 (br. s., 1 H), 2,25 (d, *J*=5,6 Hz, 1 H), 1,59 (d, *J*=12,4 Hz, 1 H), 1,44 - 1,55 (m, 2 H), 1,28 - 1,44 (m, 4 H), 1,01 - 1,16 ppm (m, 2 H)

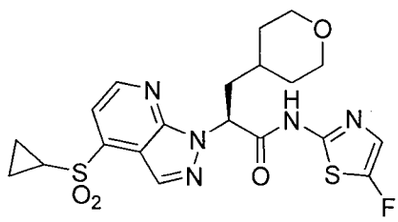
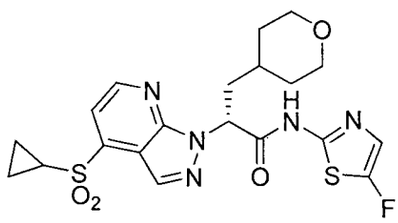
Ej.	Estructura	Método	LCMS	Datos de RMN
129	 (R)-2-(4-(ciclopropilsulfonil)-6-metoxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{26}FN_4O_5S_2$ 509, experimental 509	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,52 (s, 1 H), 7,45 (d, *J*=1,8 Hz, 1 H), 7,00 (br. s., 1 H), 6,96 (s, 1 H), 5,30 (s, 1 H), 3,95 (s, 3 H), 3,78 - 3,93 (m, 2 H), 3,13 - 3,30 (m, 2 H), 2,57 - 2,73 (m, 1 H), 2,50 (br. s., 1 H), 2,25 (d, *J*=5,6 Hz, 1 H), 1,59 (d, *J*=12,4 Hz, 1 H), 1,44 - 1,55 (m, 2 H), 1,28 - 1,44 (m, 4 H), 1,01 - 1,16 ppm (m, 2 H)
130	 2-(4-(ciclopropilsulfonil)-6-hidroxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 12	[M+H] calc. para $C_{21}H_{24}FN_4O_5S_2$ 495, experimental 495	^{1}H RMN (DMSO-d_6 ,400MHz): δ = 12,70 (s, 1 H), 10,48 (s, 1 H), 8,23 (s, 1 H), 7,33 - 7,36 (m, 2 H), 7,23 (d, *J*=1,8 Hz, 1 H), 5,62 (d, *J*=4,3 Hz, 1 H), 3,71 - 3,85 (m, 3 H), 3,06 - 3,21 (m, 2 H), 2,24 - 2,41 (m, 1 H), 2,09 - 2,24 (m, 1 H), 1,54 - 1,63 (m, 1 H), 1,48 (br. s., 1 H), 1,28 (br. s., 3 H), 1,16 (br. s., 2 H), 1,06 ppm (dd, *J*=7,8, 2,0 Hz, 2 H)

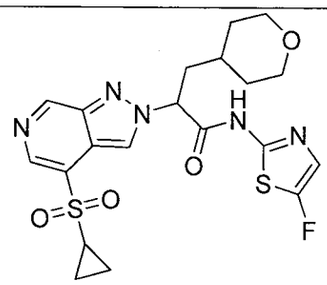
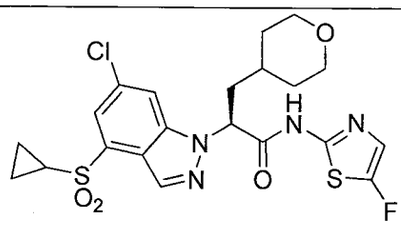
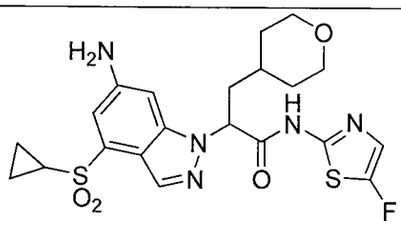
Ej.	Estructura	Método	LCMS	Datos de RMN
131	 2-(4-(ciclopropilsulfonil)-6-hidroxi-2H-indazol-2-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 12	[M+H] calc. para $C_{21}H_{24}FN_4O_5S_2$ 495, experimental 495	^{1}H RMN (DMSO-d_6 ,400MHz): δ = 13,41 (br.s., 1H), 12,74 (s, 1 H), 8,21 (s, 1 H), 7,35 (d, *J*=2,5 Hz, 1 H), 7,30 (d, *J*=2,0 Hz, 1 H), 7,21 (d, *J*=1,0 Hz, 1 H), 5,18 (d, *J*=9,3 Hz, 1 H), 3,79 - 3,87 (m, 2 H), 3,21 - 3,35 (m, 2 H), 2,93 - 3,02 (m, 1 H), 1,92 - 2,00 (m, 1 H), 1,84 (d, *J*=3,5 Hz, 1 H), 1,82 (br. s., 1 H), 1,64 (br. s., 2 H), 1,28 (br. s., 2 H), 1,14 - 1,19 (m, 2 H), 1,00 - 1,06 ppm (m, 2 H)
132	 (R)-2-(6-ciano-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{22}FN_5O_4S_2$ 505, experimental 505	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,07 - 1,14 (m, 2 H) 1,27 - 1,45 (m, 5 H) 1,46 - 1,53 (m, 1 H) 1,68 - 1,76 (m, 1 H) 2,23 - 2,32 (m, 1 H) 2,60 (ddd, *J*=14,46, 10,42, 4,42 Hz, 1 H) 2,89 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,16 - 3,28 (m, 2 H) 3,80 - 3,91 (m, 2 H) 5,83 (dd, *J*=10,61, 5,05 Hz, 1 H) 7,10 (d, *J*=2,78 Hz, 1 H) 7,99 (d, *J*=1,26 Hz, 1 H) 8,59 (s, 1 H) 8,64 (s, 1 H)

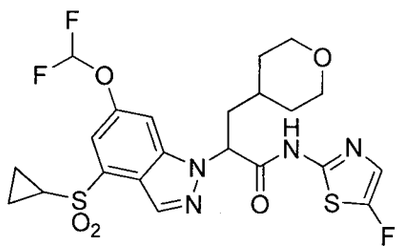
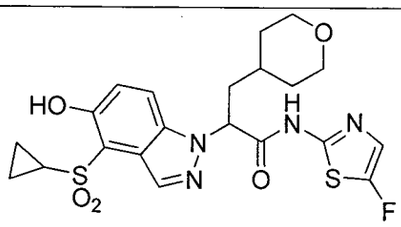
Ej.	Estructura	Método	LCMS	Datos de RMN
133	 (S)-2-(6-ciano-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{22}FN_5O_4S_2$ 505, experimental 505	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,07 - 1,14 (m, 2 H) 1,27 - 1,45 (m, 5 H) 1,46 - 1,53 (m, 1 H) 1,68 - 1,76 (m, 1 H) 2,23 - 2,32 (m, 1 H) 2,60 (ddd, *J*=14,46, 10,42, 4,42 Hz, 1 H) 2,89 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,16 - 3,28 (m, 2 H) 3,80 - 3,91 (m, 2 H) 5,83 (dd, *J*=10,61, 5,05 Hz, 1 H) 7,10 (d, *J*=2,78 Hz, 1 H) 7,99 (d, *J*=1,26 Hz, 1 H) 8,59 (s, 1 H) 8,64 (s, 1 H)
134	 2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(1,5-dimetil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{23}H_{29}N_5O_4S$ 473, experimental 473	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,01 - 1,09 (m, 2 H) 1,25 - 1,43 (m, 5 H) 1,51 (d, *J*=9,35 Hz, 1 H) 1,71 (d, *J*=11,87 Hz, 1 H) 2,17 - 2,28 (m, 4 H) 2,57 (ddd, *J*=14,15, 10,36, 4,04 Hz, 1 H) 2,81 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,14 - 3,28 (m, 2 H) 3,63 - 3,69 (m, 3 H) 3,80 - 3,90 (m, 2 H) 5,66 (dd, *J*=10,36, 5,05 Hz, 1 H) 6,24 (s, 1 H) 7,61 - 7,66 (m, 1 H) 7,74 (d, *J*=6,57 Hz, 1 H) 8,08 (d, *J*=8,34 Hz, 1 H) 8,48 (s, 1 H)

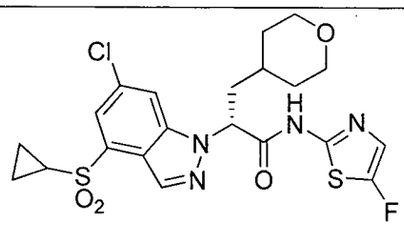
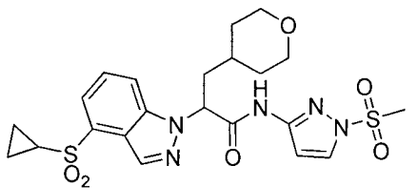
Ej.	Estructura	Método	LCMS	Datos de RMN
135	 N-(5-cianopiridin-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{24}H_{25}N_5O_4S$ 481, experimental 481	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,01 - 1,09 (m, 2 H) 1,25 - 1,43 (m, 5 H) 1,50 (dd, *J*=9,47, 1,89 Hz, 1 H) 1,72 (d, *J*=12,13 Hz, 1 H) 2,18 - 2,27 (m, 1 H) 2,60 (ddd, *J*=14,15, 10,48, 3,92 Hz, 1 H) 2,81 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,13 - 3,27 (m, 2 H) 3,79 - 3,90 (m, 2 H) 5,79 (dd, *J*=10,48, 4,93 Hz, 1 H) 7,63 (dd, *J*=8,59, 7,33 Hz, 1 H) 7,74 (d, *J*=6,57 Hz, 1 H) 8,04 - 8,12 (m, 2 H) 8,24 (d, *J*=8,84 Hz, 1 H) 8,49 (s, 1 H) 8,60 - 8,64 (m, 1 H)

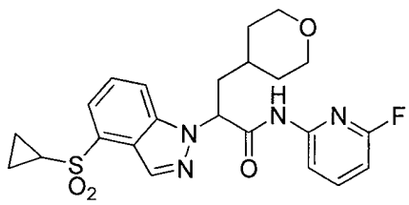
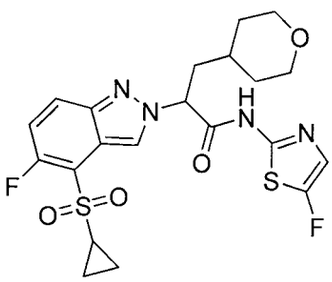
Ej.	Estructura	Método	LCMS	Datos de RMN
136	 (S)-N-(5-cianotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{23}N_5O_4S_2$ 487, experimental 487	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,01 - 1,10 (m, 2 H) 1,26 - 1,42 (m, 5 H) 1,50 (dd, *J*=9,35, 2,02 Hz, 1 H) 1,70 - 1,77 (m, 1 H) 2,23 - 2,32 (m, 1 H) 2,58 (ddd, *J*=14,27, 10,61, 3,92 Hz, 1 H) 2,81 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,15 - 3,27 (m, 2 H) 3,79 - 3,90 (m, 2 H) 5,77 (dd, *J*=10,61, 4,80 Hz, 1 H) 7,62 (dd, *J*=8,46, 7,20 Hz, 1 H) 7,74 (d, *J*=6,57 Hz, 1 H) 8,03 - 8,07 (m, 2 H) 8,46 (s, 1 H)
137	 (R)-N-(5-cianotiazol-2-il)-2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{23}N_5O_4S_2$ 487, experimental 487	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,01 - 1,10 (m, 2 H) 1,26 - 1,42 (m, 5 H) 1,50 (dd, *J*=9,35, 2,02 Hz, 1 H) 1,70 - 1,77 (m, 1 H) 2,23 - 2,32 (m, 1 H) 2,58 (ddd, *J*=14,27, 10,61, 3,92 Hz, 1 H) 2,81 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,15 - 3,27 (m, 2 H) 3,79 - 3,90 (m, 2 H) 5,77 (dd, *J*=10,61, 4,80 Hz, 1 H) 7,62 (dd, *J*=8,46, 7,20 Hz, 1 H) 7,74 (d, *J*=6,57 Hz, 1 H) 8,03 - 8,07 (m, 2 H) 8,46 (s, 1 H)

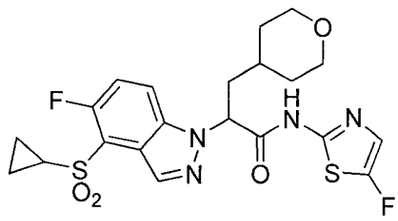
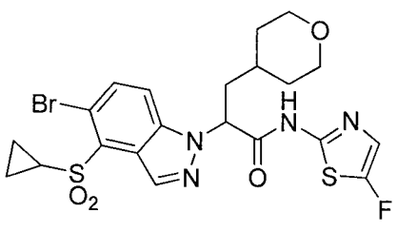
Ej.	Estructura	Método	LCMS	Datos de RMN
138	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16 & 95	[M+H] calc. para $C_{20}H_{22}FN_5O_4S_2$ 481, experimental 481	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,10 - 1,20 (m, 2 H) 1,30 - 1,43 (m, 5 H) 1,50 - 1,57 (m, 1 H) 1,76 (dd, *J*=10,23, 1,89 Hz, 1 H) 2,16 - 2,26 (m, 1 H) 2,67 (ddd, *J*=14,27, 10,99, 3,79 Hz, 1 H) 2,90 (tt, *J*=7,93, 4,71 Hz, 1 H) 3,11 - 3,28 (m, 2 H) 3,81 - 3,90 (m, 2 H) 6,05 (dd, *J*=11,12, 4,29 Hz, 1 H) 7,08 (d, *J*=2,53 Hz, 1 H) 7,71 (d, *J*=4,80 Hz, 1 H) 8,51 (s, 1 H) 8,82 (d, 1 H)
139	 (R)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16 & 95	[M+H] calc. para $C_{20}H_{22}FN_5O_4S_2$ 481, experimental 481	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,10 - 1,20 (m, 2 H) 1,30 - 1,43 (m, 5 H) 1,50 - 1,57 (m, 1 H) 1,76 (dd, *J*=10,23, 1,89 Hz, 1 H) 2,16 - 2,26 (m, 1 H) 2,67 (ddd, *J*=14,27, 10,99, 3,79 Hz, 1 H) 2,90 (tt, *J*=7,93, 4,71 Hz, 1 H) 3,11 - 3,28 (m, 2 H) 3,81 - 3,90 (m, 2 H) 6,05 (dd, *J*=11,12, 4,29 Hz, 1 H) 7,08 (d, *J*=2,53 Hz, 1 H) 7,71 (d, *J*=4,80 Hz, 1 H) 8,51 (s, 1 H) 8,82 (d, 1 H)

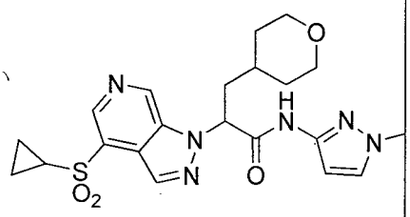
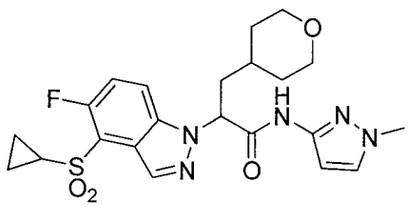
Ej.	Estructura	Método	LCMS	Datos de RMN
140	 2-(4-(ciclopropilsulfonil)-2H-pirazolo[3,4-c]piridin-2-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 13	[M+H] calc. para $C_{20}H_{23}FN_5O_4S_2$ 480, experimental 480	
141	 (S)-2-(6-cloro-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{23}ClFN_4O_4S_2$ 514,0, experimental 514,0	
142	 2-(6-amino-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 21	[M+H] calc. para $C_{21}H_{25}FN_5O_4S_2$ 494,1, experimental 494,4	

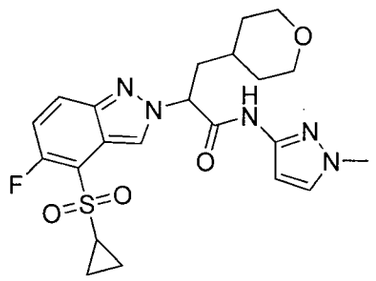
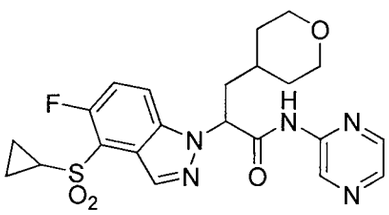
Ej.	Estructura	Método	LCMS	Datos de RMN
143	 2-(4-(ciclopropilsulfonil)-6-(difluorometoxi)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 12	[M+H] calc. para $C_{22}H_{24}F_3N_4O_5S_2$ 545,1, experimental 545,3	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,03 - 1,14 (m, 2 H) 1,23 - 1,45 (m, 5 H) 1,45 - 1,55 (m, 1 H) 1,72 (dd, *J*=12,51, 2,40 Hz, 1 H) 2,16 - 2,31 (m, 1 H) 2,55 (ddd, *J*=14,46, 10,42, 4,42 Hz, 1 H) 2,86 (tt, *J*=7,83, 4,80 Hz, 1 H) 3,22 (m, *J*=17,15, 11,57, 11,57, 2,15 Hz, 2 H) 3,76 - 3,96 (m, 2 H) 7,01 (d, *J*=73,01 Hz, 1 H) 7,10 (d, *J*=2,53 Hz, 1 H) 7,56 (d, *J*=1,77 Hz, 1 H) 7,87 (s, 1 H) 8,47 (s, 1 H)
144	 2-(4-(ciclopropilsulfonil)-5-hidroxi-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{24}FN_4O_5S_2$ 495,1, experimental 495,3	

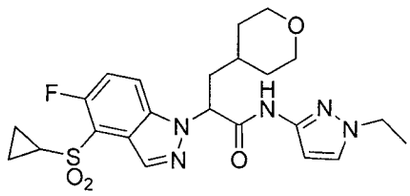
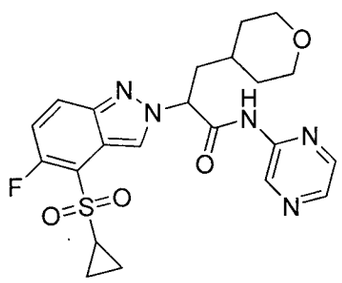
Ej.	Estructura	Método	LCMS	Datos de RMN
145	 (R)-2-(6-cloro-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{21}H_{23}ClFN_4O_4S_2$ 514,0, experimental 514,0	
146	 2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(1-(metilsulfonil)-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{28}N_5O_6S_2$ 522,1, experimental 522,1	^{1}H RMN (400 MHz, CLOROFORM-d) δ 9,00 (s, 1H), 8,66 (s, 1H), 7,92 (d, *J* = 3,03 Hz, 1H), 7,81 (d, *J* = 6,57 Hz, 1H), 7,74 (d, *J* = 8,84 Hz, 1H), 7,61 (dd, *J* = 7,33, 8,59 Hz, 1H), 7,02 (d, *J* = 2,78 Hz, 1H), 5,38 (dd, *J* = 5,05, 10,61 Hz, 1H), 3,89 (br. s., 2H), 3,09 - 3,30 (m, 5H), 2,60 - 2,71 (m, 1H), 2,46 - 2,59 (m, 1H), 2,29 (ddd, *J* = 5,05, 8,65, 14,08 Hz, 1H), 1,28 - 1,55 (m, 6H), 1,25 (br. s., 1H), 1,01 - 1,20 (m, 2H)

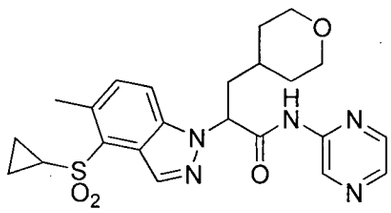
Ej.	Estructura	Método	LCMS	Datos de RMN
147	 2-(4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(6-fluoropiridin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{23}H_{26}FN_4O_4S$ 473,2, experimental 473,2	^{1}H RMN (400 MHz, CLOROFORM-d) δ 8,92 (s, 1H), 8,67 (s, 1H), 8,04 (dd, *J* = 1,64, 7,96 Hz, 1H), 7,73 - 7,86 (m, 3H), 7,60 (dd, *J* = 7,33, 8,59 Hz, 1H), 6,68 (dd, *J* = 2,27, 8,08 Hz, 1H), 5,39 (dd, *J* = 4,93, 10,48 Hz, 1H), 3,81 - 3,97 (m, 2H), 3,11 - 3,34 (m, 3H), 2,46 - 2,70 (m, 2H), 2,29 (ddd, *J* = 4,93, 8,59, 14,02 Hz, 1H), 1,62 (d, *J* = 12,88 Hz, 1H), 1,31 - 1,55 (m, 4H), 1,26 (qd, *J* = 4,29, 7,66 Hz, 1H), 0,96 - 1,15 (m, 2H)
148	 2-(4-(ciclopropilsulfonil)-5-fluoro-2H-indazol-2-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 19	[M+H] calc. para $C_{21}H_{23}F_2N_4O_4S_2$ 497,1, experimental 497,1	^{1}H RMN (400 MHz, CLOROFORM-d) δ 8,61 (s, 1H), 8,04 (dd, *J* = 4,17, 9,22 Hz, 1H), 7,24 - 7,35 (m, 2H), 7,03 (br. s., 1H), 5,34 (dd, *J* = 5,43, 9,98 Hz, 1H), 3,91 (br. s., 2H), 3,18 - 3,34 (m, 2H), 2,80 - 2,97 (m, 1H), 2,37 - 2,53 (m, 1H), 2,20 - 2,37 (m, 1H), 1,68 (br. s., 1H), 1,45 - 1,55 (m, 2H), 1,26 - 1,45 (m, 4H), 1,00 - 1,15 (m, 2H)

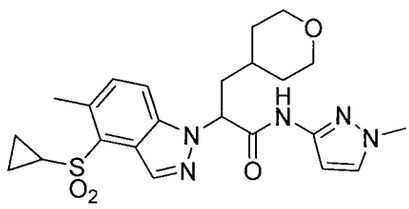
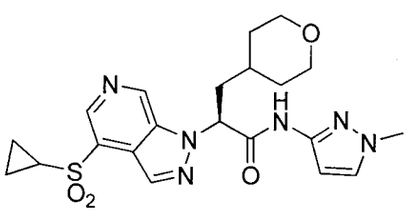
Ej.	Estructura	Método	LCMS	Datos de RMN
149	 2-(4-(ciclopropilsulfonil)-5-fluoro-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 19	[M+H] calc. para $C_{21}H_{23}F_2N_4O_4S_2$ 497,1, experimental 497,1	^{1}H RMN (400 MHz, CLOROFORM-d) δ 8,72 (s, 1H), 7,73 (dd, *J* = 2,91, 9,22 Hz, 1H), 7,37 (t, *J* = 9,35 Hz, 1H), 7,07 (d, *J* = 2,27 Hz, 1H), 5,46 (dd, *J* = 4,93, 10,48 Hz, 1H), 3,92 (ddd, *J* = 2,53, 11,37, 13,39 Hz, 2H), 3,14 - 3,31 (m, 2H), 2,83 - 2,94 (m, 1H), 2,45 - 2,61 (m, 1H), 2,28 (ddd, *J* = 4,93, 8,78, 14,08 Hz, 1H), 1,58 - 1,69 (m, 1H), 1,32 - 1,58 (m, 5H), 1,21 (d, *J* = 3,79 Hz, 1H), 1,04 - 1,17 (m, 2H)
150	 2-(5-bromo-4-(ciclopropilsulfonil)-1H-indazol-1-il)-N-(5-fluorotiazol-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 19	[M+H] calc. para $C_{21}H_{23}BrFN_4O_4S_2$ 558, experimental 558	^{1}H RMN (400 MHz, DMSO-d_6) δ 9,00 (s, 1H), 7,82 (d, *J* = 7,58 Hz, 1H), 7,56 (d, *J* = 7,58 Hz, 1H), 7,38 (d, *J* = 2,53 Hz, 1H), 5,82 (dd, *J* = 5,68, 9,73 Hz, 1H), 3,73 - 3,86 (m, 2H), 3,09 - 3,20 (m, 2H), 2,89 - 3,04 (m, 1H), 2,45 - 2,61 (m, 1H) 2,20 - 2,36 (m, 1H), 1,64 (d, *J* = 7,83 Hz, 1H), 1,51 (d, *J* = 13,14 Hz, 1H), 1,20 - 1,37 (m, 5H), 0,97 - 1,09 (m, 2H)

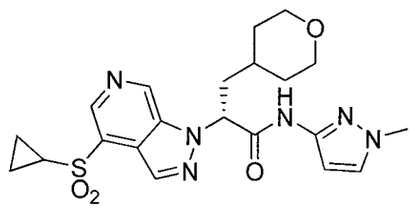
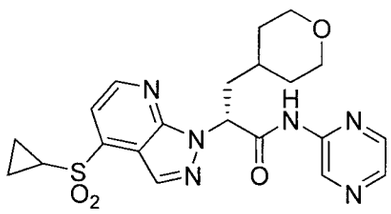
Ej.	Estructura	Método	LCMS	Datos de RMN
151	 2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-c]piridin-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*Ver* Comp. 13	[M+H] calc. para $C_{21}H_{26}N_6O_4S$ 460, experimental 460	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,03 - 1,13 (m, 2 H) 1,17 - 1,36 (m, 5 H) 1,48 - 1,70 (m, 2 H) 2,28 (d, *J*=6,82 Hz, 1 H) 2,44 (br. s., 1 H) 3,03 - 3,23 (m, 3 H) 3,69 - 3,84 (m, 5 H) 5,87 (d, *J*=3,54 Hz, 1 H) 6,37 (d, *J*=2,02 Hz, 1 H) 7,55 (d, *J*=2,02 Hz, 1 H) 8,51 (s, 1 H) 8,68 (s, 1 H) 9,67 (s, 1 H) 11,08 (s, 1 H)
152	 2-(4-(ciclopropilsulfonil)-5-fluoro-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*Ver* Comp. 22	[M+H] calc. para $C_{22}H_{27}FN_5O_4S$ 476, experimental 476	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,58 - 8,83 (m, 2 H), 7,74 (dd, *J*=9,1, 3,0 Hz, 1 H), 7,34 (t, *J*=9,3 Hz, 1 H), 7,23 (d, *J*=2,0 Hz, 1 H), 6,61 (d, *J*=2,3 Hz, 1 H), 5,33 (dd, *J*=10,4, 5,1 Hz, 1 H), 3,81 - 3,94 (m, 2 H), 3,76 (s, 3 H), 3,08 - 3,32 (m, 2 H), 2,90 (dd, *J*=4,8, 3,3 Hz, 1 H), 2,49 (d, *J*=3,8 Hz, 1 H), 2,22 - 2,37 (m, 1 H), 1,59 (d, *J*=12,4 Hz, 1 H), 1,19 - 1,55 (m, 5 H), 1,04 - 1,19 (m, 2 H), 0,78 - 0,93 ppm (m, 1 H)

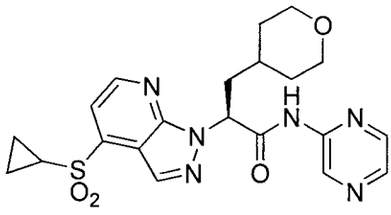
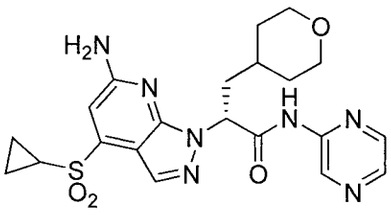
Ej.	Estructura	Método	LCMS	Datos de RMN
153	 2-(4-(ciclopropilsulfonil)-5-fluoro-2H-indazol-2-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*Ver* Comp. 22	[M+H] calc. para $C_{22}H_{27}FN_5O_4S$ 476, experimental 476	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,16 (s, 1 H), 8,59 (s, 1 H), 8,04 (dd, *J*=9,3, 3,5 Hz, 1 H), 7,28 (d, 1 H), 7,24 (d, *J*=2,5 Hz, 1 H), 6,63 (d, *J*=2,3 Hz, 1 H), 5,27 (dd, *J*=9,9, 5,6 Hz, 1 H), 3,93 (dd, *J*=11,4, 2,3 Hz, 1 H), 3,87 (d, *J*=10,9 Hz, 1 H), 3,77 (s, 3 H), 3,23 - 3,37 (m, 2 H), 2,78 - 2,94 (m, 1 H), 2,42 (dd, *J*=9,6, 4,5 Hz, 1 H), 2,27 - 2,37 (m, 1 H), 1,59 - 1,84 (m, 2 H), 1,28 - 1,52 (m, 5 H), 0,95 - 1,18 ppm (m, 2 H)
154	 2-(4-(ciclopropilsulfonil)-5-fluoro-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*Ver* Comp. 22	[M+H] calc. para $C_{22}H_{25}FN_5O_4S$ 474, experimental 474	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,39 - 9,52 (m, 1 H), 9,05 (s, 1 H), 8,80 (s, 1 H), 8,31 - 8,40 (m, 1 H), 8,18 - 8,29 (m, 1 H), 7,77 (dd, *J*=9,2, 2,9 Hz, 1 H), 7,39 (t, *J*=9,5 Hz, 1 H), 5,39 (dd, *J*=10,4, 5,1 Hz, 1 H), 3,76 - 4,00 (m, 2 H), 3,09 - 3,34 (m, 2 H), 2,74 - 2,96 (m, 1 H), 2,43 - 2,62 (m, 1 H), 2,19 - 2,43 (m, 1 H), 1,57 - 1,66 (m, 1 H), 1,24 - 1,55 (m, 6 H), 1,03 - 1,19 ppm (m, 2 H)

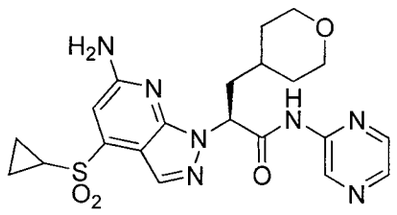
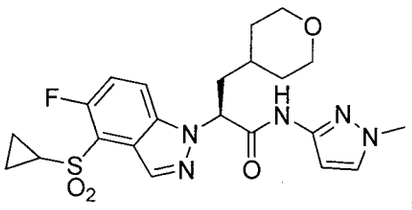
Ej.	Estructura	Método	LCMS	Datos de RMN
155	 2-(4-(ciclopropilsulfonil)-5-fluoro-1H-indazol-1-il)-N-(1-etil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*Ver* Comp. 22	[M+H] calc. para $C_{23}H_{29}FN_5O_4S$ 490, experimental 490	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,38 (s, 1H), 8,71 (s, 1H), 7,75-7,78 (m, 1H), 7,23 - 7,36 (m, 2 H), 6,67 - 6,72 (m, 1 H), 5,25 - 5,46 (m, 1 H), 4,00 - 4,12 (m, 2 H), 3,83 - 3,95 (m, 2 H), 3,12 - 3,34 (m, 2 H), 2,81 - 2,94 (m, 1 H), 2,39 - 2,59 (m, 1 H), 2,23 - 2,39 (m, 1 H), 1,32 - 1,54 (m, 10 H), 0,96 - 1,19 ppm (m, 2 H)
156	 2-(4-(ciclopropilsulfonil)-5-fluoro-2H-indazol-2-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*Ver* Comp. 22	[M+H] calc. para $C_{22}H_{25}FN_5O_4S$ 474, experimental 474	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,53 (s, 2 H), 8,81 (s, 1 H), 8,42 (d, *J*=3,0 Hz, 2 H), 7,78 (dd, *J*=9,0, 3,4 Hz, 1 H), 7,41 (t, *J*=9,5 Hz, 1 H), 5,43 (dd, *J*=10,1, 5,3 Hz, 1 H), 3,89 - 4,13 (m, 2 H), 3,18 - 3,42 (m, 2 H), 2,78 - 2,96 (m, 1 H), 2,52 (dd, *J*=9,9, 4,5 Hz, 1 H), 2,21 - 2,41 (m, 1 H), 1,65 (d, *J*=12,6 Hz, 1 H), 1,38 - 1,56 (m, 5 H), 1,31 - 1,37 (m, 1 H), 1,11 - 1,24 ppm (m, 2 H)

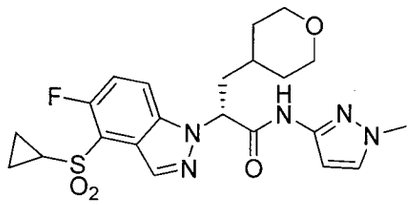
Ej.	Estructura	Método	LCMS	Datos de RMN
157	 2-(4-(ciclopropilsulfonil)-5-metil-1H-indazol-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*Ver* Comp. 22	[M+H] calc. para $C_{23}H_{28}N_5O_4S$ 470, experimental 470	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,53 (br. s., 1H), 9,31 (br. s., 1 H), 8,77 (s, 1 H), 8,27 - 8,50 (m, 2 H), 7,64 (d, *J*=8,6 Hz, 1 H), 7,43 (d, *J*=8,8 Hz, 1 H), 5,38 (dd, *J*=10,4, 5,1 Hz, 1 H), 3,80 - 4,00 (m, 2 H), 3,11 - 3,34 (m, 2 H), 2,86 (s, 3 H), 2,69 (tt, *J*=8,0, 4,8 Hz, 1 H), 2,44 - 2,60 (m, 1 H), 2,29 (ddd, *J*=13,9, 8,3, 5,1 Hz, 1 H), 1,62 (d, *J*=12,6 Hz, 1 H), 1,34 - 1,55 (m, 5 H), 1,25 - 1,33 (m, 1 H), 0,96 - 1,14 ppm (m, 2 H

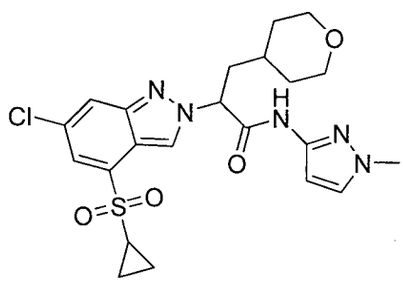
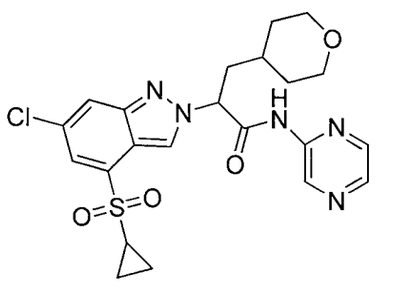
Ej.	Estructura	Método	LCMS	Datos de RMN
158	 2-(4-(ciclopropilsulfonil)-5-metil-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*Ver* Comp. 22	[M+H] calc. para $C_{23}H_{30}N_5O_4S$ 472, experimental 472	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 9,26 (s, 1 H), 8,67 (s, 1 H), 7,64 (d, *J*=8,8 Hz, 1 H), 7,38 (d, *J*=8,6 Hz, 1 H), 7,15 - 7,32 (m, 1 H), 6,67 (d, *J*=2,5 Hz, 1 H), 5,34 (dd, *J*=10,5, 4,9 Hz, 1 H), 3,88 (td, *J*=11,2, 2,7 Hz, 2 H), 3,78 (s, 3 H), 3,08 - 3,31 (m, 2 H), 2,85 (s, 3 H), 2,60 - 2,80 (m, 1 H), 2,39 - 2,60 (m, 1 H), 2,27 (ddd, *J*=14,0, 8,5, 5,1 Hz, 1 H), 1,62 (d, *J*=12,6 Hz, 1 H), 1,30 - 1,51 (m, 5 H), 1,21 - 1,29 (m, 1 H), 1,03 (d, *J*=7,3 Hz, 1 H), 1,02 ppm (s, 1 H)
159	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-c]piridin-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 13	[M+H] calc. para $C_{21}H_{26}N_6O_4S$ 460, experimental 460	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,03 - 1,13 (m, 2 H) 1,17 - 1,36 (m, 5 H) 1,48 - 1,70 (m, 2 H) 2,28 (d, *J*=6,82 Hz, 1 H) 2,44 (br. s., 1 H) 3,03 - 3,23 (m, 3 H) 3,69 - 3,84 (m, 5 H) 5,87 (d, *J*=3,54 Hz, 1 H) 6,37 (d, *J*=2,02 Hz, 1 H) 7,55 (d, *J*=2,02 Hz, 1 H) 8,51 (s, 1 H) 8,68 (s, 1 H) 9,67 (s, 1 H) 11,08 (s, 1 H)

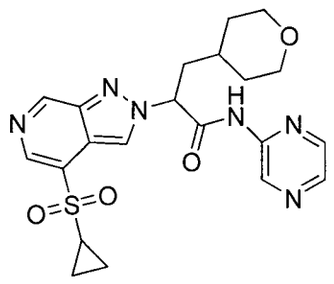
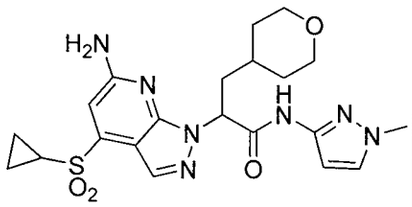
Ej.	Estructura	Método	LCMS	Datos de RMN
160	 (R)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-c]piridin-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 13	[M+H] calc. para $C_{21}H_{26}N_6O_4S$ 460, experimental 460	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,03 - 1,13 (m, 2 H) 1,17 - 1,36 (m, 5 H) 1,48 - 1,70 (m, 2 H) 2,28 (d, *J*=6,82 Hz, 1 H) 2,44 (br. s., 1 H) 3,03 - 3,23 (m, 3 H) 3,69 - 3,84 (m, 5 H) 5,87 (d, *J*=3,54 Hz, 1 H) 6,37 (d, *J*=2,02 Hz, 1 H) 7,55 (d, *J*=2,02 Hz, 1 H) 8,51 (s, 1 H) 8,68 (s, 1 H) 9,67 (s, 1 H) 11,08 (s, 1 H)
161	 (R)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16 & 92	[M+H] calc. para $C_{21}H_{24}N_6O_4S$ 458, experimental 458	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,09 - 1,19 (m, 2 H) 1,33 - 1,46 (m, 5 H) 1,56 (dd, *J*=9,47, 1,89 Hz, 1 H) 1,76 (dd, *J*=9,73, 1,89 Hz, 1 H) 2,20 - 2,30 (m, 1 H) 2,73 (ddd, *J*=14,15, 11,12, 3,54 Hz, 1 H) 2,91 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,11 - 3,28 (m, 2 H) 3,81 - 3,90 (m, 2 H) 6,10 (dd, *J*=11,12, 4,29 Hz, 1 H) 7,71 (d, *J*=4,55 Hz, 1 H) 8,31 (d, *J*=2,53 Hz, 1 H) 8,36 (dd, *J*=2,53, 1,52 Hz, 1 H) 8,53 (s, 1 H) 8,83 (d, *J*=4,80 Hz, 1 H) 9,29 (s, 1 H)

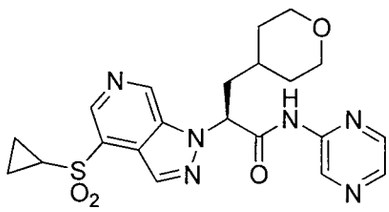
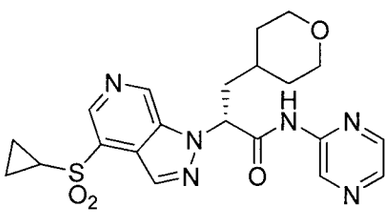
Ej.	Estructura	Método	LCMS	Datos de RMN
162	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16 & 92	[M+H] calc. para $C_{21}H_{24}N_6O_4S$ 458, experimental 458	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,09 - 1,19 (m, 2 H) 1,33 - 1,46 (m, 5 H) 1,56 (dd, *J*=9,47, 1,89 Hz, 1 H) 1,76 (dd, *J*=9,73, 1,89 Hz, 1 H) 2,20 - 2,30 (m, 1 H) 2,73 (ddd, *J*=14,15, 11,12, 3,54 Hz, 1 H) 2,91 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,11 - 3,28 (m, 2 H) 3,81 - 3,90 (m, 2 H) 6,10 (dd, *J*=11,12, 4,29 Hz, 1 H) 7,71 (d, *J*=4,55 Hz, 1 H) 8,31 (d, *J*=2,53 Hz, 1 H) 8,36 (dd, *J*=2,53, 1,52 Hz, 1 H) 8,53 (s, 1 H) 8,83 (d, *J*=4,80 Hz, 1 H) 9,29 (s, 1 H)
163	 (R)-2-(6-amino-4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16	[M+H] calc. para $C_{21}H_{25}N_7O_4S$ 473, experimental 473	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 0,99 - 1,06 (m, 2 H) 1,29 - 1,42 (m, 5 H) 1,52 (d, *J*=9,35 Hz, 1 H) 1,71 - 1,79 (m, 1 H) 2,13 - 2,23 (m, 1 H) 2,57 - 2,66 (m, 1 H) 2,90 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,13 - 3,27 (m, 2 H) 3,86 (t, *J*=10,74 Hz, 2 H) 5,90 (dd, *J*=10,99, 4,42 Hz, 1 H) 8,17 (s, 1 H) 8,27 - 8,38 (m, 3 H) 9,31 (s, 1 H)

Ej.	Estructura	Método	LCMS	Datos de RMN
164	 (S)-2-(6-amino-4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16	[M+H] calc. para $C_{21}H_{25}N_7O_4S$ 473, experimental 473	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 0,99 - 1,06 (m, 2 H) 1,29 - 1,42 (m, 5 H) 1,52 (d, *J*=9,35 Hz, 1 H) 1,71 - 1,79 (m, 1 H) 2,13 - 2,23 (m, 1 H) 2,57 - 2,66 (m, 1 H) 2,90 (tt, *J*=7,96, 4,80 Hz, 1 H) 3,13 - 3,27 (m, 2 H) 3,86 (t, *J*=10,74 Hz, 2 H) 5,90 (dd, *J*=10,99, 4,42 Hz, 1 H) 8,17 (s, 1 H) 8,27 - 8,38 (m, 3 H) 9,31 (s, 1 H)
165	 (S)-2-(4-(ciclopropilsulfonil)-5-fluoro-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 22	[M+H] calc. para $C_{22}H_{27}FN_5O_4S$ 476, experimental 476	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,58 - 8,83 (m, 2 H), 7,74 (dd, *J*=9,1, 3,0 Hz, 1 H), 7,34 (t, *J*=9,3 Hz, 1 H), 7,23 (d, *J*=2,0 Hz, 1 H), 6,61 (d, *J*=2,3 Hz, 1 H), 5,33 (dd, *J*=10,4, 5,1 Hz, 1 H), 3,81 - 3,94 (m, 2 H), 3,76 (s, 3 H), 3,08 - 3,32 (m, 2 H), 2,90 (dd, *J*=4,8, 3,3 Hz, 1 H), 2,49 (d, *J*=3,8 Hz, 1 H), 2,22 - 2,37 (m, 1 H), 1,59 (d, *J*=12,4 Hz, 1 H), 1,19 - 1,55 (m, 5 H), 1,04 - 1,19 (m, 2 H), 0,78 - 0,93 ppm (m, 1 H)

Ej.	Estructura	Método	LCMS	Datos de RMN
166	 (R)-2-(4-(ciclopropilsulfonil)-5-fluoro-1H-indazol-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 22	[M+H] calc. para $C_{22}H_{27}FN_5O_4S$ 476, experimental 476	^{1}H RMN (CLOROFORM-d ,400MHz): δ = 8,58 - 8,83 (m, 2 H), 7,74 (dd, *J*=9,1, 3,0 Hz, 1 H), 7,34 (t, *J*=9,3 Hz, 1 H), 7,23 (d, *J*=2,0 Hz, 1 H), 6,61 (d, *J*=2,3 Hz, 1 H), 5,33 (dd, *J*=10,4, 5,1 Hz, 1 H), 3,81 - 3,94 (m, 2 H), 3,76 (s, 3 H), 3,08 - 3,32 (m, 2 H), 2,90 (dd, *J*=4,8, 3,3 Hz, 1 H), 2,49 (d, *J*=3,8 Hz, 1 H), 2,22 - 2,37 (m, 1 H), 1,59 (d, *J*=12,4 Hz, 1 H), 1,19 - 1,55 (m, 5 H), 1,04 - 1,19 (m, 2 H), 0,78 - 0,93 ppm (m, 1 H)

Ej.	Estructura	Método	LCMS	Datos de RMN
167	 2-(6-cloro-4-(ciclopropilsulfonil)-2H-indazol-2-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{27}ClN_5O_4S$ 492, experimental 492	^{1}H RMN (400 MHz, CLOROFORM-d) δ 9,17 (s, 1H), 8,47 (d, *J* = 1,01 Hz, 1H), 8,04 (d, *J* = 1,01 Hz, 1H), 7,69 (d, *J* = 1,77 Hz, 1H), 7,18 - 7,31 (m, 1H), 6,62 (d, *J* = 2,27 Hz, 1H), 5,26 (dd, *J* = 5,81, 9,85 Hz, 1H), 3,82 - 4,00 (m, 2H), 3,72 - 3,81 (m, 3H), 3,26 (td, *J* = 1,89, 11,43 Hz, 2H), 2,48 - 2,62 (m, 1H), 2,25 - 2,48 (m, 2H), 1,61 - 1,76 (m, 1H), 1,47 - 1,55 (m, 1H), 1,26 - 1,47 (m, 5H), 0,97 - 1,11 (m, 2H)
168	 2-(6-cloro-4-(ciclopropilsulfonil)-2H-indazol-2-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 10	[M+H] calc. para $C_{22}H_{25}ClN_5O_4S$ 490,1, experimental 490,1	^{1}H RMN (400 MHz, CLOROFORM-d) δ 9,59 (s, 1H), 9,49 (br. s., 1H), 8,52 (s, 1H), 8,38 (br. s., 1H), 8,26 (s, 1H), 8,08 (s, 1H), 7,71 (d, *J* = 1,52 Hz, 1H), 5,33 (dd, *J* = 5,81, 9,85 Hz, 1H), 3,81 - 4,02 (m, 2H), 3,18 - 3,32 (m, 2H), 2,42 - 2,66 (m, 2H), 2,26 - 2,42 (m, 1H), 1,70 (d, *J* = 12,13 Hz, 1H), 1,62 (br. s., 1H), 1,49 - 1,58 (m, 1H), 1,29 - 1,49 (m, 4H), 1,00 - 1,14 (m, 2H)

Ej.	Estructura	Método	LCMS .	Datos de RMN
169	 2-(4-(ciclopropilsulfonil)-2H-pirazolo[3,4-c]piridin-2-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 13 & 140	[M+H] calc. para $C_{21}H_{24}N_6O_4S$ 458, experimental 458	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,04 - 1,14 (m, 2 H) 1,17 - 1,40 (m, 5 H) 1,48 - 1,71 (m, 2 H) 2,23 - 2,35 (m, 1 H) 2,53 - 2,60 (m, 1 H) 3,02 - 3,21 (m, 3 H) 3,70 - 3,88 (m, 2 H) 5,97 (dd, *J*=9,85, 5,56 Hz, 1 H) 8,38 - 8,49 (m, 2 H) 8,57 (s, 1 H) 9,00 (s, 1 H) 9,27 (d, *J*=1,26 Hz, 1 H) 9,56 (s, 1 H) 11,56 (s, 1 H)
170	 2-(6-amino-4-(ciclopropilsulfonil)-1H-pirazolo[3,4-b]piridin-1-il)-N-(1-metil-1H-pirazol-3-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 16	[M+H] calc. para $C_{21}H_{27}N_7O_4S$ 475, experimental 475	^{1}H RMN (400 MHz, METANOL-d_4) δ ppm 1,11 - 1,19 (m, 2 H) 1,28 - 1,44 (m, 5 H) 1,49 - 1,56 (m, 1 H) 1,73 - 1,81 (m, 1 H) 2,24 (ddd, *J*=13,77, 8,97, 4,55 Hz, 1 H) 2,67 - 2,77 (m, 1 H) 2,85 - 2,95 (m, 1 H) 3,10 - 3,28 (m, 2 H) 3,79 - 3,90 (m, 5 H) 6,08 (dd, *J*=11,37, 4,29 Hz, 1 H) 7,72 (d, *J*=4,80 Hz, 1 H) 7,75 (s, 1 H) 8,53 (s, 1 H) 8,84 (d, 1 H)

Ej.	Estructura	Método	LCMS	Datos de RMN
171	 (S)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-c]piridin-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 20	[M+H] calc. para $C_{21}H_{25}N_6O_4S$ 458, experimental 458	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,06 - 1,12 (m, 2 H) 1,20 - 1,37 (m, 5 H) 1,50 (d, *J*=11,62 Hz, 1 H) 1,66 (d, *J*=11,12 Hz, 1 H) 2,25 - 2,35 (m, 1 H) 2,52 - 2,58 (m, 1 H) 3,04 - 3,17 (m, 3 H) 3,71 - 3,83 (m, 2 H) 6,06 (dd, *J*=10,11, 5,31 Hz, 1 H) 8,40 (d, *J*=2,53 Hz, 1 H) 8,42 - 8,46 (m, 1 H) 8,55 (s, 1 H) 8,70 (s, 1 H) 9,24 (d, *J*=1,26 Hz, 1 H) 9,68 (s, 1 H).
172	 (R)-2-(4-(ciclopropilsulfonil)-1H-pirazolo[3,4-c]piridin-1-il)-N-(pirazin-2-il)-3-(tetrahidro-2H-piran-4-il)propanamida	*ver* Comp. 20	[M+H] calc. para $C_{21}H_{25}N_6O_4S$ 458, experimental 458	^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1,06 - 1,12 (m, 2 H) 1,20 - 1,37 (m, 5 H) 1,50 (d, *J*=11,62 Hz, 1 H) 1,66 (d, *J*=11,12 Hz, 1 H) 2,25 - 2,35 (m, 1 H) 2,52 - 2,58 (m, 1 H) 3,04 - 3,17 (m, 3 H) 3,71 - 3,83 (m, 2 H) 6,06 (dd, *J*=10,11, 5,31 Hz, 1 H) 8,40 (d, *J*=2,53 Hz, 1 H) 8,42 - 8,46 (m, 1 H) 8,55 (s, 1 H) 8,70 (s, 1 H) 9,24 (d, *J*=1,26 Hz, 1 H) 9,68 (s, 1 H).

Ensayo biológico

[00498] La actividad de los compuestos como activadores de glucoquinasa se puede ensayar *in vitro*, *in vivo* o en una línea celular. A continuación se provee una actividad enzimática del ensayo de glucoquinasa.

[00499] La glucoquinasa purificada se puede obtener de la siguiente forma. El ADN que

codifica los residuos 12-465 de la secuencia de longitud completa de la enzima humana se pueden amplificar por PCR y clonarse en los HindIII y EcoRI de pFLAG-CTC (Sigma). La SEC. ID. No. 1 correspondes a los residuos 12-465 de glucoquinasa.

[00500] La expresión de la proteína de glucoquinasa recombinante puede ser llevada a cabo por transformación y desarrollo de las células DH10b-T1r E.coli que incorporan el plásmido (pFLAG-CTC) en el medio LB. La expresión de la proteína puede ser inducida en este sistema por el agregado de IPTG al medio de cultivo.

[00501] La proteína recombinante puede ser aislada de los extractos celulares por el pasaje sobre la resina Sefarosa Q de rápida fluidez (Pharmacia). Este extracto GK parcialmente purificado puede ser purificado además por un segundo pasaje sobre Poros HQ10 (Applied Biosystems). La pureza de GK may se puede determinar sobre gel SDS-PAGE desnaturalizado. La GK purificada puede ser concentrada hasta una concentración final de 20,0 mg/ml. Después de la congelación flash en nitrógeno líquido, las proteínas se pueden almacenar a -78°C en un buffer que contiene TRIS-HCl 25mM pH 7,6, NaCl50mM, y TCEP 0,5 mM.

[00502] Debe observarse que una variedad de otros sistemas de expresión y huéspedes también son adecuados para la expresión de glucoquinasa, como lo apreciarían fácilmente los expertos en la técnica.

[00503] Las propiedades de activación de los compuestos para GK se pueden determinar utilizando un formato de placa de 384 pocillos negro en las siguientes condiciones de reacción: Hepes 25 mM pH 7,2, NaCl 25 mM, $MgCl_2$ 10 mM, 0,01% de Brij35, DTT 1 mM, 5 µM de ATP, Glucosa 5 mM 2% de DMSO. La cantidad de ATP consumida se puede determinar en forma cuantitativa por la adición de un volumen igual de reactivo de luciferasa (Kit de ensayo de quinasa luminiscente de luciferasa + luciferina del escarabajo ---KinaseGlo de Promega). La intensidad de la luminiscencia se puede medir utilizando el Analist HT de LJL Biosystems.

[00504] La reacción del ensayo se puede iniciar de la siguiente forma: 4 µl de mezcla de sustrato (12,5 µM de ATP y 12,5 mM de glucosa) se agregó a cada pocillo de la placa, seguido de la adición de 2 µl de activador (diluciones en serie 2 veces para 11 puntos de datos para cada activador) que contiene 10% de DMSO. Se puede agregar 4 µL de solución 1,25 nM de GK para iniciar la reacción. A continuación la mezcla de reacción se puede incubar a temperatura ambiente durante 60 min, y templarse y desarrollarse por la adición de 10 µL de reactivo de luciferasa. Las intensidades de luminiscencia de las mezclas de reacción resultantes se pueden medir después de una incubación de 10 min a temperatura ambiente. La intensidad de luminiscencia se puede medir utilizando el Analist HT de LJL Biosystems.

[00505] Los valores pK_{act} y$\%ACT_{max}$ se pueden calcular por ajuste de curva no-lineal de las concentraciones del compuesto y las intensidades de luminiscencia a una ecuación estándar de inhibición/activación. K_{act} es la concentración que muestra 50% del incremento máximo en la actividad de GK observada utilizando una concentración del activador de saturación. $\%Act_{max}$ representa la ganancia máxima calculada en la actividad enzimática de GK a una concentración de saturación del compuesto. Los valores pK_{act} y$\%ACT_{max}$ para los compuestos selectos de la presente invención se muestran en la Tabla 1.

TABLA 1: pK_{act} y$\%ACT_{max}$ **de compuestos ejemplificados contra GK**

Compuesto	pK_{act}	$\%ACT_{max}$
1	≤4,8	≤ 90
2	≤4,8	≤ 90
3	≤4,8	≤ 90
4	4,9 – 5,4	101 - 105
5	5,9 – 6,4	≥ 111
6	4,9 – 5,4	≥ 111
7	4,9 – 5,4	≤ 90
8	4,9 – 5,4	≤ 90
9	4,9 – 5,4	≤ 90
10	5,5 – 5,8	≥ 111
11	≥6,5	101 - 105
12	5,5 – 5,8	≤ 90
13	≥6,5	106 - 110
14	≥6,5	≥ 111
15	5,9 – 6,4	90 - 100
16	≥6,5	106 - 110
19	≥6,5	≤ 90
20 (Free Base)	5,9 – 6,4	101 - 105
20 (TFA Salt)	5,5 – 5,8	106 - 110
22	≥6,5	≥ 111
23	≥6,5	≥ 111
24	≤4,8	≤ 90
25	≤4,8	≤ 90
26	≤4,8	≤ 90

Compuesto	pK_{act}	$\%ACT_{max}$
27	5,5 – 5,8	≤ 90
28	4,9 – 5,4	≥ 111
29	5,9 – 6,4	≥ 111
30	4,9 – 5,4	≤ 90
31	≤4,8	≤ 90
32	4,9 – 5,4	101 - 105
33	5,5 – 5,8	≥ 111
34	5,5 – 5,8	≥ 111
35	≤4,8	≤ 90
36	5,5 – 5,8	≥ 111
37	5,5 – 5,8	≥ 111
38	≤4,8	≥ 111
39	5,5 – 5,8	≥ 111
40	≤4,8	≤ 90
41	5,5 – 5,8	≤ 90
42	5,5 – 5,8	≥ 111
43	≤4,8	≤ 90
44	5,9 – 6,4	≥ 111
45	4,9 – 5,4	≥ 111
46	≤4,8	101 - 105
47	4,9 – 5,4	≥ 111
48	5,9 – 6,4	≥ 111
49	4,9 – 5,4	90 - 100
50	≤4,8	≤ 90
51	5,9 – 6,4	≥ 111
52	≤4,8	90 - 100
53	≤4,8	≤ 90
54	4,9 – 5,4	≤ 90
55	4,9 – 5,4	≤ 90
56	≤4,8	≤ 90
57	4,9 – 5,4	101 - 105
58	≤4,8	101 - 105
59	≥6,5	106 - 110

Compuesto	pK_{act}	$\%ACT_{max}$
60	≤4,8	≤ 90
61	5,9 – 6,4	90 - 100
62	5,9 – 6,4	90 - 100
63	4,9 – 5,4	≥ 111
64	≥6,5	≥ 111
65	5,9 – 6,4	90 - 100
66	≥6,5	101 - 105
67	≥6,5	106 - 110
68	4,9 – 5,4	101 - 105
69	≥6,5	106 - 110
70	5,5 – 5,8	101 - 105
71	5,5 – 5,8	≤ 90
72	≥6,5	≤ 90
73	≤4,8	90 - 100
74	5,5 – 5,8	90 - 100
75	5,9 – 6,4	90 - 100
76	≥6,5	106 - 110
77	≤4,8	101 - 105
78	5,5 – 5,8	90 - 100
79	≥6,5	90 - 100
80	≥6,5	101 - 105
81	4,9 – 5,4	101 - 105
82	≥6,5	106 - 110
83	4,9 – 5,4	≤ 90
84	≥6,5	106 - 110
85	5,5 – 5,8	90 - 100
86	≤4,8	≤ 90
87	5,5 – 5,8	90 - 100
88	≤4,8	≤ 90
89	5,5 – 5,8	101 - 105
90	≤4,8	90 - 100
91	5,9 – 6,4	101 - 105
92	4,9 – 5,4	≤ 90

Compuesto	pK_{act}	$\%ACT_{max}$
93	≤4,8	≤ 90
94	≥6,5	90 - 100
95	5,5 – 5,8	101 - 105
96	5,9 – 6,4	101 - 105
97	5,9 – 6,4	106 - 110
98	5,9 – 6,4	90 - 100
99	4,9 – 5,4	90 - 100
100	5,9 – 6,4	≤ 90
101	5,9 – 6,4	90 - 100
102	5,9 – 6,4	90 - 100
103	5,5 – 5,8	101 - 105
104	5,5 – 5,8	90 - 100
105 (TFA Salt)	5,9 – 6,4	≤ 90
105 (Free Base)	≥6,5	≤ 90
106	≤4,8	90 - 100
107	≥6,5	≥ 111
108	4,9 – 5,4	≥ 111
109	≥6,5	101 - 105
110	≤4,8	106 - 110
111	5,9 – 6,4	106 - 110
112	≥6,5	106 - 110
113	5,9 – 6,4	101 - 105
114	≥6,5	101 - 105
115	≥6,5	106 - 110
116	4,9 – 5,4	≤ 90
117	≥6,5	106 - 110
118	≤4,8	≤ 90
119	5,9 – 6,4	90 - 100
120	≥6,5	90 - 100
121	≥6,5	90 - 100
122	4,9 – 5,4	≥ 111
123	≥6,5	≥ 111
124	4,9 – 5,4	≥ 111

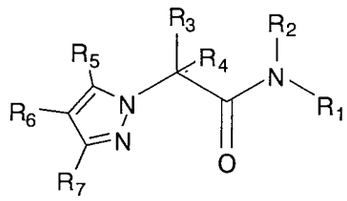
Compuesto	pK_{act}	$\%ACT_{max}$
125	5,5 – 5,8	≥ 111
126	≤4,8	≤ 90
127	≥6,5	101 - 105
128	≥6,5	90 - 100
129	4,9 – 5,4	≤ 90
130	≥6,5	101 - 105
131	≤4,8	≤ 90
132	5,5 – 5,8	90 - 100
133	≥6,5	101 - 105
134	5,5 – 5,8	≥ 111
135	5,9 – 6,4	106 - 110
136	5,9 – 6,4	≥ 111
137	4,9 – 5,4	≤ 90
138	5,9 – 6,4	90 - 100
139	≤4,8	106 - 110
140	≤4,8	≤ 90
141	≥6,5	90 - 100
142	≥6,5	101 - 105
143	≥6,5	≤ 90
144	≥6,5	106 - 110
145	4,9 – 5,4	≤ 90
146	4,9 – 5,4	≤ 90
147	5,5 – 5,8	≥ 111
148	4,9 – 5,4	≤ 90
149	≥6,5	≥ 111
150	5,9 – 6,4	≥ 111
151	5,5 – 5,8	90 - 100
152	≥6,5	106 - 110
153	≤4,8	106 - 110
154	≥6,5	106 - 110
155	≥6,5	106 - 110
156	≥6,5	101 - 105
157	5,9 – 6,4	≥ 111

Compuesto	pK_{act}	$\%ACT_{max}$
158	5,9 – 6,4	≥ 111
159	5,5 – 5,8	101 - 105
160	4,9 – 5,4	90 - 100
161	≤4,8	≤ 90
162	5,5 – 5,8	106 - 110
163	5,5 – 5,8	≤ 90
164	5,9 – 6,4	106 - 110
165	≥6,5	90 - 100
166	4,9 – 5,4	90 - 100
167	4,9 – 5,4	≤ 90
168	≤4,8	≤ 90
169	≤4,8	≤ 90
170	≤4,8	≤ 90
171	5,5 – 5,8	106 - 110

[00506] Será evidente para los expertos en la técnica que varias modificaciones y variantes se pueden realizar en los compuestos, las composiciones, los kits, y los métodos de la presente invención sin apartarse del espíritu o alcance de la invención. De este modo, se entiende que la presente invención cubre las modificaciones y variantes de esta invención siempre que estén dentro del alcance de las reivindicaciones adjuntas y sus equivalentes.

Reivindicaciones

1.-Un compuesto que tiene la fórmula:



o un polimorfo, solvato, éster, tautómero, enantiómero, sal o prodroga del mismo aceptable para uso farmacéutico, donde

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es $–L-R_{18}$;

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10),

oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es $–L_1-R_{22}$;

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es $–L_1-R_{22}$;

o cualquiera dos R_5, R_6 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado

por carbono, oxígeno, nitrógeno, y azufre;

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

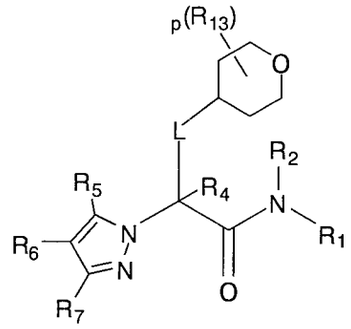
R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5),

cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido,

con la condición que (a) R_1 no sea 5-(3-acetamidociclobutil)-1H-pirazol-3-ilo cuando R_5 y R_6, junto con el anillo al cual ellos están unidos, formen un indazol-1-ilo no sustituido; y (b) R_1 no sea 5-(2-clorobencil)tiazol-2-ilo cuando R_3 sea fenilo y R_2, R_4, R_5, R_6 y R_7 sean todos hidrógeno.

2-El compuesto de la reivindicación 1 que comprende:

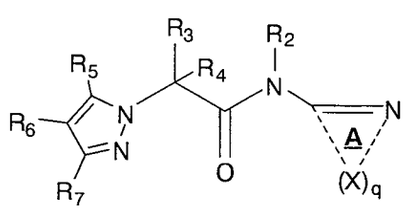


donde

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9; y

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido.

3-El compuesto de la reivindicación 1 que comprende:



donde

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble; y

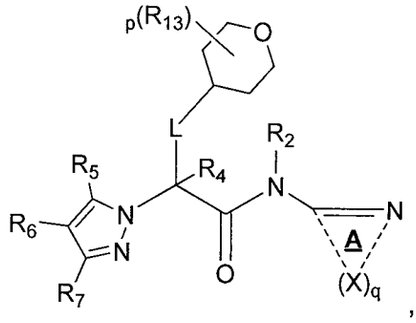
R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no

sustituido,

con la condición que (a) el anillo A no sea 5-(3-acetamidociclobutil)-1H-pirazol-3-ilo cuando R_5 y R_6, junto con el anillo al cual ellos están unidos, formen un indazol-1-ilo no sustituido; y (b) el anillo A no sea 5-(2-clorobencil)tiazol-2-ilo cuando R_3 sea fenilo y R_2, R_4, R_5, R_6 y R_7 sean todos hidrógeno.

4-El compuesto de la reivindicación 1 que comprende:



donde

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo

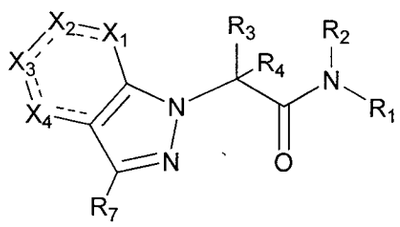
(C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $-L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble; y

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido.

5-El compuesto de la reivindicación 1 que comprende:



donde

X_1, X_2, X_3 y X_4 se seleccionan cada uno de ellos independientemente del grupo integrado por CR_9R_{10}, CO, CS, $C(NR_{11})$, NR_{12}, S y O;

R_9 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_9 y R_{10} se toman juntos para formar oxo, con la condición que R_{10} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble;

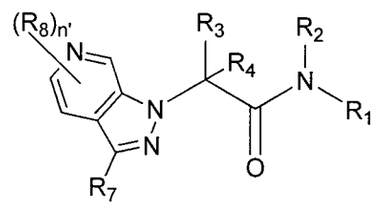
R_{11} se selecciona del grupo integrado por hidrógeno, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

R_{12} se selecciona del grupo integrado por hidrógeno, oxi, hidroxi, carboniloxi, alcoxi (C1-

10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{12} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_7, R_9, R_{10}, R_{11} y R_{12} se toman juntos para formar un anillo sustituido o no sustituido.

6- El compuesto de la reivindicación 1 que comprende:

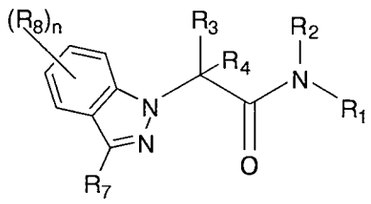


donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3; y

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido.

7- El compuesto de la reivindicación 1 que comprende:

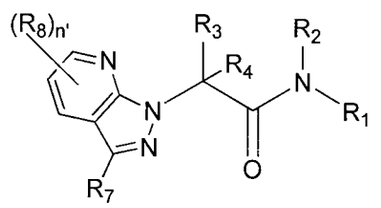


donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4; y

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido.

8-El compuesto de la reivindicación 1 que comprende:

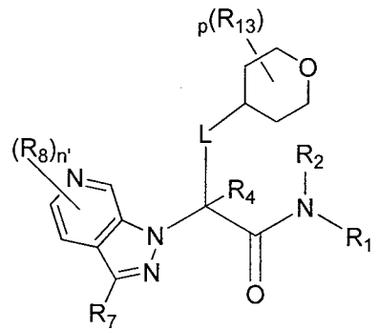


donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3; y

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido.

9-El compuesto de la reivindicación 1 que comprende:



donde

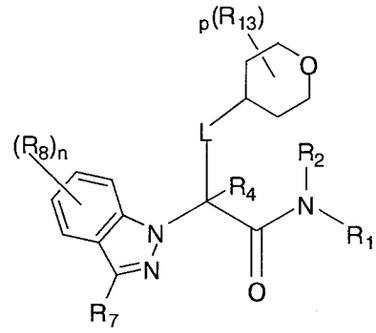
n' se selecciona del grupo integrado por 0, 1, 2 y 3;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido.

10-El compuesto de la reivindicación 1 que comprende:



donde

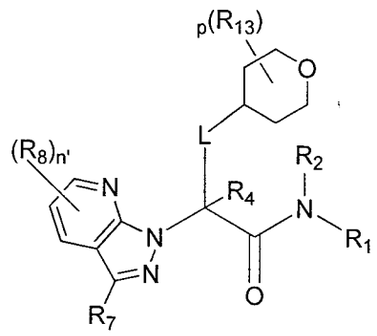
n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido.

11-El compuesto de la reivindicación 1 que comprende:



donde

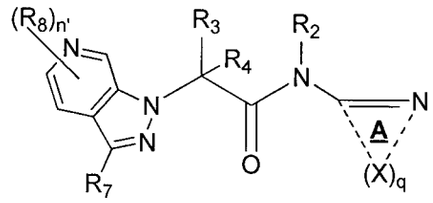
n' se selecciona del grupo integrado por 0, 1, 2 y 3;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido; y

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido.

12-El compuesto de la reivindicación 1 que comprende:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

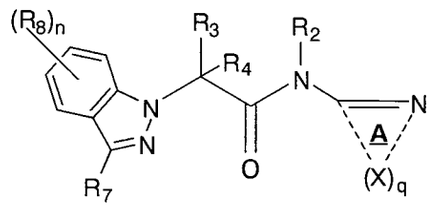
R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5),

bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble; y

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido.

13-El compuesto de la reivindicación 1 que comprende:



,

donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo

(C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

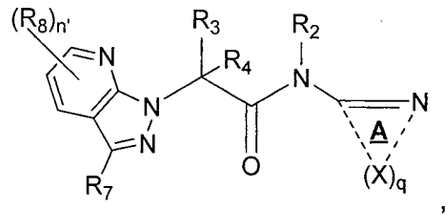
R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $-L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble; y

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido.

14-El compuesto de la reivindicación 1 que comprende:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

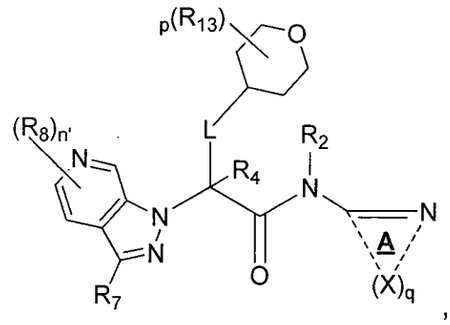
R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10),

iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble; y

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobiciciclоalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido.

15-El compuesto de la reivindicación 1 que comprende:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo,

cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

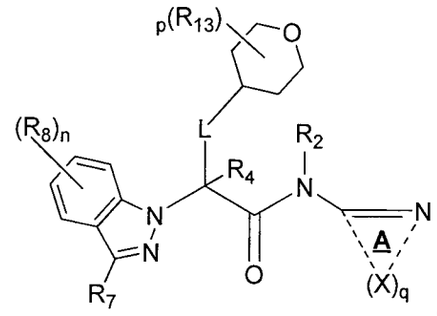
R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12),

arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble; y

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido.

16-El compuesto de la reivindicación 1 que comprende:



,

donde

n se selecciona del grupo integrado por 0, 1, 2, 3 y 4;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo

(C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $-L_1-R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $-L_1-R_{22}$;

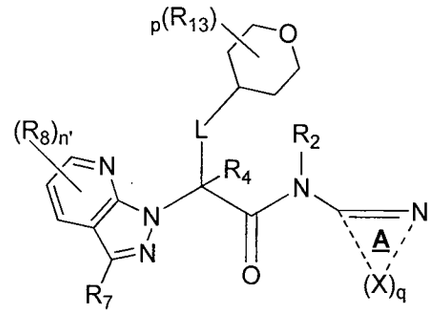
R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble; y

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi,

carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido.

17-El compuesto de la reivindicación 1 que comprende:



donde

n' se selecciona del grupo integrado por 0, 1, 2 y 3;

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

q se selecciona del grupo integrado por 3, 4 y 5;

cada X se selecciona independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

R_8 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, cicloalquilo (C3-12) sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_8 es $–L_1–R_{22}$, o R_8 y R_7 o dos R_8 se toman juntos para formar un anillo sustituido o no sustituido;

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble; y

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10),

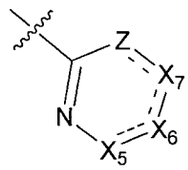
heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,
o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido.

18-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 5-11, donde R_1 es un heteroarilo sustituido o no sustituido.

19-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 5-11, donde R_1 se selecciona del grupo integrado por tiazolilo, pirazinilo, pirazolilo y piridilo, cada uno sustituido o no sustituido.

20-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 5-11, donde R_1 se selecciona del grupo integrado por tiazol-2-ilo; 2-piridilo; 5-metil-tiazol-2-ilo; 6-metil-pirid-2-ilo; 4-metil-pirid-2-ilo; 5-bromo-6-metil-pirid-2-ilo; 5-fenil-pirid-2-ilo; benzotiazol-2-ilo; un metil éster del ácido nicotínico; 5-bromo-pirid-2-ilo; 2-pirazinilo; 1-metil-pirazol-3-ilo y 5-fluoro-tiazol-2-ilo.

21-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 5-11, donde R_1 comprende:



donde
X_5, X_6 y X_7 se seleccionan cada uno de ellos independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;
Z se selecciona del grupo integrado por $CR_{14}R_{15}$, NR_{16}, O y S;
R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-

5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $-L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble; y

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido;

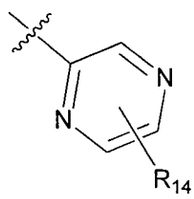
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo

(C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

22-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 5-11, donde R_1 comprende:

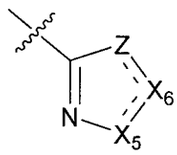


donde

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-

5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$.

23-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 5-11, donde R_1 comprende:



donde

X_5 y X_6 se seleccionan cada uno de ellos independientemente del grupo integrado por $CR_{14}R_{15}$, CO, CS, NR_{16}, O, S, SO y SO_2;

Z se selecciona del grupo integrado por $CR_{14}R_{15}$, NR_{16}, O y S;

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

R_{15} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{15} esté ausente cuando el átomo al cual está unido forma

parte de un enlace doble; y

R_{16} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, con la condición que R_{16} esté ausente cuando el átomo al cual está unido forma parte de un enlace doble,

o cualquiera dos R_{14}, R_{15} y R_{16} se toman juntos para formar un anillo sustituido o no sustituido;

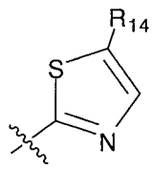
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10),

iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

24-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 5-11, donde R_1 comprende:



donde

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{14} es $–L_1-R_{22}$;

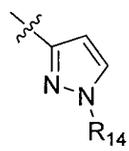
L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5),

heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

25-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 2 y 5-11, donde R_1 comprende:



donde

R_{14} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, carboxamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), oxaalquilo (C1-5), oxoalquilo (C1-5), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no

sustituido, o R_{14} es $-L_1-R_{22}$.

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

26-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-25, donde R_2 es hidrógeno.

27-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 3, 5-8, 12-14 y 18-

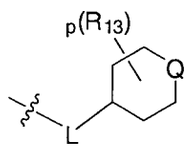
26 donde

R_3 es –L-R_{18};

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; y

R_{18} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

28-El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 3, 5-8, 12-14 y 18-26 donde R_3 comprende:



donde

p se selecciona del grupo integrado por 0, 1, 2, 3, 4, 5, 6, 7, 8 y 9;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y el anillo al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

Q se selecciona del grupo integrado por O, S, CS, CO, SO, SO_2, $CR_{19}R_{20}$ y NR_{21};

R_{13} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo

(C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o dos R_{13} se toman juntos para formar un anillo sustituido o no sustituido;

R_{19} y R_{20} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

R_{21} se selecciona del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

29-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-28, donde L se selecciona del grupo integrado por $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-C(O)-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2CH_2C(O)-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$, $-OCH_2CH_2-$, $-CH_2CH_2O-$, $-N(CH_3)-$, $-NHCH_2-$, $-CH_2NH-$, $-CH_2NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CH_2NH-$, $-NH-C(O)-$, $-NCH_3-C(O)-$, $-C(O)NH-$, $-C(O)NCH_3-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, $-C(O)CH_2NH-$, $-CH_2NHC(O)-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, $-S-$, $-SCH_2-$, $-CH_2S-$, $-SCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2CH_2S-$, $-C(O)S-$, $-C(O)SCH_2-$, $-CH_2C(O)S-$, $-C(O)CH_2S-$, y $-CH_2SC(O)-$, cada uno sustituido o no sustituido.

30-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-28, donde

L se selecciona del grupo integrado por $-(CR_{24}R_{25})_s-$;

s se selecciona del grupo integrado por 1, 2, 3, 4, 5 y 6; y

R_{24} y R_{25} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

31-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-28, donde L es –CH_2-.

32-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-31, donde R_4 es hidrógeno.

33-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 18-32, donde R_5 se selecciona del grupo integrado por hidrógeno, halo y un alquilo (C1-3) sustituido o no sustituido.

34-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 18-33, donde R_6 se selecciona del grupo integrado por hidrógeno, halo, un alquilo (C1-3) sustituido o no sustituido; un alquilo (C1-3)–sulfonilo sustituido o no sustituido y un cicloalquilo (C1-6)-sulfonilo sustituido o no sustituido.

35-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 18-33, donde

R_6 es –L_1-R_{22};

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado

por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

36-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-35, donde R_7 se selecciona del grupo integrado por hidrógeno, halo y un alquilo (C1-3) sustituido o no sustituido.

37-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-35, donde

R_7 es $-L_1$-R_{22};

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del

conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

38-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 18-37, donde R_5 y R_6, junto con los átomos al cual ellos están unidos, forman un arilo sustituido o no sustituido.

39-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-4 y 18-37, donde R_5 y R_6, junto con los átomos al cual ellos están unidos, forman un heteroarilo sustituido o no sustituido.

40-El compuesto de acuerdo con cualquiera de las reivindicaciones 6-39, donde R_8 se selecciona del grupo integrado por hidrógeno, halo, un alquilo (C1-3) sustituido o no sustituido, un sulfonilalquilo (C1-3)sustituido o no sustituido, un alquilo (C1-3)-sulfonilo sustituido o no sustituido y un cicloalquilo (c3-12)-sulfonilo sustituido o no sustituido.

41-El compuesto de acuerdo con cualquiera de las reivindicaciones 6-39, donde R_8 se selecciona del grupo integrado por sulfonilmetilo, metilsulfonilo, ciclopropilsulfonilo y ciclopentilsulfonilo, cada uno sustituido o no sustituido.

42-El compuesto de acuerdo con cualquiera de las reivindicaciones 6-39, donde

R_8 es $-L_1-R_{22}$;

L_1 está ausente o un conector que suministra 1, 2, 3, 4, 5 o 6 separaciones de átomo entre R_{22} y el anillo al cual L_1 está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre;

R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo

(C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

43-El compuesto de acuerdo con cualquiera de las reivindicaciones 6-39, donde R_8 es $-SO_2-R_{22}$; R_{22} se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{22} es $-NR_{27}R_{28}$; y R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

44-El compuesto de acuerdo con cualquiera de las reivindicaciones 6-8, 12-14 y 18-43, donde R_3 es un (tetrahidro-2H-piran-4-il)metilo sustituido o no sustituido y R_8 es un ciclopropilsulfonilo sustituido o no sustituido.

45-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-44, donde R_{22} se selecciona del grupo integrado por un alquilo (C1-5) sustituido o no sustituido; un

cicloalquilo (C3-6) sustituido o no sustituido; un arilo (C4-8) sustituido o no sustituido; y un heteroarilo (C1-6) sustituido o no sustituido.

46-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-44, donde R_{22} es ciclopropilo.

47-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-44, donde

R_{22} es $-NR_{27}R_{28}$; y

R_{27} y R_{28} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, hidroxi, alcoxi, ariloxi, heteroariloxi, carbonilo, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_{27} y R_{28} se toman juntos para formar un anillo sustituido o no sustituido.

48-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-47, donde

L_1 se selecciona del grupo integrado por $-(CR_{24}R_{25})_s-$, $-NR_{26}-$, -O-, -S-, -CO-, -CS-, -SO-, $-SO_2-$, y combinaciones de los mismos;

s se selecciona del grupo integrado por 1, 2, 3, 4, 5 y 6;

R_{24} y R_{25} se seleccionan cada uno de ellos independientemente del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-

12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido; y

R_{26} se selecciona del grupo integrado por hidrógeno, ciano, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido.

49-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-47, donde L_1 es $-SO_2-$.

50-El compuesto de acuerdo con cualquiera de las reivindicaciones 1-49, donde el compuesto está en la forma de una aceptable para uso farmacéutico.

51-Una composición farmacéutica que comprende en la forma de principio activo un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50, y uno o más excipientes aceptables para uso farmacéutico.

52-Un kit que comprende:

un compuesto de cualquiera de las reivindicaciones 1-50; e

instrucciones, las cuales comprenden una o más formas de información seleccionadas del grupo integrado por la indicación de un estado de enfermedad por el cual el compuesto debe administrarse, la información de almacenamiento para el compuesto, la información de dosificación e instrucciones respecto a la forma de administrar el compuesto.

53-Un artículo de fabricación que comprende:

un compuesto de cualquiera de las reivindicaciones 1-50; y
materiales de empaque.

54-Un método para activar glucoquinasa que comprende poner en contacto glucoquinasa con un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50.

55-Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 para uso como medicamento.

56-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para activar la glucoquinasa.

57-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para tratar un estado de enfermedad por el cual la glucoquinasa provee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad.

58-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para tratar la hiperglucemia.

59-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para tratar la diabetes.

60-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para tratar la dislipidemia.

61-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para tratar la obesidad.

62-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para tratar la resistencia a la insulina.

63-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para tratar el síndrome metabólico X.

64-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la

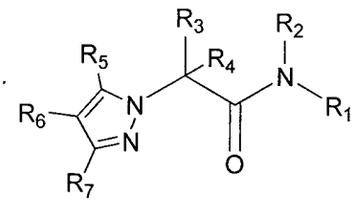
producción de un medicamento para tratar la intolerancia a la glucosa.

65-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para tratar el síndrome del ovario poliquístico.

66-Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-50 en la producción de un medicamento para tratar la enfermedad cardiovascular.

Resumen

Se proveen compuestos para uso con glucoquinasa que comprenden la fórmula:



donde las variables son como se definen en la presente. Además se proveen composiciones farmacéuticas, kits y artículos de fabricación que comprenden estos compuestos; métodos e intermediarios útiles para producir los compuestos; y métodos para utilizar dichos compuestos.

FIGURA 1

[SEC ID NO: 1]

MKLMALTLVEQILAEFQLQEEDLKKVMRRMQKEMDRGLRLETHEEASVKMLPTYVRSTPE
GSEVGDFLSLDLGGTNFRVMLVKVGEGEEGQWSVKTKHQMYSIPEDAMTGTAEMLFDYIS
ECISDFLDKHQMKHKKLPLGFTFSFPVRHEDIDKGILLNWTKGFKASGAEGNNVVGLLRD
AIKRRGDFEMDVVAMVNDTVATMISCYYEDHQCEVGMIVGTGCNACYMEEMQNVELVEGD
EGRMCVNTEWGAFGDSGELDEFLLEYDRLVDESSANPGQQLYEKLIGGKYMGELVRLVLL
RLVDENLLFHGEASEQLRTRGAFETRFVSQVESDTGDRKQIYNILSTLGLRPSTTDCDIV
RRACESVSTRAAHMCSAGLAGVINRMRESRSEDVMRITVGVDGSVYKLHPSFKERFHASV
RRLTPSCEITFIESEEGSGRGAALVSAVACKKACMLGQ

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DIVISION DE NUEVAS CREACIONES
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(71)Solicitante(s) **TAKEDA SAN DIEGO, INC.**

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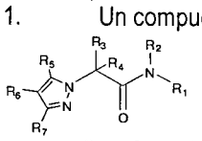
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Reivindicación(es):

1. Un compuesto que tiene la fórmula:



o un polimorfo, solvato, éster, tautómero, enantiómero, sal o prodroga del mismo aceptable para uso farmacéutico, donde

R_1 se selecciona del grupo integrado por heterocicloalquilo (C3-12), heterobicicicloalquilo (C3-12), heteroarilo, y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_2 se selecciona del grupo integrado por hidrógeno y un sustituyente que puede convertirse a hidrógeno *in vivo*;

R_3 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 es –L-R_{18};

R_4 se selecciona del grupo integrado por hidrógeno, carbonilo, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), carbonilalquilo (C1-3), tiocarbonilalquilo (C1-3), sulfonilalquilo (C1-3), sulfinilalquilo (C1-3), aminoalquilo (C1-10), iminoalquilo (C1-3), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-5), arilalquilo (C1-10), heteroarilalquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo, heteroarilo, bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_3 y R_4 se toman juntos para formar un anillo sustituido o no sustituido;

R_5 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_6 es –L_1-R_{22};

R_7 se selecciona del grupo integrado por hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C1-10), ariloxi (C4-12), heteroariloxi (C1-10), carbonilo, oxicarbonilo, amido, amino, alquilamino (C1-10), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C1-10), haloalquilo (C1-10), hidroxialquilo (C1-10), carbonilalquilo (C1-10), tiocarbonilalquilo (C1-10), sulfonilalquilo (C1-10), sulfinilalquilo (C1-10), azaalquilo (C1-10), oxaalquilo (C1-10), oxoalquilo (C1-10), iminoalquilo (C1-10), cicloalquilo (C3-12)–alquilo (C1-5), heterocicloalquilo (C3-12)–alquilo (C1-10), arilalquilo (C1-10), heteroarilo (C1-10)–alquilo (C1-5), bicicloarilo (C9-12)–alquilo (C1-5), heterobicicloarilo (C8-12)–alquilo (C1-5), heteroalquilo (C1-10), cicloalquilo (C3-12), heterocicloalquilo (C3-12), bicicloalquilo (C9-12), heterobicicicloalquilo (C3-12), arilo (C4-12), heteroarilo (C1-10), bicicloarilo (C9-12) y heterobicicloarilo (C4-12), cada uno sustituido o no sustituido, o R_7 es –L_1-R_{22};

o cualquiera dos R_5, R_6 y R_7 se toman juntos para formar un anillo sustituido o no sustituido;

L es un conector que suministra 0, 1, 2, 3, 4, 5 o 6 separaciones de átomo entre el C y R_{18} al cual L está unido, donde los átomos del conector que suministran la separación se seleccionan del grupo integrado por carbono, oxígeno, nitrógeno, y azufre; ...

00792

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 103,411
FECHA : DICIEMBRE 6 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-154094- -00000-0000

Fecha: 2010-12-07 14:25:56 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 793

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA P&O	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	387632475	06/12/2010	11,550,000.00

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

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

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

00793

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 103,424
FECHA : DICIEMBRE 6 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-154094- -00000-0000
Fecha: 2010-12-07 14:25:56 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 793

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	387632475	06/12/2010	11,550,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
56	50005-01-01 SOLICITUDES	*** REIVINDICACION UNITARIA ADICIONAL	1,456,000.00
		TOTAL : $	1,456,000.00

SON: UN MILLON CUATROCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
MARGARITA CASTELLANOS ABONDANO
Apoderado(a) y/o Representante de
TAKEDA SAN DIEGO INC

REFERENCIA		
	Radicación No.	10 154094
	Solicitud internacional	PCT/US2009/044190
	Fecha inicio fase nacional	16/12/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	00405

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene 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.

2. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

3. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Continua en la página siguiente...

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.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha 07 ENE. 2011.
adpa11