SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-030354- -00000-0000
Fecha: 2011-03-11 15:33:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 568

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

PROPIEDAD INDUSTRIAL

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. 11-030354

54. TITULO: **INHIBIDORES DE CMET**

52. CLASIFICACION INTERNACIONAL: **C07D 471/04, C07D 487/04, C07D 519/00, A61K 31/437, A61P 35/00**

71. SOLICITANTE: **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

DOMICILIO: **1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045, JAPON**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., _____

14-03-2011

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

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FORMULARIO UNICO DE SOLICITUD DE PATENTES
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

①

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

[X] **Capítulo I** [ ] **Capítulo II**

② **SOLICITANTE (71)**	Nombre: **TAKEDA PHARMACEUTICAL COMPANY LIMITED** Dirección: **1-1, Doshomachi 4-chome Chuo-ku, Osaka-shi Osaka 541-0045 JAPON** Nacionalidad o Domicilio: **Osaka - JAPON** Lugar de Constitución: **JAPON** Teléfono: Fax: E-mail:	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual Nùmero
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④ **INVENTOR (ES) (72)**	**VER ANEXO # 1**	

⑤ **PCT (86)**

Solicitud Internacional No. **PCT/US2009/053913** Fecha **14/08/2009**

Publicación Internacional No. **WO 2010/019899 A1** Fecha **18/02/2010**

⑥ **Título (54)** **INHIBIDORES DE CMET**

⑦ **Clasificación Internacional (51)** **C07D 471/04, C07D 487/04, C07D 519/00, A61K 31/437, A61P 35/00**

⑧ **Prioridad** SI [X] NO [ ]

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US	14/08/2008	61/088,959
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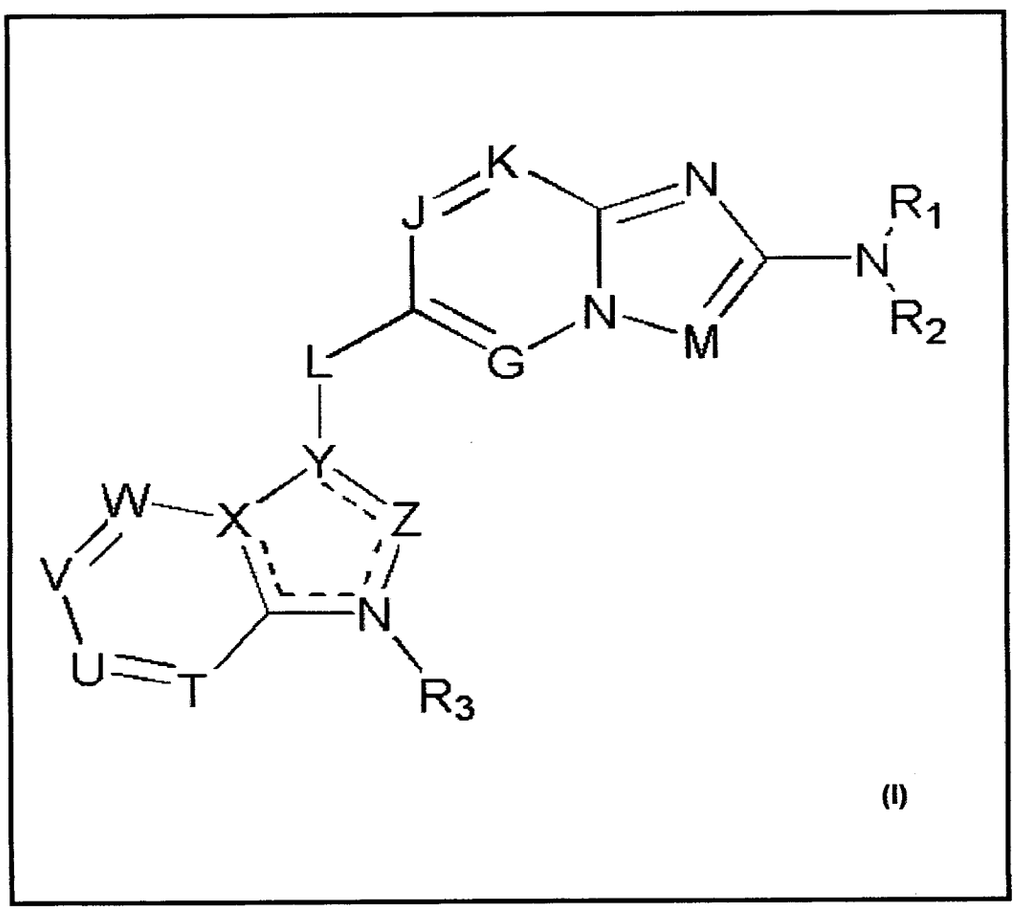
⑨ **Comprobante de pago No.** **11-0013356 y 11-0013357** **Fecha** **Febrero 14 de 2011**

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.
- [X] 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:



(I)

(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.

11 MAR. 2011

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - P2135

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Calle 94 A No. 7 A-09
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P2135

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
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RECIBO DE CAJA

No. 11 - 0013356

Bogotá D.C., Febrero 14 de 2011 - 14:04:42

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	387648796	14/02/2011	6.178.800.00
CONSIGNACION	BANCO DE BOGOTA	062754387	387648800	14/02/2011	3.209.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____
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Recibo de Caja Aplicado al Expediente No. _____

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NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

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RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641 RE

*** Soporte del Pago ***

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*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	998 VALOR COMPLEMENTO TARIFA A#O ANTRIOR	1.215.000.00	1.215.000.00
				$1.215.000.00

SON: **UN MILL&OACUTE;N DOSCIENTOSQUINCE MIL PESOS MONEDA CORRIENTE*

Responsable: _____
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Recibo de Caja Aplicado al Expediente No. _____

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61/161,007 17 March 2009 (17.03.2009) US

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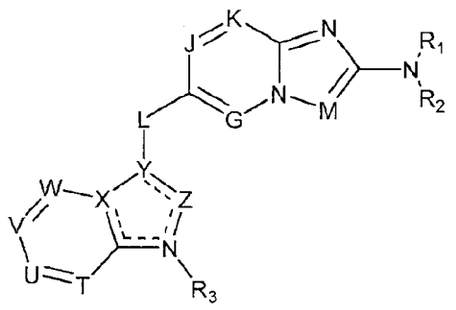
(74) Agents: **BRUSTEIN, Mitchell, R.** et al.; c/o Takeda San Diego, Inc., 10410 Science Center Drive, San Diego, CA 92121 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM,

[Continued on next page]

(54) Title: cMET INHIBITORS



(I)

(57) Abstract: Compounds of the following formula are provided for use with cMET: 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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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

cMET INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention relates to compounds that may be used to inhibit cMET, as well as compositions of matter, kits and articles of manufacture comprising these compounds. The invention also relates to methods for inhibiting cMET 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.

BACKGROUND OF THE INVENTION

[0002] cMET kinase is a receptor tyrosine kinase. HGF (hepatocyte growth factor, also known as scatter factor), the ligand for cMET, is secreted by cells of mesodermal origin whereas cMET is predominantly expressed on cells of epithelial/endothelial origin resulting in paracrine epithelial-mesenchymal cell signaling (Stoker, M. et al., Nature 327: 239-242 (1987)). Binding of HGF to the extracellular region of cMET activates the intracellular cMET tyrosine kinase activity. cMET is believed to be involved in protein phosphorylation events that regulate cell proliferation, apoptosis, motility, and dissociation of cell-cell interactions, morphogenesis, angiogenesis, and epithelial-mesenchymal transition. Misregulation of cMET can lead to unregulated cell proliferation and survival. cMET is thought to be a key regulator of invasive growth, cancer tumorgenesis, and progression to metastasis (Trusolino, T. and Comoglio, P. Nature Reviews Cancer: 2: 289-300 (2002)). cMET gene amplification, alteration, mutation, and protein over expression or activation of cMET through autocrine or paracrine mechanisms have been detected in a wide variety of carcinomas. For example, in human gastric cancer tissue, cMET has been found to be over expressed and amplified (Smolen, G.A., et al. PNAS 103: 2316-2321, (2006)). In human glioblastomas and carcinomas of lung, thyroid and breast, cMET has been found to be activated as a result of increased HGF levels and autocrine signaling (Birchmeier, C. et al. Rev. Mol. Cell Biol. 4: 915–925, (2003)). In human lung cancer tissue, cMET signaling has been found to be upregulated as a mechanism of drug resistance (Engelman, J.A., et al. Science 316: 1049-1043, (2007)). Activating mutations in cMET, although not as common, have been reported in sporadic and hereditary papillary renal carcinomas, head and neck squamous carcinomas as well as gastric and lung cancers. Furthermore, increased

expression, the most common cMET alteration found in a wide variety of human tumors (including but not limited to renal, ovarian, hepatocellular, non-small cell lung, bone, liver metastasis of colon, oral squamous cell, esophageal, gastric, pancreatic, and prostatic cancers) correlates with poor prognosis (Benvenuti, S. and Comoglio, P.M., J. Cell. Physiol. 213: 316-325, (2007)).

[0003] There is a continued need to find new therapeutic agents to treat human diseases. Inhibition of cMET is an especially attractive target for the discovery of new therapeutics due to their important role in cancer and other diseases.

SUMMARY OF THE INVENTION

[0004] The present invention relates to compounds that have activity for inhibiting cMET. 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.

[0005] In one embodiment, a pharmaceutical composition is provided that comprises a cMET inhibitor according to the present invention as an active ingredient. Pharmaceutical compositions according to the invention may optionally comprise 0.001%-100% of one or more inhibitors of this invention. Pharmaceutical compositions according to the invention may optionally comprise one or more compounds selected from the group consisting of excipients, diluents, lubricants, binders, adjuvants, carriers, wetting agents, emulsifying agents, solubilizing agents, and pH buffering agents. The 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.

[0006] The invention is also directed to kits and other articles of manufacture for treating disease states associated with cMET.

[0007] In one embodiment, a kit is provided that comprises a composition comprising at least one cMET inhibitor of the present invention in combination with instructions. The instructions may indicate the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the

composition. The kit may also comprise packaging materials. The packaging material may comprise a container for housing the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0008] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one cMET inhibitor of the present invention in combination with packaging materials. The packaging material may comprise a container for housing the composition. The container may optionally comprise a label indicating the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0009] 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.

[0010] Also provided are methods for using compounds, compositions, kits and articles of manufacture according to the present invention.

[0011] In one embodiment, the compounds, compositions, kits and articles of manufacture are used to inhibit cMET.

[0012] In another embodiment, the compounds, compositions, kits and articles of manufacture are used to treat a disease state for which cMET possess activity that contributes to the pathology and/or symptomology of the disease state.

[0013] In another embodiment, a compound according to the present invention is administered to a subject wherein cMET activity within the subject is altered, preferably reduced.

[0014] In another embodiment, a prodrug of a compound according to the present invention is administered to a subject that is converted to the compound *in vivo* where it inhibits cMET.

[0015] In another embodiment, a method of inhibiting cMET is provided that comprises contacting a cMET with a compound according to the present invention.

[0016] In another embodiment, a method of inhibiting cMET is provided that comprises causing a compound according to the present invention to be present in a subject in order to inhibit cMET *in vivo*.

[0017] In another embodiment, a method of inhibiting a cMET is provided that comprises administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits cMET *in vivo*. It is noted that the compounds of the present invention may be the first or second compounds.

[0018] In another embodiment, a therapeutic method is provided that comprises administering a compound according to the present invention.

[0019] In another embodiment, a method is provided for treating a condition in a patient that is known to be mediated by cMET, or which is known to be treated by cMET inhibitors, the method comprising administering to the patient a therapeutically effective amount of a compound according to the present invention.

[0020] In another embodiment, a method is provided for treating a disease state for which cMET possess activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: causing a compound according to the present invention to be present in a subject in a therapeutically effective amount for the disease state.

[0021] In another embodiment, a method is provided for treating a disease state for which cMET possess activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: administering a first compound to a subject that is converted *in vivo* to a second compound such that the second compound is present in the subject in a therapeutically effective amount for the disease state. It is noted that the compounds of the present invention may be the first or second compounds.

[0022] In another embodiment, a method is provided for treating a disease state for which cMET possess activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: administering a compound according to the present invention to a subject such that the compound is present in the subject in a therapeutically effective amount for the disease state.

[0023] 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 cMET, or that is known to be treated by cMET inhibitors.

[0024] It is noted in regard to all of the above embodiments that the present invention is intended to encompass all pharmaceutically acceptable ionized forms (*e.g.*, salts) and solvates (*e.g.*, hydrates) of the compounds, regardless of whether such ionized forms and solvates are specified since it is well known in the art to administer pharmaceutical agents in an ionized or

solvated form. It is also noted that unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all possible stereoisomers (*e.g.*, enantiomers or diastereomers depending on the number of chiral centers), independent of whether the compound is present as an individual isomer or a mixture of isomers. Further, unless otherwise specified, recitation of a compound is intended to encompass all possible resonance forms and tautomers. With regard to the claims, the language "compound comprising the formula," "compound having the formula" and "compound of 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.

[0025] It is further noted that prodrugs may also be administered which are altered *in vivo* and become a compound according to the present invention. The various methods of using the compounds of the present invention are intended, regardless of whether prodrug delivery is specified, to encompass the administration of a prodrug that is converted *in vivo* to a compound according to the present invention. It is also noted that certain compounds of the present invention may be altered *in vivo* prior to inhibiting cMET and thus may themselves be prodrugs for another compound. Such prodrugs of another compound may or may not themselves independently have cMET inhibitory activity.

DEFINITIONS

[0026] Unless otherwise stated, the following terms used in the specification and claims shall have the following meanings for the purposes of this Application.

[0027] 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.

[0028] "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.

[0029] "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.

[0030] "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.

[0031] "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.

[0032] "Alkoxy" means an oxygen moiety having a further alkyl substituent. The alkoxy groups of the present invention can be optionally substituted.

[0033] "Alkyl" represented by itself means a straight or branched, saturated or unsaturated, 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.

[0034] "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.

[0035] "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.

[0036] "Alkynyl" means a straight or branched, carbon chain that contains at least one carbon-carbon triple bond ($-C\equiv C-$ or $-C\equiv CR$, 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.

[0037] "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, "alkynylene," either alone or represented along with another radical, can be a (C_2) alkynylene, a (C_3) alkynylene or a (C_4) alkynylene.

[0038] "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.

[0039] "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.

[0040] "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).

[0041] "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").

[0042] "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.

[0043] "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.

[0044] "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.

[0045] "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.

[0046] "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.

[0047] "Carbamoyl" means the radical -OC(O)NRR', wherein R and R' are each independently hydrogen or further substituents.

[0048] "Carbocycle" means a ring consisting of carbon atoms.

[0049] "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.

[0050] "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.

[0051] As used herein, "cMet" is synonymous with "c-Met", "MET", "Met", "heptaocyte growth factor receptor" and other designations known to those skilled in the art.

[0052] "Cyano" means the radical -CN.

[0053] "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.

[0054] "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.

[0055] "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.

[0056] "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.

[0057] "Halo" means fluoro, chloro, bromo or iodo.

[0058] "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.

[0059] "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.

[0060] "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.

[0061] "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.

[0062] "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.

[0063] "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.

[0064] "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.

[0065] "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.

[0066] "Hydroxy" means the radical -OH.

[0067] "IC_{50}" means the molar concentration of an inhibitor that produces 50% inhibition of the target enzyme.

[0068] "Imino" means the radical –CR(=NR') and/or –C(=NR')-, wherein R and R' are each independently hydrogen or a further substituent.

[0069] "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).

[0070] "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.

[0071] "Nitro" means the radical -NO_2.

[0072] "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.

[0073] "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.

[0074] "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.

[0075] "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.

[0100] The term "pharmaceutically acceptable excipient" refers to those typically used in preparing pharmaceutical compositions and should be pharmaceutically pure and non-toxic in the amounts used. They generally are a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient or an aid to the storage, administration, or manufacture of the composition. Some examples of pharmaceutically acceptable excipients are found in Remington's Pharmaceutical Sciences and the Handbook of Pharmaceutical Excipients and include diluents, vehicles, carriers, ointment bases, binders, disintegrates, lubricants, glidants, sweetening agents, flavoring agents, gel bases, sustained release matrices, stabilizing agents, preservatives, solvents, suspending agents, buffers, emulsifiers, dyes, propellants, coating agents, and others.

[0076] "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.

[0077] 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.

[0078] "Polycyclic ring" includes bicyclic and multi-cyclic rings. The individual rings comprising the polycyclic ring can be fused, spiro or bridging rings.

[0079] "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.

[0080] "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.

[0081] "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.

[0082] "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).

[0083] "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).

[0084] "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, aminocarbonyl, 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, aminocarbonyl, 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.

[0085] "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.

[0086] "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.

[0087] "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.

[0088] "Thio" denotes replacement of an oxygen by a sulfur and includes, but is not limited to, -SR, -S- and =S containing groups.

[0089] "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.

[0090] "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.

[0091] "Treatment" or "treating" means any administration of a compound of the present invention and includes:

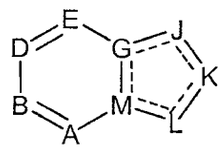
(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(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

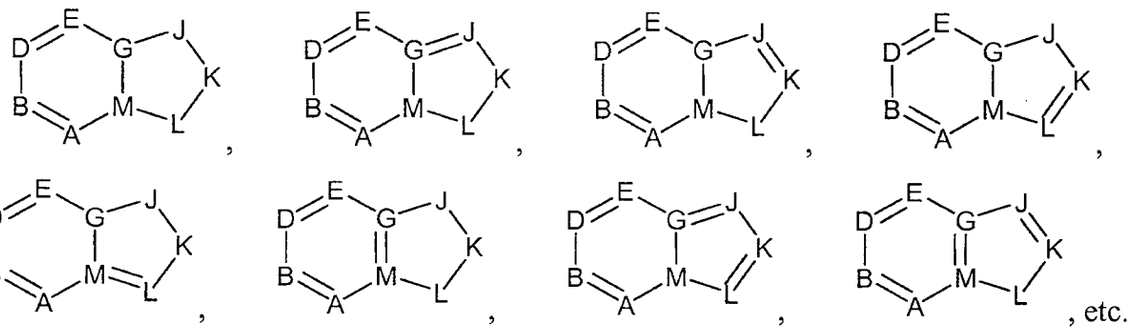
(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (*i.e.*, reversing the pathology and/or symptomatology).

[0092] 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 the substituents on the carbon atom are. 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.

[0093] 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.

[0094] 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

[0095] The present invention relates to compounds that may be used to inhibit cMET. 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 members of the same protein family and thus may be used to address disease states associated with these other family members.

[0096] cMET belongs to the phosphoryl transferase family of enzymes that transfer phosphorous-containing groups from one substrate to another. By the conventions set forth by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB) enzymes of this type have Enzyme Commission (EC) numbers starting with 2.7.-.- (*See*, Bairoch A., The ENZYME database in Nucleic Acids Res. 28:204-305 (2000)). Kinases are a class of enzymes that function in the catalysis of phosphoryl transfer. The protein kinases constitute one of the largest subfamilies of structurally related phosphoryl transferases and are responsible for the control of a wide variety of cellular signal transduction processes. (*See*, Hardie, G. and Hanks, S. (1995) The Protein Kinase Facts Book, I and II, Academic Press, San Diego, CA).

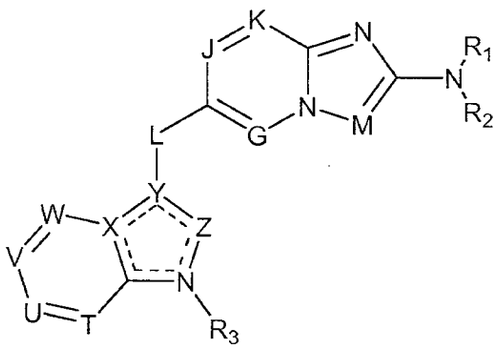
[0101] Disregulation of cMET is implicated in such diseases as cancers (including carcinomas (*e.g.*, bladder, breast, cervical, cholangiocarcinoma, colorectal, esophageal, gastric, head and neck, kidney, liver, lung, nasopharygeal, ovarian, pancreatic, prostate and thyroid); musculoskeletal sarcomas (*e.g.*, osteosarcoma, synovial sarcoma, and rhabdomyosarcoma); soft tissue sarcomas (*e.g.*, MFH/fibrosrcoma, leiomyosarcoma, and Kaposi's sarcoma); hematopoietic malignancies (*e.g.*, multiple myeloma, lymphomas, adult T cell leukemia, acute myelogenous leukemia, and chronic myeloid leukemia); and other neoplasms (*e.g.*, glioblastomas, astrocytomas, melanoma, mesothelioma, and Wilm's tumor)); and proliferative diseases (*e.g.*, myeloproliferative disorders, atherosclerosis, and fibrosis of the lung).

[0102] It is noted that the compounds of the present invention may also possess inhibitory activity for other receptor tyrosine kinase family members and thus may be used to address

disease states associated with these other family members. In particular, the compounds of the present invention may be used to modulate the activity of other proteins in the Met subfamily (*e.g.*, Ron and Sea).

cMET Inhibitors

[0103] In one of its aspects, the present invention relates to compounds that are useful as cMET inhibitors. In one embodiment, cMET inhibitors of the present invention comprise:



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

G is selected from the group consisting of CR_4 and N;

J is selected from the group consisting of CR_5 and N;

K is selected from the group consisting of CR_6 and N;

M is selected from the group consisting of CR_7 and N;

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

T is selected from the group consisting of CR_8 and N;

U is selected from the group consisting of CR_9 and N;

V is selected from the group consisting of CR_{10} and N;

W is selected from the group consisting of CR_{11} and N;

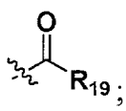
X is selected from the group consisting of CR_{12} and N;

Y is selected from the group consisting of CR_{13} and N;

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

R_1 is selected from the group consisting of hydrogen, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl,

(C_{1-10})alkylcarbonyl, (C_{3-12})cycloalkyl(C_{1-5})carbonyl, hetero(C_{3-12})cycloalkyl(C_{1-10})carbonyl, aryl(C_{1-10})carbonyl, hetero(C_{1-10})aryl(C_{1-5})carbonyl, (C_{9-12})bicycloaryl(C_{1-5})carbonyl, hetero(C_{8-12})bicycloaryl(C_{1-5})carbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 has the formula



R_2 is hydrogen or a substituent convertible *in vivo* to hydrogen;

R_3 is selected from the group consisting of hydrogen, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is absent when the nitrogen to which it is bound forms part of a double bond;

R_4 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

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

R_8 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

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, aminocarbonyl, amino, (C_{1-10})alkylamino,

sulfonamido, amido, 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, amino(C_{1-10})alkyl, amido(C_{1-10})alkylamino(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, carbonyl(C_{4-12})aryl, hetero(C_{4-10})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, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, amido, 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, amino(C_{1-10})alkyl, amido(C_{1-10})alkylamino(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, carbonyl(C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})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, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} is absent when the carbon to which it is bound forms part of a double bond;

R_{13} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{13} is absent when the carbon to which it is bound forms part of a double bond;

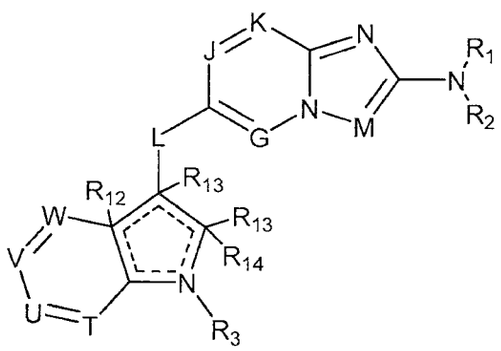
R_{14} and R_{15} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{15} is absent when the carbon to which it is bound forms part of a double bond;

R_{16} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{16} is absent when the nitrogen to which it is bound forms part of a double bond; and

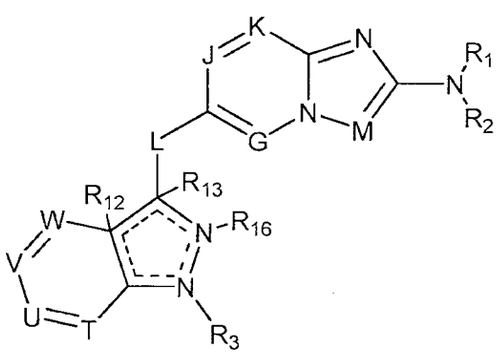
R_{19} selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

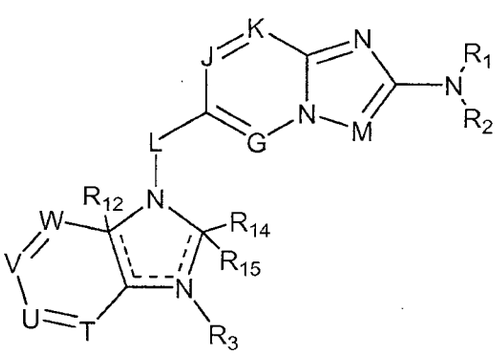
[0104] In another embodiment, cMET inhibitors of the present invention comprise:



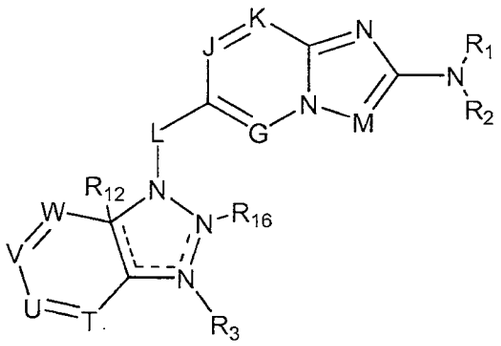
[0105] In another embodiment, cMET inhibitors of the present invention comprise:



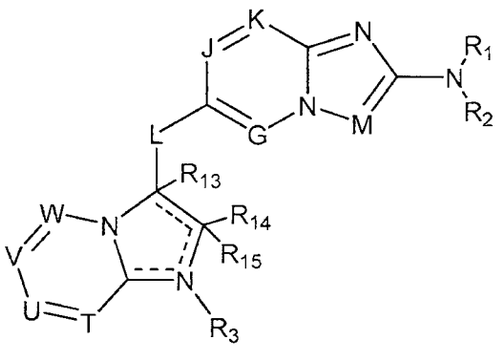
[0106] In another embodiment, cMET inhibitors of the present invention comprise:



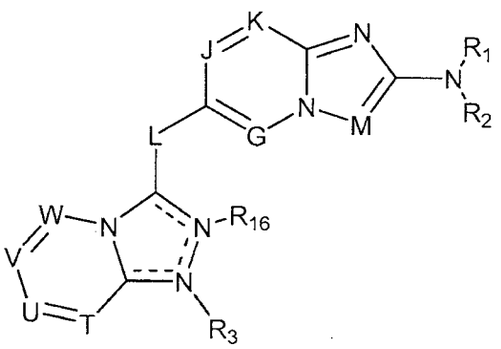
[0107] In another embodiment, cMET inhibitors of the present invention comprise:



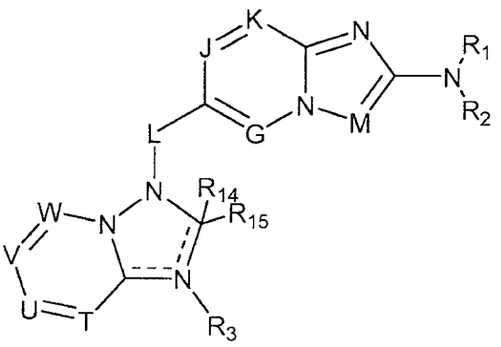
[0108] In another embodiment, cMET inhibitors of the present invention comprise:



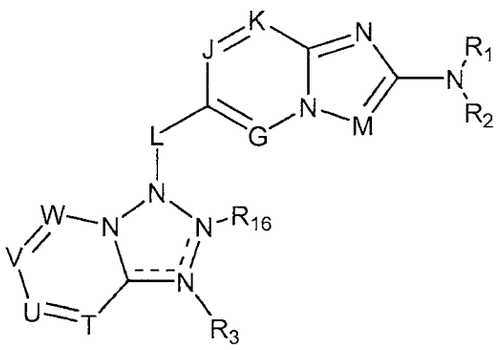
[0109] In another embodiment, cMET inhibitors of the present invention comprise:



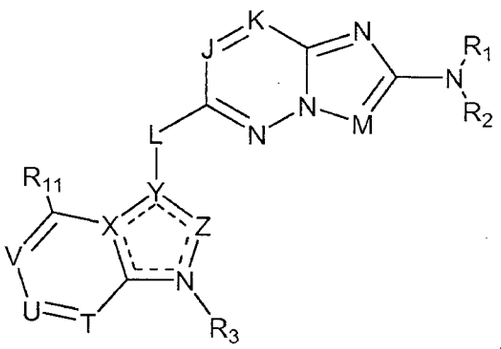
[0110] In another embodiment, cMET inhibitors of the present invention comprise:



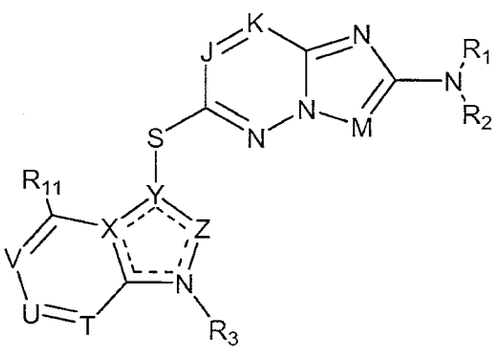
[0111] In another embodiment, cMET inhibitors of the present invention comprise:



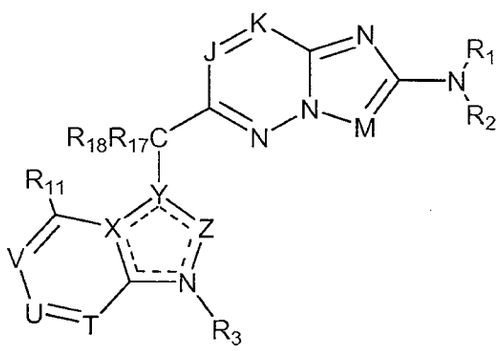
[0112] In a further embodiment, cMET inhibitors of the present invention comprise:



[0113] In still a further embodiment, cMET inhibitors of the present invention comprise:

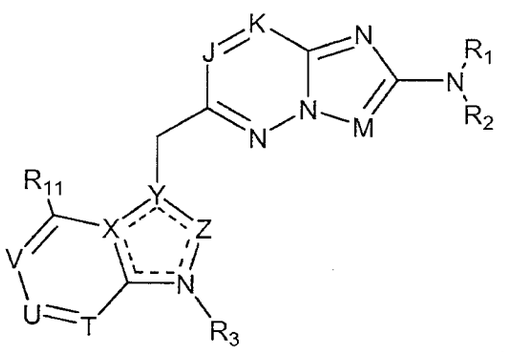


[0114] In yet a further embodiment, cMET inhibitors of the present invention comprise:

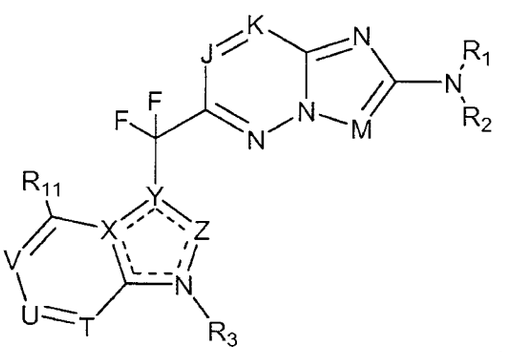


wherein R_{17} and R_{18} are each independently elected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

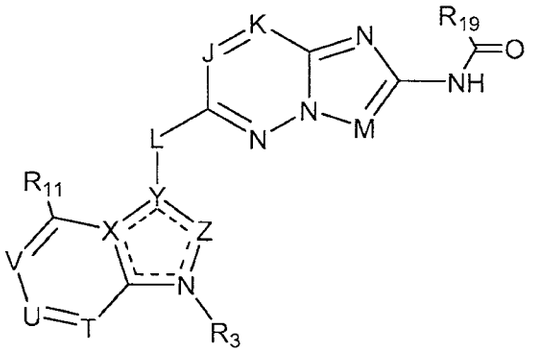
[0115] In another embodiment, cMET inhibitors of the present invention comprise:



[0116] In still another embodiment, cMET inhibitors of the present invention comprise:

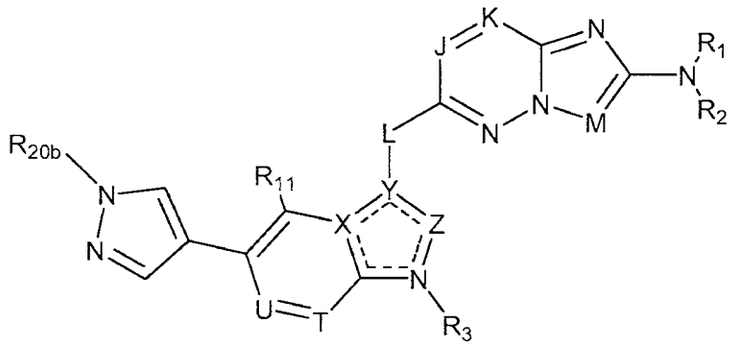


[0117] In yet another embodiment, cMET inhibitors of the present invention comprise:



wherein R_{19} selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

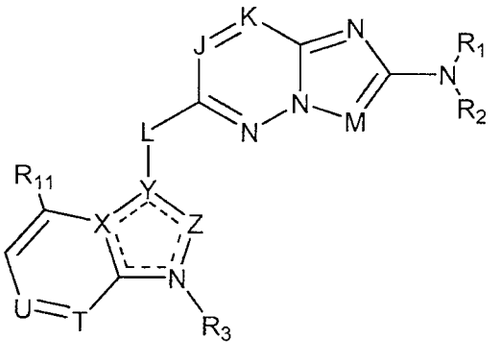
[0118] In a further embodiment, cMET inhibitors of the present invention comprise:



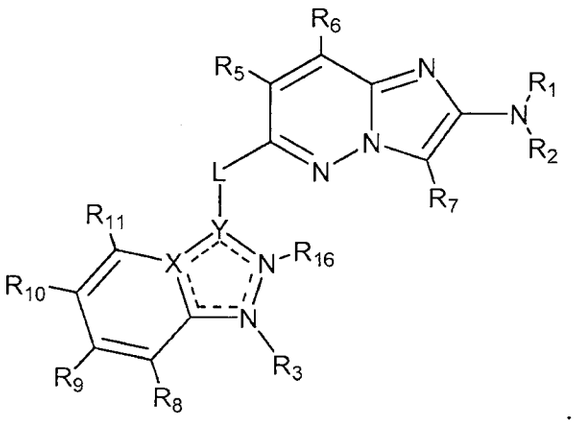
wherein R_{20b} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

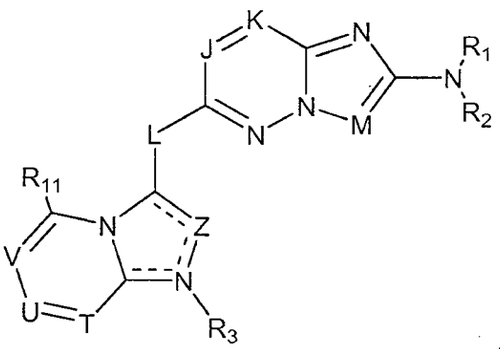
[0119] In still a further embodiment, cMET inhibitors of the present invention comprise:



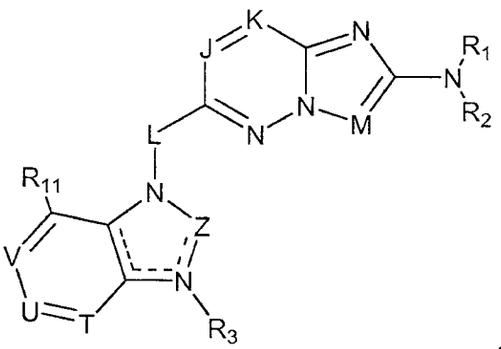
[0120] In yet a further embodiment, cMET inhibitors of the present invention comprise:



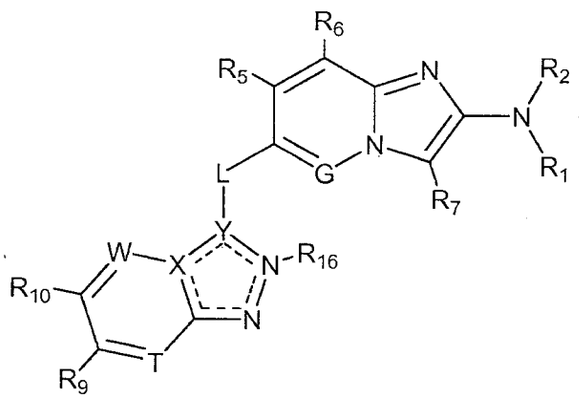
[0121] In another embodiment, cMET inhibitors of the present invention comprise:



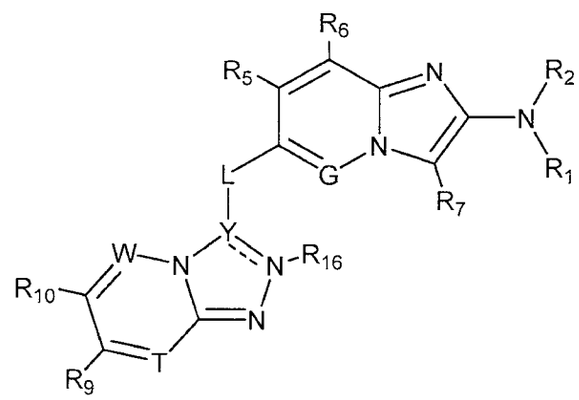
[0122] In still another embodiment, cMET inhibitors of the present invention comprise:



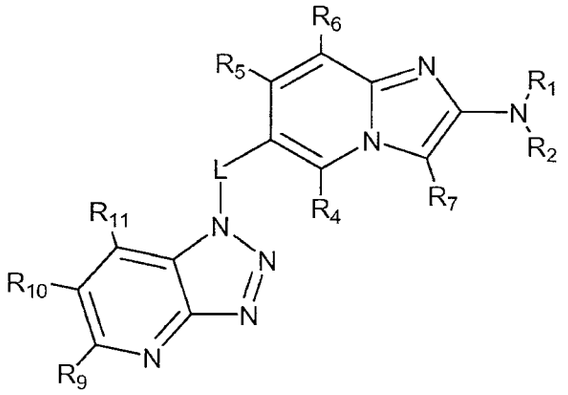
[0123] In a further embodiment, cMET inhibitors of the present invention comprise:



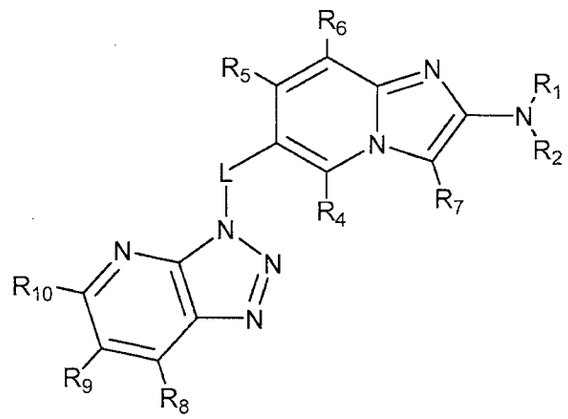
[0124] In another embodiment, cMET inhibitors of the present invention comprise:



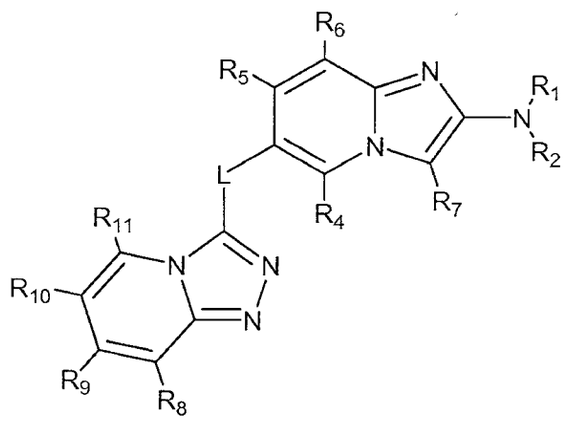
[0125] In still another embodiment, cMET inhibitors of the present invention comprise:



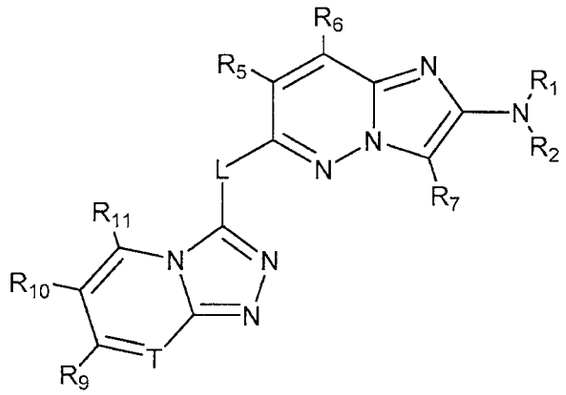
[0126] In yet another embodiment, cMET inhibitors of the present invention comprise:



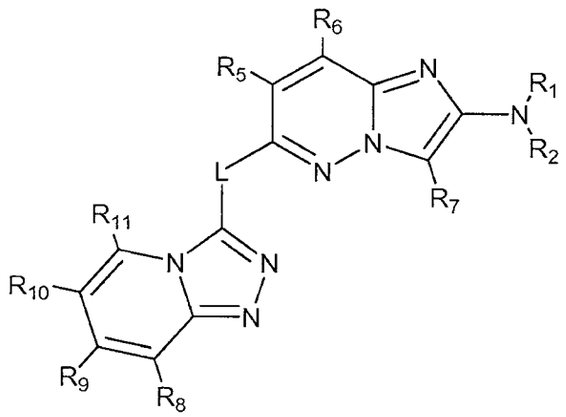
[0127] In a further embodiment, cMET inhibitors of the present invention comprise:



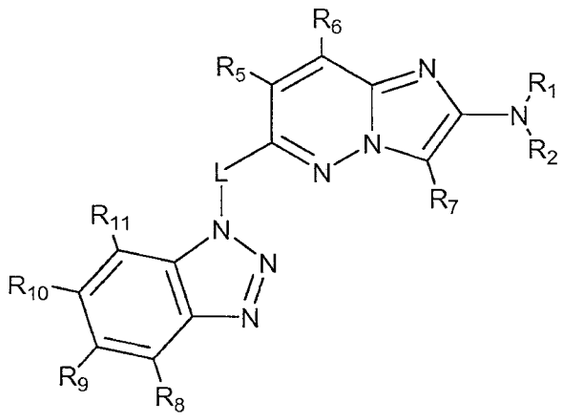
[0128] In still a further embodiment, cMET inhibitors of the present invention comprise:



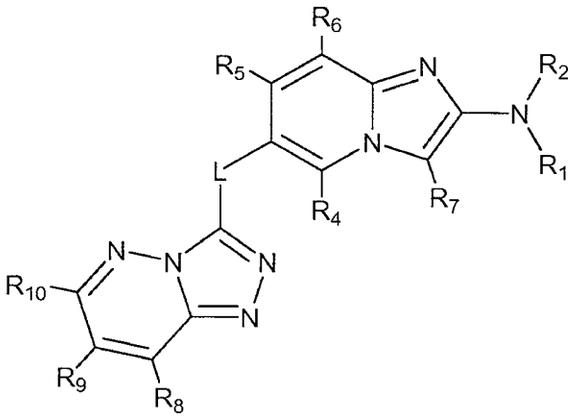
[0129] In yet a further embodiment, cMET inhibitors of the present invention comprise:



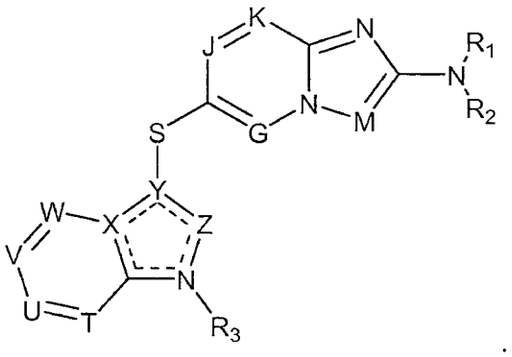
[0130] In still another embodiment, cMET inhibitors of the present invention comprise:



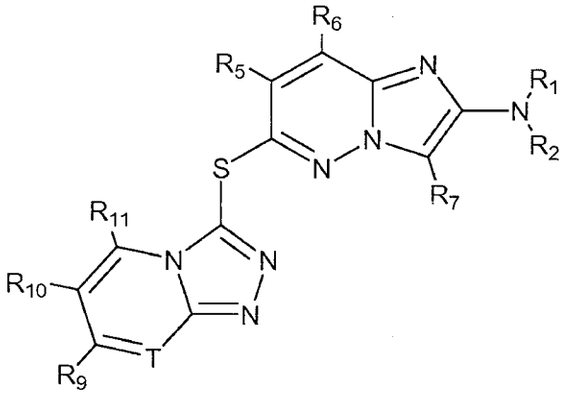
[0131] In another embodiment, cMET inhibitors of the present invention comprise:



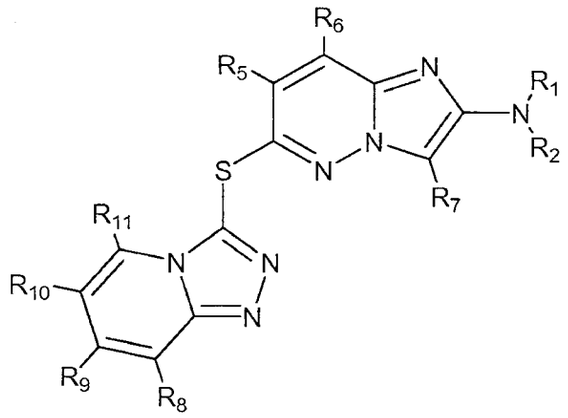
[0132] In still another embodiment, cMET inhibitors of the present invention comprise:



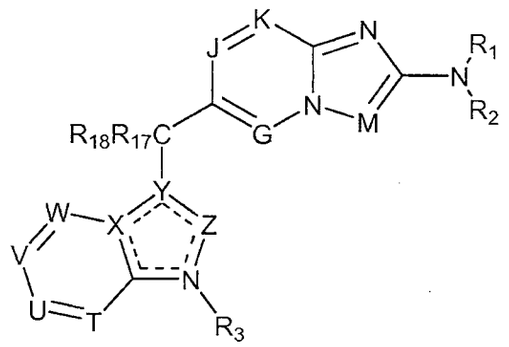
[0133] In yet another embodiment, cMET inhibitors of the present invention comprise:



[0134] In a further embodiment, cMET inhibitors of the present invention comprise:

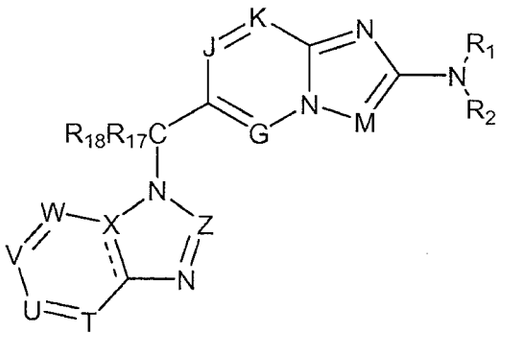


[0135] In still a further embodiment, cMET inhibitors of the present invention comprise:



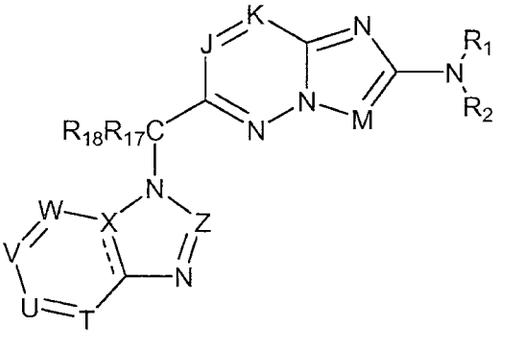
wherein R_{17} and R_{18} are each independently elected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0136] In yet a further embodiment, cMET inhibitors of the present invention comprise:



wherein R_{17} and R_{18} are each independently elected 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

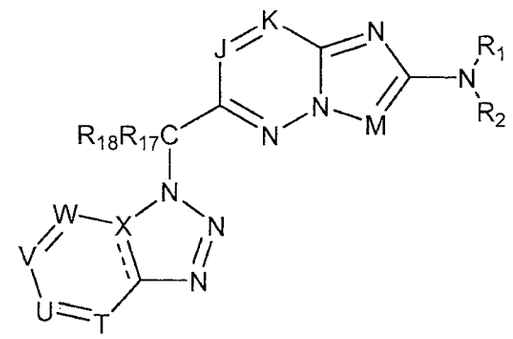
[0137] In another embodiment, cMET inhibitors of the present invention comprise:



wherein R_{17} and R_{18} are each independently elected 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, aminocarbonyl, 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,

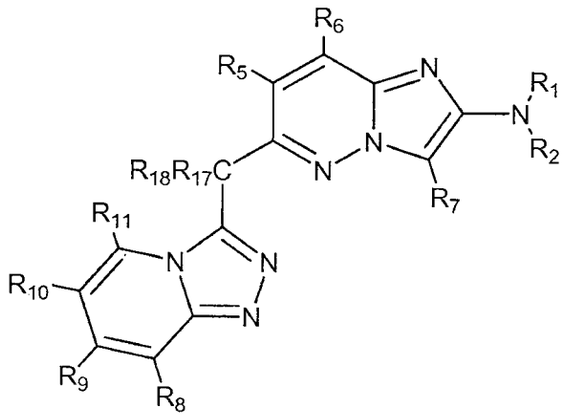
(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,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

[0138] In still another embodiment, cMET inhibitors of the present invention comprise:



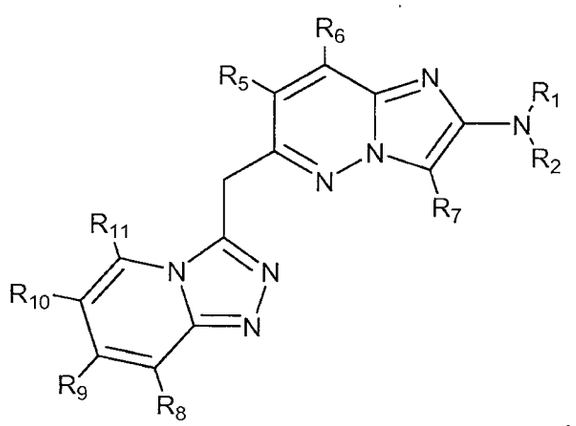
wherein R_{17} and R_{18} are each independently elected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0139] In a further embodiment, cMET inhibitors of the present invention comprise:

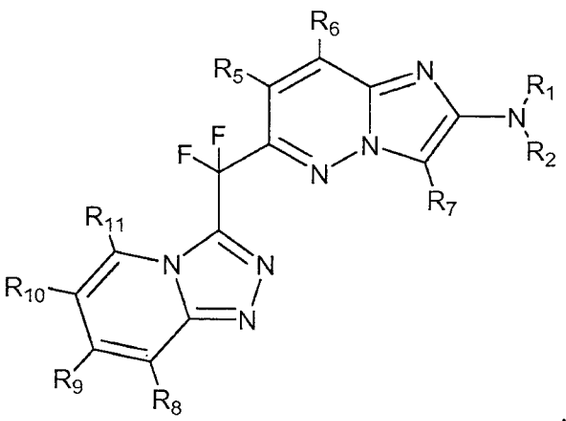


wherein R_{17} and R_{18} are each independently elected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

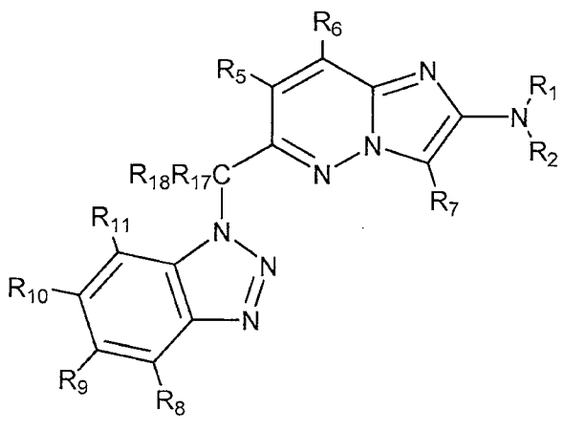
[0140] In another embodiment, cMET inhibitors of the present invention comprise:



[0141] In still another embodiment, cMET inhibitors of the present invention comprise:

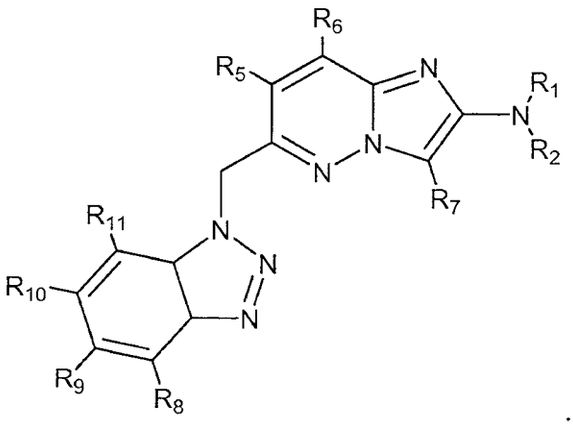


[0142] In still a further embodiment, cMET inhibitors of the present invention comprise:



wherein R_{17} and R_{18} are each independently elected 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0143] In another embodiment, cMET inhibitors of the present invention comprise:



[0144] In another of its aspects, the present invention relates to methods of making compounds that are useful as cMET inhibitors.

[0145] In still another of its aspects, the present invention relates to intermediates that are useful in making cMET inhibitors.

[0146] In one variation of each of the above embodiments and variations, G is CR_4. In another variation of each of the above embodiments and variations, G is N.

[0147] In still another variation of each of the above embodiments and variations, J is CR_5. In yet another variation of each of the above embodiments and variations, J is N.

[0148] In a further variation of each of the above embodiments and variations, K is CR_6. In still a further variation of each of the above embodiments and variations, K is N.

[0149] In yet a further variation of each of the above embodiments and variations, M is CR_7. In another variation of each of the above embodiments and variations, M is N.

[0150] In another variation of each of the above embodiments and variations,

L is a linker selected from the group consisting of $-(CR_{27}R_{28})_r-$, -CO-, -CS-, $-C(=NR_{29})-$, $-NR_{30}-$, -O-, -S-, -SO-, $-SO_2-$ and combinations thereof;

r is selected from the group consisting of 1, 2 and 3;

R_{27} 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{28} 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{29} is selected from the group consisting of hydrogen, 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; and

R_{30} is selected from the group consisting of hydrogen, 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.

[0151] In still another variation of each of the above embodiments and variations, L is a substituted or unsubstituted (C_{1-5})alkyl. In yet another variation of each of the above embodiments and variations, L is -CH_2-. In a further variation of each of the above embodiments and variations, L is -$CH(CH_3)$-. In still a further variation of each of the above embodiments and variations, L is -$C(CH_3)_2$-. In yet a further variation of each of the above embodiments and variations, L is–CF_2-. In a further variation of each of the above embodiments and variations, L is –S-. In another variation of each of the above embodiments and variations, L is –SO-. In still another variation of each of the above embodiments and variations, L is –SO_2-. In yet another variation of each of the above embodiments and variations, L is –CO-. In another variation of each of the above embodiments and variations, L is -O-. In still another variation of each of the above embodiments and variations, L is -NH-. In yet another variation of each of the above embodiments and variations, L is -CH_2-. In a further variation of each of the above embodiments and variations, L is -CO-NH-. In still a further variation of each of the above embodiments and variations, L is -NH-CO-. In yet a further variation of each of the above embodiments and variations, L is -SO_2-NH-. In another variation of each of the above embodiments and variations, L is -NH-SO_2-. In still another variation of each of the above embodiments and variations, L is -NH-NH-. In yet another variation of each of the above embodiments and variations, L is -CO-O-. In a further variation of each of the above embodiments and variations, L is -O-CO-.

[0152] In still a further variation of each of the above embodiments and variations, T is CR_8. In yet a further variation of each of the above embodiments and variations, T is N.

[0153] In another variation of each of the above embodiments and variations, U is CR_9. In still another variation of each of the above embodiments and variations, U is N.

[0154] In yet another variation of each of the above embodiments and variations, V is CR_{10}. In a further variation of each of the above embodiments and variations, V is N.

[0155] In still a further variation of each of the above embodiments and variations, W is CR_{11}. In yet a further variation of each of the above embodiments and variations, W is N.

[0156] In another variation of each of the above embodiments and variations, X is CR_{12}. In still another variation of each of the above embodiments and variations, X is N.

[0157] In yet another variation of each of the above embodiments and variations, Y is CR_{13}. In a further variation of each of the above embodiments and variations, Y is N.

[0158] In still a further variation of each of the above embodiments and variations, Z is $CR_{14}R_{15}$. In yet a further variation of each of the above embodiments and variations, Z is NR_{16}.

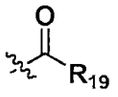
[0159] In another variation of each of the above embodiments and variations, T, Y and Z are each N. In still another variation of each of the above embodiments and variations, G is CR_4, J is CR_5, K is CR_6, M is CR_7, T is CR_8, U is CR_9, V is CR_{10}, W is CR_{11}, X is CR_{12} and Y is CR_{13}. In yet another variation of each of the above embodiments and variations, G is CR_4, J is CR_5, K is CR_6, M is CR_7, T is CR_8, U is CR_9, V is CR_{10}, W is CR_{11} and Y is CR_{13}. In a further variation of each of the above embodiments and variations, G, J, K, M, U, V, W, and X are each CH. In still a further variation of each of the above embodiments and variations, W, Y and Z are each N. In yet a further variation of each of the above embodiments and variations, G, J, K, M, T, U, V, and X are each CH. In another variation of each of the above embodiments and variations, G, X and Z are each N. In still another variation of each of the above embodiments and variations, J, K, M, T, U, V, W and Y are each CH. In yet another variation of each of the above embodiments and variations, X and Z are each N. In a further variation of each of the above embodiments and variations, G, J, K, M, T, U, V, W and Y are each CH. In still a further variation of each of the above embodiments and variations, T is CR_8, U is CR_9, V is CR_{10}, W is CR_{11}, X is CR_{12}, Y is N and Z is $CR_{14}R_{15}$. In yet a further variation of each of the above embodiments and variations, T is CR_8, U is CR_9, V is CR_{10}, W is CR_{11}, X is N, Y is CR_{13} and Z is NR_{16}. In another variation of each of the above embodiments and variations, G is N, J is CR_5, K is CR_6 and M is CR_7. In a further variation of each of the above embodiments and variations, J is CR_5, K is CR_6, T is CR_8, U is CR_9, V is CR_{10} and Z is NR_{16}. In still a further variation of each of the above embodiments and variations, one and only one of G and W is N. In another variation of each of the above embodiments and variations, G is N and W is CR_{11}. In still another variation of each of the above embodiments and variations, G is CR_4 and W is N. In yet a further variation of each of the above embodiments and variations, one and only one of W and Z is

N. In another variation of each of the above embodiments and variations, one and only one of W and X is N. In still another variation of each of the above embodiments and variations, one and only one of W, X and Z is N. In a further variation of each of the above embodiments and variations, G is N; and J, K, M, T, U, V and W are each CH. In still a further variation of each of the above embodiments and variations, G is N, J; K, M, T, U and W are each CH; and V is CR_{10}. In still a further variation of each of the above embodiments and variations, G is N, J; K, M, T, U and W are each CH; and V is CR_{10}, wherein R_{10} is a substituted or unsubstituted hetero(C_{1-10})aryl.

[0160] In a further variation of each of the above embodiments and variations, CR_5, CR_6, CR_7, CR_8 and CR_9 are each hydrogen.

[0161] In a further variation of each of the above embodiments and variations, R_1 is selected from the group consisting of hydrogen, carbonyl, oxycarbonyl, aminocarbonyl, (C_{1-10})alkylcarbonyl, (C_{3-12})cycloalkyl(C_{1-5})carbonyl, hetero(C_{3-12})cycloalkyl(C_{1-10})carbonyl, aryl(C_{1-10})carbonyl, hetero(C_{1-10})aryl(C_{1-5})carbonyl, (C_{9-12})bicycloaryl(C_{1-5})carbonyl, hetero(C_{8-12})bicycloaryl(C_{1-5})carbonyl, (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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

[0162] In yet another variation of each of the above embodiments and variations, R_1 is hydrogen. In a further variation of each of the above embodiments and variations, R_1 has the formula



wherein R_{19} selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0163] In still a further variation of each of the above embodiments and variations, R_2 is hydrogen. In another variation of each of the above embodiments and variations, R_2 is halo. In another variation of each of the above embodiments and variations, R_2 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations, R_2 is methyl.

[0164] In yet a further variation of each of the above embodiments and variations, R_3 is absent. In still a further variation of each of the above embodiments and variations, R_3 is hydrogen. In another variation of each of the above embodiments and variations, R_3 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations, R_3 is methyl.

[0165] In still a further variation of each of the above embodiments and variations, R_4 is hydrogen. In another variation of each of the above embodiments and variations, R_4 is halo. In another variation of each of the above embodiments and variations, R_4 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations, R_4 is methyl.

[0166] In still a further variation of each of the above embodiments and variations, R_5 is hydrogen. In another variation of each of the above embodiments and variations, R_5 is halo. In another variation of each of the above embodiments and variations, R_5 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations, R_5 is methyl.

[0167] In still a further variation of each of the above embodiments and variations, R_6 is hydrogen. In another variation of each of the above embodiments and variations, R_6 is halo. In another variation of each of the above embodiments and variations, R_6 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations, R_6 is methyl.

[0168] In still a further variation of each of the above embodiments and variations, R_7 is hydrogen. In another variation of each of the above embodiments and variations, R_7 is halo. In another variation of each of the above embodiments and variations, R_7 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations, R_7 is methyl.

[0169] In still a further variation of each of the above embodiments and variations, R_8 is hydrogen. In another variation of each of the above embodiments and variations, R_8 is halo. In another variation of each of the above embodiments and variations, R_8 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations, R_8 is methyl.

[0170] In yet a further variation of each of the above embodiments and variations, R_9 has the formula -C(=O)-NHR_{20a} wherein R_{20a} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0171] In another variation of each of the above embodiments and variations, R_9 has the formula -((C_{1-3})alkyl)-NHR_{20a} wherein R_{20a} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0172] In still another variation of each of the above embodiments and variations, R_9 has the formula -CH_2-NHR_{20a} wherein R_{20a} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

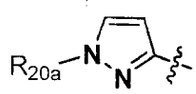
[0173] In yet another variation of each of the above embodiments and variations, R_9 has the formula -NHR_{20a} wherein R_{20a} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0174] In a further variation of each of the above embodiments and variations, wherein R_9 has the formula -NH-C(=O)R_{20a} wherein R_{20a} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

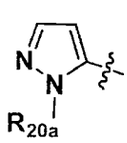
[0175] In still a further variation of each of the above embodiments and variations, R_9 is a substituted or unsubstituted (C_{1-3})alkoxy. In another variation of each of the above embodiments and variations, R_9 is hydrogen. In another variation of each of the above embodiments and variations, R_9 is halo. In a further variation of each of the above embodiments and variations, R_9 is a substituted or unsubstituted (C_{1-3})alkyl. In still another variation of each of the above embodiments and variations, R_9 is methyl. In another variation of each of the above embodiments and variations, R_9 is $-CF_3$.

[0176] In still another variation of each of the above embodiments and variations, R_9 has the formula



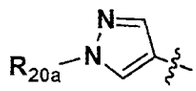
wherein R_{20a} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0177] In yet another variation of each of the above embodiments and variations, R_9 has the formula



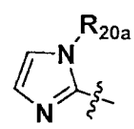
wherein R_{20a} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0178] In a further variation of each of the above embodiments and variations, R_9 has the formula



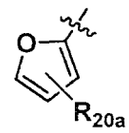
wherein R_{20a} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0179] In still a further variation of each of the above embodiments and variations, R_9 has the formula



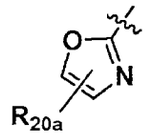
wherein R_{20a} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0180] In yet a further variation of each of the above embodiments and variations, R_9 has the formula



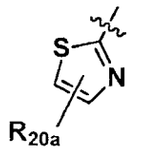
wherein R_{20a} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0181] In another variation of each of the above embodiments and variations, R_9 has the formula



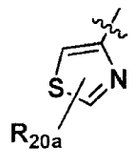
wherein R_{20a} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0182] In still another variation of each of the above embodiments and variations, R_9 has the formula



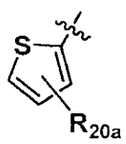
wherein R_{20a} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0183] In yet another variation of each of the above embodiments and variations, R_9 has the formula



wherein R_{20a} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

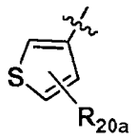
[0184] In a further variation of each of the above embodiments and variations, R_9 has the formula



wherein R_{20a} 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, aminocarbonyl, 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,

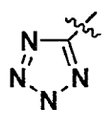
(C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0185] In still a further variation of each of the above embodiments and variations, R_9 has the formula

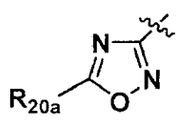


wherein R_{20a} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0186] In yet a further variation of each of the above embodiments and variations, R_9 has the formula



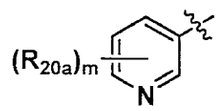
[0187] In another variation of each of the above embodiments and variations, R_9 has the formula



wherein R_{20a} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0188] In still another variation of each of the above embodiments and variations, R_9 has the formula

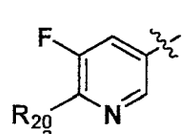


wherein

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

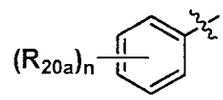
R_{20a} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0189] In yet another variation of each of the above embodiments and variations, R_9 has the formula



wherein R_{20a} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0190] In a further variation of each of the above embodiments and variations, R_9 has the formula

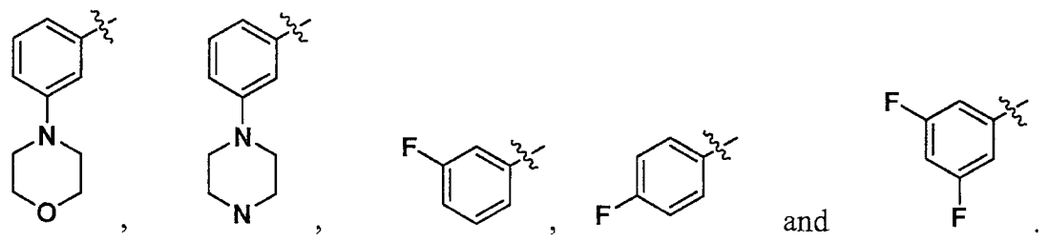


wherein

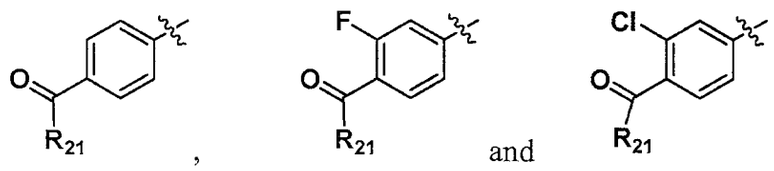
n is selected from the group consisting of 0, 1, 2, 3, 4 and 5; and

R_{20a} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0191] In still a further variation of each of the above embodiments and variations, R_9 has a formula selected from the group consisting of



[0192] In yet a further variation of each of the above embodiments and variations, R_9 has a formula selected from the group consisting of



wherein R_{21} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0193] In still another variation of each of the above embodiments and variations, R_{10} has the formula -C(=O)-NHR$_{20b}$ wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0194] In yet another variation of each of the above embodiments and variations, R_{10} has the formula -((C_{1-3})alkyl)-NHR_{20b} wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0195] In a further variation of each of the above embodiments and variations, R_{10} has the formula -CH_2-NHR_{20b} wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

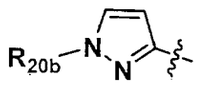
[0196] In still a further variation of each of the above embodiments and variations, R_{10} has the formula -NHR_{20b} wherein R_{20b} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0197] In yet a further variation of each of the above embodiments and variations, R_{10} has the formula -NH-C(=O)R_{20b} wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

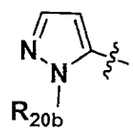
[0198] In a further variation of each of the above embodiments and variations, R_{10} is hydrogen. In still another variation of each of the above embodiments and variations, R_{10} is halo. In a further variation of each of the above embodiments and variations, R_{10} is selected from the group consisting of Cl, Br and I. In still a further variation of each of the above embodiments and variations, R_{10} is a substituted or unsubstituted (C_{1-3})alkyl. In a further variation of each of the above embodiments and variations, R_{10} is methyl. In still a further variation of each of the above embodiments and variations, R_{10} is $-CF_3$. In another variation of each of the above embodiments and variations, R_{10} is a substituted or unsubstituted (C_{1-3})alkoxy. In a further variation of each of the above embodiments and variations, R_{10} is cyano.

[0199] In yet a further variation of each of the above embodiments and variations, R_{10} has the formula



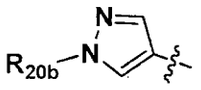
wherein R_{20b} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (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, R_{10} has the formula



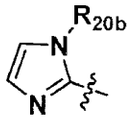
wherein R_{20b} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0201] In still another variation of each of the above embodiments and variations, R_{10} has the formula



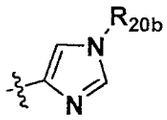
wherein R_{20b} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0202] In yet another variation of each of the above embodiments and variations, R_{10} has the formula



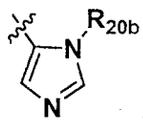
wherein R_{20b} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0203] In yet another variation of each of the above embodiments and variations, R_{10} has the formula



wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0204] In yet another variation of each of the above embodiments and variations, R_{10} has the formula



wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0205] In another variation of each of the above embodiments and variations, R_{10} is a substituted or unsubstituted hetero(C_{1-10})aryl. In still another variation of each of the above

embodiments and variations, R_{10} is a substituted or unsubstituted hetero(C_{1-5})aryl. In yet another variation of each of the above embodiments and variations, R_{10} is a substituted or unsubstituted hetero(C_{3-12})cycloalkyl. In a further variation of each of the above embodiments and variations, R_{10} is a substituted or unsubstituted hetero(C_{3-6})cycloalkyl.

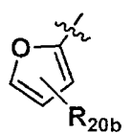
[0206] In a further variation of each of the above embodiments and variations, R_{10} is a substituted 5-membered heteroaryl group having 1-3 heteroatoms, wherein the heteroaryl ring has at least one oxo group in the ring or at least one hydroxy substituent. In one particular variation, the heteroaryl group has 1-3 nitrogen atoms.

[0207] In a further variation of each of the above embodiments and variations, R_{10} is a substituted 5-membered heterocycloalkyl group having 1-3 heteroatoms, wherein the heterocycloalkyl ring has at least one oxo group in the ring or at least one hydroxy substituent. In one particular variation, the heterocycloalkyl group has 1-3 nitrogen atoms.

[0208] In a further variation of each of the above embodiments and variations, R_{10} is a substituted 6-membered heteroaryl group having 1-3 heteroatoms, wherein the heteroaryl ring has at least one oxo group in the ring or at least one hydroxy substituent. In one particular variation, the heteroaryl group has 1-3 nitrogen atoms.

[0209] In a further variation of each of the above embodiments and variations, R_{10} is a substituted 6-membered heterocycloalkyl group having 1-3 heteroatoms, wherein the heterocycloalkyl ring has at least one oxo group in the ring or at least one hydroxy substituent. In one particular variation, the heterocycloalkyl group has 1-3 nitrogen atoms.

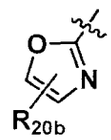
[0210] In yet another variation of each of the above embodiments and variations, R_{10} has the formula



wherein R_{20b} 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, aminocarbonyl, 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,

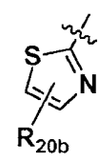
(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each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

[0211] In a further variation of each of the above embodiments and variations, R_{10} has the formula



wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

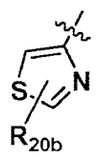
[0212] In still a further variation of each of the above embodiments and variations, R_{10} has the formula



wherein R_{20b} 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, aminocarbonyl, 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,

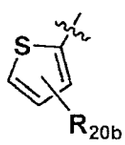
hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,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

[0213] In yet a further variation of each of the above embodiments and variations, R_{10} has the formula



wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

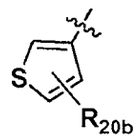
[0214] In another variation of each of the above embodiments and variations, R_{10} has the formula



wherein R_{20b} 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, aminocarbonyl, 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,

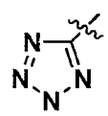
(C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl,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

[0215] In still another variation of each of the above embodiments and variations, R_{10} has the formula

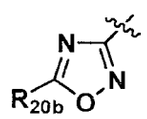


wherein R_{20b} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0216] In yet another variation of each of the above embodiments and variations, R_{10} has the formula

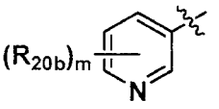


[0217] In a further variation of each of the above embodiments and variations, R_{10} has the formula



wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0218] In still a further variation of each of the above embodiments and variations, R_{10} has the formula

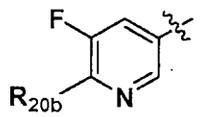


wherein

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

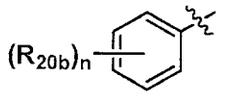
R_{20b} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0219] In yet a further variation of each of the above embodiments and variations, R_{10} has the formula



wherein R_{20b} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0220] In another variation of each of the above embodiments and variations, R_{10} has the formula



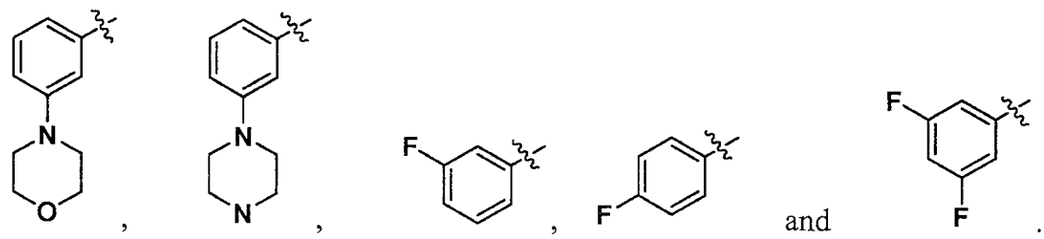
wherein

n is selected from the group consisting of 0, 1, 2, 3, 4 and 5; and

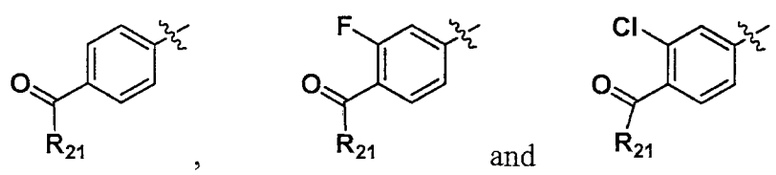
R_{20b} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0221] In still another variation of each of the above embodiments and variations, R_{10} has a formula selected from the group consisting of



[0222] In yet another variation of each of the above embodiments and variations, R_{10} has a formula selected from the group consisting of



wherein R_{21} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0223] In a further variation of each of the above embodiments and variations, R_{11} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{11} is halo. In yet a further variation of each of the above embodiments and variations, R_{11} is a

substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{11} is methyl.

[0224] In yet a further variation of each of the above embodiments and variations, R_{12} is absent. In a further variation of each of the above embodiments and variations, R_{12} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{12} is halo. In yet a further variation of each of the above embodiments and variations, R_{12} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{12} is methyl.

[0225] In still another variation of each of the above embodiments and variations, R_{13} is absent. In a further variation of each of the above embodiments and variations, R_{13} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{13} is halo. In yet a further variation of each of the above embodiments and variations, R_{13} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{13} is methyl.

[0226] In a further variation of each of the above embodiments and variations, R_{14} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{14} is halo. In yet a further variation of each of the above embodiments and variations, R_{14} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{14} is methyl.

[0227] In still a further variation of each of the above embodiments and variations, R_{15} is absent. In a further variation of each of the above embodiments and variations, R_{15} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{15} is halo. In yet a further variation of each of the above embodiments and variations, R_{15} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{15} is methyl.

[0228] In yet a further variation of each of the above embodiments and variations, R_{16} is absent. In a further variation of each of the above embodiments and variations, R_{16} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{16} is halo. In yet a further variation of each of the above embodiments and variations, R_{16} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{16} is methyl.

[0229] In a further variation of each of the above embodiments and variations, R_{17} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{17} is

halo. In another variation of each of the above embodiments and variations, R_{17} is fluoro. In yet a further variation of each of the above embodiments and variations, R_{17} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{17} is methyl. In one variation of each of the above embodiments and variations containing R_{17}, R_{17} is unsubstituted.

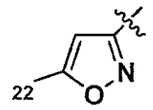
[0230] In a further variation of each of the above embodiments and variations, R_{18} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{18} is halo. In another variation of each of the above embodiments and variations, R_{18} is fluoro. In yet a further variation of each of the above embodiments and variations, R_{18} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{18} is methyl. In one variation of each of the above embodiments and variations containing R_{18}, R_{18} is unsubstituted.

[0231] In another variation of each of the above embodiments and variations, R_{19} is selected from the group consisting of hydrogen, 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, (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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0232] In another variation of each of the above embodiments and variations, R_{19} is a substituted or unsubstituted (C_{1-5})alkyl. In still another variation of each of the above embodiments and variations, R_{19} is methyl. In yet another variation of each of the above embodiments and variations, R_{19} is trifluoromethyl. In a further variation of each of the above embodiments and variations, R_{19} is isopropyl. In still a further variation of each of the above embodiments and variations, R_{19} is butyl. In yet a further variation of each of the above embodiments and variations, R_{19} is a substituted or unsubstituted (C_{3-6})cycloalkyl. In another variation of each of the above embodiments and variations, R_{19} is cyclopropyl. In still another variation of each of the above embodiments and variations, R_{19} is cyclopentyl. In another variation of each of the above embodiments and variations, R_{19} is a substituted or unsubstituted hetero(C_{3-12})cycloalkyl. In another variation of each of the above embodiments

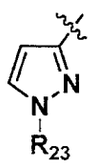
and variations, R_{19} is a substituted or unsubstituted (C_{4-12})aryl. In another variation of each of the above embodiments and variations, R_{19} is a substituted or unsubstituted hetero(C_{4-10})aryl.

[0233] In yet another variation of each of the above embodiments and variations, R_{19} has the formula



wherein R_{22} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0234] In a further variation of each of the above embodiments and variations, R_{19} has the formula



wherein R_{23} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0235] In still a further variation of each of the above embodiments and variations, R_{19} has the formula



wherein R_{24} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

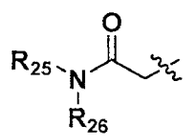
[0236] In one variation of each of the above embodiments and variations containing R_{19}, R_{19} is unsubstituted.

[0237] In a further variation of each of the above embodiments and variations, R_{20a} is selected from the group consisting of hydrogen, carbonyl, oxycarbonyl, aminocarbonyl, (C_{1-10})alkylcarbonyl, (C_{3-12})cycloalkyl(C_{1-5})carbonyl, hetero(C_{3-12})cycloalkyl(C_{1-10})carbonyl, aryl(C_{1-10})carbonyl, hetero(C_{1-10})aryl(C_{1-5})carbonyl, (C_{9-12})bicycloaryl(C_{1-5})carbonyl, hetero(C_{8-12})bicycloaryl(C_{1-5})carbonyl, (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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

[0238] In yet a further variation of each of the above embodiments and variations, R_{20a} is hydrogen. In another variation of each of the above embodiments and variations, R_{20a} is a substituted or unsubstituted (C_{1-5})alkyl. In still another variation of each of the above embodiments and variations, R_{20a} is methyl. In yet another variation of each of the above embodiments and variations, R_{20a} is ethyl. In a further variation of each of the above embodiments and variations, R_{20a} is propyl. In still a further variation of each of the above embodiments and variations, R_{20a} is a substituted or unsubstituted aryl. In yet a further variation of each of the above embodiments and variations, R_{20a} is a substituted or unsubstituted phenyl. In another variation of each of the above embodiments and variations, R_{20a} is a substituted or unsubstituted (C_{3-12})cycloalkyl. In still another variation of each of the above embodiments and variations, R_{20a} is a substituted or unsubstituted cyclohexyl. In yet another variation of each of the above embodiments and variations, R_{20a} is a substituted or unsubstituted hetero(C_{4-10})aryl. In a further variation of each of the above embodiments and variations, R_{20a} is a substituted or unsubstituted hydroxy(C_{1-6})alkyl. In still a further variation of each of the above embodiments and variations, R_{20a} is hydroxyethyl. In yet a further variation of each of the above embodiments and variations, R_{20a} is halo. In another variation of each of the above embodiments and variations, R_{20a} is fluoro. In still another variation of each of the above embodiments and variations, R_{20a} is a substituted or unsubstituted hetero(C_{3-6})cycloalkyl(C_{1-4})alkyl.

[0239] In yet another variation of each of the above embodiments and variations, R_{20a} has the formula



wherein R_{25} and R_{26} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

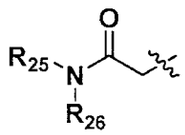
[0240] In one variation of each of the above embodiments and variations containing R_{20a}, R_{20a} is unsubstituted.

[0241] In a further variation of each of the above embodiments and variations, R_{20b} is selected from the group consisting of hydrogen, carbonyl, oxycarbonyl, aminocarbonyl, (C_{1-10})alkylcarbonyl, (C_{3-12})cycloalkyl(C_{1-5})carbonyl, hetero(C_{3-12})cycloalkyl(C_{1-10})carbonyl, aryl(C_{1-10})carbonyl, hetero(C_{1-10})aryl(C_{1-5})carbonyl, (C_{9-12})bicycloaryl(C_{1-5})carbonyl, hetero(C_{8-12})bicycloaryl(C_{1-5})carbonyl, (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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

[0242] In yet a further variation of each of the above embodiments and variations, R_{20b} is hydrogen. In another variation of each of the above embodiments and variations, R_{20b} is a substituted or unsubstituted (C_{1-5})alkyl. In still another variation of each of the above embodiments and variations, R_{20b} is methyl. In yet another variation of each of the above embodiments and variations, R_{20b} is ethyl. In a further variation of each of the above embodiments and variations, R_{20b} is propyl. In still a further variation of each of the above embodiments and variations, R_{20b} is a substituted or unsubstituted aryl. In yet a further variation of each of the above embodiments and variations, R_{20b} is a substituted or unsubstituted phenyl. In another variation of each of the above embodiments and variations, R_{20b} is a substituted or unsubstituted (C_{3-12})cycloalkyl. In still another variation of each of the above embodiments and variations, R_{20b} is a substituted or unsubstituted cyclohexyl. In yet another variation of each of the above embodiments and variations, R_{20b} is a substituted or

unsubstituted hetero(C_{4-10})aryl. In a further variation of each of the above embodiments and variations, R_{20b} is a substituted or unsubstituted hydroxy(C_{1-6})alkyl. In still a further variation of each of the above embodiments and variations, R_{20b} is hydroxyethyl. In yet a further variation of each of the above embodiments and variations, R_{20b} is halo. In another variation of each of the above embodiments and variations, R_{20b} is fluoro. In still another variation of each of the above embodiments and variations, R_{20b} is a substituted or unsubstituted hetero(C_{3-6})cycloalkyl(C_{1-4})alkyl.

[0243] In yet another variation of each of the above embodiments and variations, R_{20b} has the formula



wherein R_{25} and R_{26} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0244] In one variation of each of the above embodiments and variations containing R_{20b}, R_{20b} is unsubstituted.

[0245] In a further variation of each of the above embodiments and variations, R_{21} is a substituted or unsubstituted (C_{1-5})alkylamino. In still a further variation of each of the above embodiments and variations, R_{21} is CH_3NH-. In one variation of each of the above embodiments and variations containing R_{21}, R_{21} is unsubstituted.

[0246] In yet a further variation of each of the above embodiments and variations, R_{22} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above

embodiments and variations, R_{22} is methyl. In one variation of each of the above embodiments and variations containing R_{22}, R_{22} is unsubstituted.

[0247] In still another variation of each of the above embodiments and variations, R_{23} is a substituted or unsubstituted (C_{1-3})alkyl. In yet another variation of each of the above embodiments and variations, R_{23} is methyl. In one variation of each of the above embodiments and variations containing R_{23}, R_{23} is unsubstituted.

[0248] In a further variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted (C_{1-5})alkyl. In still a further variation of each of the above embodiments and variations, R_{24} is isopropyl. In yet a further variation of each of the above embodiments and variations, R_{24} is tert-butyl. In another variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted (C_{3-6})cycloalkyl. In still another variation of each of the above embodiments and variations, R_{24} is cyclopropyl. In yet another variation of each of the above embodiments and variations, R_{24} is cyclopentyl. In another variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted aryl. In a further variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted phenyl. In still a further variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted hetero(C_{3-12})cycloalkyl. In yet a further variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted pyrrolidinyl. In another variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted piperidinyl. In one variation of each of the above embodiments and variations containing R_{24}, R_{24} is unsubstituted.

[0249] In still another variation of each of the above embodiments and variations, R_{25} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{25} is halo. In yet a further variation of each of the above embodiments and variations, R_{25} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{25} is methyl. In one variation of each of the above embodiments and variations containing R_{25}, R_{25} is unsubstituted.

[0250] In yet another variation of each of the above embodiments and variations, R_{26} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{26} is halo. In yet a further variation of each of the above embodiments and variations, R_{26} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{26} is methyl. In one variation of each of the above embodiments and variations containing R_{26}, R_{26} is unsubstituted.

[0251] In yet another variation of each of the above embodiments and variations, R_{27} is hydrogen. In a further variation of each of the above embodiments and variations, R_{27} is halo. In still a further variation of each of the above embodiments and variations, R_{27} is a substituted or unsubstituted (C_{1-3}) alkyl.

[0252] In yet another variation of each of the above embodiments and variations, R_{28} is hydrogen. In a further variation of each of the above embodiments and variations, R_{28} is halo. In still a further variation of each of the above embodiments and variations, R_{28} is a substituted or unsubstituted (C_{1-3}) alkyl.

[0253] In yet a further variation of each of the above embodiments and variations, R_{29} is hydrogen. In still another variation of each of the above embodiments and variations, R_{29} is a substituted or unsubstituted (C_{1-3})alkyl.

[0254] In another variation of each of the above embodiments and variations, R_{30} is selected from the group consisting of hydrogen, 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. In yet a further variation of each of the above embodiments and variations, R_{30} is hydrogen. In still another variation of each of the above embodiments and variations, R_{30} is a substituted or unsubstituted (C_{1-3})alkyl.

[0255] In a further variation of each of the above embodiments and variations, n is 1. In still a further variation of each of the above embodiments and variations, n is 2. In still another variation of each of the above embodiments and variations, r is 1. In yet another variation of each of the above embodiments and variations, r is 2.

[0256] In yet a further variation of each of the above embodiments and variations, m is 1. In another variation of each of the above embodiments and variations, m is 2.

[0257] It is noted that the compounds of the present invention may be in the form of a pharmaceutically acceptable salt, ester, 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. Examples of substituents that are convertible *in vivo* to a

biologically active compound include, but are not limited to, biohydrolyzable moieties such as biohydrolyzable esters, biohydrolyzable amides and biohydrolyzable carbamates.

[0258] It is further noted that the compound may be present as a mixture of stereoisomers, or the compound may be present as a single stereoisomer.

[0259] In another of its aspects, there is provided a pharmaceutical composition comprising as a compound according to any one of the above embodiments and variations; and one or more pharmaceutically acceptable excipients. 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.

[0260] The present invention also provides 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.

[0261] 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.

[0262] 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.

[0263] 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.

[0264] In another of its aspects, there is provided a method of inhibiting cMET comprising contacting cMET with a compound of any one of the above embodiments and variations.

[0265] In yet another of its aspects, there is provided a method of inhibiting cMET comprising causing a compound of any one of the above embodiments and variations to be present in a subject in order to inhibit cMET in vivo.

[0266] In a further of its aspects, there is provided a method of inhibiting cMET comprising administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits cMET in vivo, the second compound being a compound according to any one of the above embodiments and variations.

[0267] In another of its aspects, there is provided a method of treating a disease state for which cMET possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising causing a compound of any one of the above embodiments and variations to be present in a subject in a therapeutically effective amount for the disease state.

[0268] In yet another of its aspects, there is provided a method of treating a disease state for which cMET possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising administering a compound of any one of the above embodiments and variations to a subject, wherein the compound is present in the subject in a therapeutically effective amount for the disease state.

[0269] In a further of its aspects, there is provided a method of treating a disease state for which cMET possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits cMET in vivo, the second compound being a compound according to any one of the above embodiments and variations.

[0270] In one variation of each of the above methods, the disease state is cancer. In particular variations, the cancer is selected from the group consisting of carcinomas (*e.g.*, bladder, breast, cervical, cholangiocarcinoma, colorectal, esophageal, gastric, head and neck, kidney, liver, lung, nasopharygeal, ovarian, pancreatic, prostate and thyroid); musculoskeletal sarcomas (*e.g.*, osteosarcoma, synovial sarcoma, and rhabdomyosarcoma); soft tissue

sarcomas (*e.g.*, MFH/fibrosrcoma, leiomyosarcoma, and Kaposi's sarcoma); hematopoietic malignancies (*e.g.*, multiple myeloma, lymphomas, adult T cell leukemia, acute myelogenous leukemia, and chronic myeloid leukemia); and other neoplasms (*e.g.*, glioblastomas, astrocytomas, melanoma, mesothelioma, and Wilm's tumor). In other particular variations, the cancer is selected from the group consisting of gastric cancer, lung cancer, colon cancer, breast cancer and other solid tumors.

[0271] In another variation of each of the above methods, the disease state is a proliferative disease. In particular variations, the proliferative disease is selected from the group consisting of myeloproliferative disorders, atherosclerosis, and fibrosis of the lung.

Salts, Hydrates, and Prodrugs of cMET Inhibitors

[0272] 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.

[0273] 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, glucoheptonate, 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.

[0274] 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.

[0275] The present invention also relates to N-oxides of compounds according to the present invention. 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. It is understood that N-oxides can be prepared by metabolic processes *in vitro* and *in vivo*.

[0276] 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.

[0277] 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.

[0278] 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.

[0279] 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 cMET Inhibitors

[0280] 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.

[0281] 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.

[0282] 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.

[0283] The cMET inhibitors and compositions comprising them may be administered or coadministered in any conventional dosage form. Co-administration in the context of this invention is intended to mean the administration of more than one therapeutic agent, one of which includes a cMET inhibitor, in the course of a coordinated treatment to achieve an improved clinical outcome. Such co-administration may also be coextensive, that is, occurring during overlapping periods of time.

[0284] 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.

[0285] 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.

[0286] 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.

[0287] 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.

[0288] 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 inhibitor of the present invention to reduce cMET activity in vivo, thereby treating the disease state of the subject.

[0289] 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 cMET inhibitors, optionally 0.1-95%, and optionally 1-95%.

[0290] Salts, preferably sodium salts, of the inhibitors may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. The formulations may further include other active compounds to obtain desired combinations of properties.

Formulations for Oral Administration

[0291] 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.

[0292] 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.

[0293] 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.

[0294] Examples of lubricants that may be used include, but are not limited to, talc, starch, magnesium or calcium stearate, lycopodium and stearic acid.

[0295] Examples of diluents that may be used include, but are not limited to, lactose, sucrose, starch, kaolin, salt, mannitol, and dicalcium phosphate.

[0296] Examples of glidants that may be used include, but are not limited to, colloidal silicon dioxide.

[0297] 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.

[0298] 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.

[0299] 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.

[0300] 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.

[0301] 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.

[0302] 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.

[0303] Examples of film coatings that may be used include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0304] 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.

[0305] 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.

[0306] 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.

[0307] 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.

[0308] 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.

[0309] 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.

[0310] 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.

[0311] 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.

[0312] 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.

[0313] 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.

[0314] Coloring and flavoring agents may optionally be used in all of the above dosage forms.

[0315] Particular examples of preservatives that may be used include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol.

[0316] Particular examples of non-aqueous liquids that may be used in emulsions include mineral oil and cottonseed oil.

[0317] Particular examples of emulsifying agents that may be used include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate.

[0318] Particular examples of suspending agents that may be used include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as sodium cyclamate and saccharin.

[0319] Particular examples of wetting agents that may be used include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether.

[0320] Particular examples of organic acids that may be used include citric and tartaric acid.

[0321] Sources of carbon dioxide that may be used in effervescent compositions include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof.

[0322] Particular examples of flavoring agents that may be used include natural flavors extracted from plants such fruits, and synthetic blends of compounds that produce a pleasant taste sensation.

[0323] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule.

Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

[0324] Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Pat. Nos. Re 28,819 and 4,358,603.

Injectables, Solutions, and Emulsions

[0325] The present invention is also directed to compositions designed to administer the compounds of the present invention by parenteral administration, generally characterized by subcutaneous, intramuscular or intravenous injection. Injectables may be prepared in any conventional form, for example as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions.

[0326] 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.

[0327] 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.

[0328] 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.

[0329] 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.

[0330] 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.

[0331] 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.

[0332] 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.

[0333] 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.

[0334] 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.

[0335] The concentration of an inhibitor in the parenteral formulation may be adjusted so that an injection administers a pharmaceutically effective amount sufficient to produce the desired pharmacological effect. The exact concentration of an inhibitor and/or dosage to be used will ultimately depend on the age, weight and condition of the patient or animal as is known in the art.

[0336] Unit-dose parenteral preparations may be packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration should be sterile, as is known and practiced in the art.

[0337] 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 cMET inhibitor to the treated tissue(s). The inhibitor may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment will be a function of the location of where the composition is parenterally administered, the carrier and other variables that may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens may need to be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations. Hence, the concentration ranges set forth herein are intended to be exemplary and are not intended to limit the scope or practice of the claimed formulations.

[0338] The cMET inhibitor may optionally be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease state and may be empirically determined.

Lyophilized Powders

[0339] 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.

[0340] 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 cMET inhibitor is added to the resulting mixture, preferably above room temperature, more preferably at about 30-35 °C, and stirred until it dissolves. The resulting mixture is diluted by adding more buffer to a desired concentration. The resulting mixture is sterile filtered or treated to remove particulates and to insure sterility, and apportioned into vials for lyophilization. Each vial may contain a single dosage or multiple dosages of the inhibitor.

Topical Administration

[0341] 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.

[0342] The cMET inhibitors may be formulated as aerosols for topical application, such as by inhalation (see, U.S. Pat. Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

[0343] The inhibitors may also be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the cMET inhibitor alone or in combination with other pharmaceutically acceptable excipients can also be administered.

Formulations for Other Routes of Administration

[0344] 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

[0345] 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 cMET Inhibitors

[0346] The invention is also directed to kits and other articles of manufacture for treating diseases associated with cMET. It is noted that diseases are intended to cover all conditions for which the cMET possess activity that contributes to the pathology and/or symptomology of the condition.

[0347] In one embodiment, a kit is provided that comprises a composition comprising at least one inhibitor of the present invention in combination with instructions. The instructions may indicate the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also comprise packaging materials. The packaging material may comprise a container for housing the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0348] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one inhibitor of the present invention in combination with packaging materials. The packaging material may comprise a container for housing the composition. The container may optionally comprise a label indicating the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also optionally

comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0349] 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.

[0350] 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.

[0351] 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

[0352] The compounds of the present invention are stable and can be used safely. In particlar, the compounds of the present invention are useful as cMet inhibitors 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

[0353] A wide variety of therapeutic agents may have a therapeutic additive or synergistic effect with the inhibitors of the present invention. Combination therapies that comprise one or more compounds of the present invention with one or more other therapeutic agents can be used, for example, to: 1) enhance the therapeutic effect(s) of the one or more compounds of the present invention and/or the one or more other therapeutic agents; 2) reduce the side effects exhibited by the one or more compounds of the present invention and/or the one or more other therapeutic agents; and/or 3) reduce the effective dose of the one or more compounds of the present invention and/or the one or more other therapeutic agents. For example, such therapeutic agents may additively or synergistically combine with the inhibitors of the present invention to inhibit undesirable cell growth, such as inappropriate cell growth resulting in undesirable benign conditions or tumor growth.

[0354] In one embodiment, a method is provided for treating a cell proliferative disease state comprising treating cells with a compound according to the present invention in combination with an anti-proliferative agent, wherein the cells are treated with the compound according to the present invention before, at the same time, and/or after the cells are treated with the anti-proliferative agent, referred to herein as combination therapy. It is noted that treatment of one agent before another is referred to herein as sequential therapy, even if the agents are also administered together. It is noted that combination therapy is intended to cover when agents are administered before or after each other (sequential therapy) as well as when the agents are administered at the same time.

[0355] Examples of therapeutic agents that may be used in combination with the inhibitors of the present invention include, but are not limited to, anticancer agents, alkylating agents, antibiotic agents, antimetabolic agents, hormonal agents, plant-derived agents, and biologic agents.

[0356] Alkylating agents are polyfunctional compounds that have the ability to substitute alkyl groups for hydrogen ions. Examples of alkylating agents include, but are not limited to, bischloroethylamines (nitrogen mustards, e.g. chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard), aziridines (e.g. thiotepa), alkyl alkone sulfonates (e.g. busulfan), nitrosoureas (e.g. carmustine, lomustine, streptozocin), nonclassic alkylating agents (altretamine, dacarbazine, and procarbazine), platinum compounds (carboplastin and cisplatin). These compounds react with phosphate, amino, hydroxyl, sulfihydryl, carboxyl, and imidazole groups. Under physiological conditions, these drugs ionize and produce positively charged ion that attach to susceptible nucleic acids and proteins, leading to cell cycle arrest and/or cell death. Combination therapy including an inhibitor of the present invention and an alkylating agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0357] Antibiotic agents are a group of drugs that produced in a manner similar to antibiotics as a modification of natural products. Examples of antibiotic agents include, but are not limited to, anthracyclines (e.g. doxorubicin, daunorubicin, epirubicin, idarubicin and anthracenedione), mitomycin C, bleomycin, dactinomycin, plicatomycin. These antibiotic agents interfere with cell growth by targeting different cellular components. For example, anthracyclines are generally believed to interfere with the action of DNA topoisomerase II in the regions of transcriptionally active DNA, which leads to DNA strand scissions. Bleomycin is generally believed to chelate iron and forms an activated complex, which then

binds to bases of DNA, causing strand scissions and cell death. Combination therapy including an inhibitor of the present invention and an antibiotic agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0358] Antimetabolic agents are a group of drugs that interfere with metabolic processes vital to the physiology and proliferation of cancer cells. Actively proliferating cancer cells require continuous synthesis of large quantities of nucleic acids, proteins, lipids, and other vital cellular constituents. Many of the antimetabolites inhibit the synthesis of purine or pyrimidine nucleosides or inhibit the enzymes of DNA replication. Some antimetabolites also interfere with the synthesis of ribonucleosides and RNA and/or amino acid metabolism and protein synthesis as well. By interfering with the synthesis of vital cellular constituents, antimetabolites can delay or arrest the growth of cancer cells. Examples of antimetabolic agents include, but are not limited to, fluorouracil (5-FU), floxuridine (5-FUdR), methotrexate, leucovorin, hydroxyurea, thioguanine (6-TG), mercaptopurine (6-MP), cytarabine, pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, and gemcitabine. Combination therapy including an inhibitor of the present invention and a antimetabolic agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0359] Hormonal agents are a group of drug that regulate the growth and development of their target organs. Most of the hormonal agents are sex steroids and their derivatives and analogs thereof, such as estrogens, androgens, and progestins. These hormonal agents may serve as antagonists of receptors for the sex steroids to down regulate receptor expression and transcription of vital genes. Examples of such hormonal agents are synthetic estrogens (e.g. diethylstibestrol), antiestrogens (e.g. tamoxifen, toremifene, fluoxymesterol and raloxifene), antiandrogens (bicalutamide, nilutamide, and flutamide), aromatase inhibitors (e.g., aminoglutethimide, anastrozole and tetrazole), ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone. Combination therapy including an inhibitor of the present invention and a hormonal agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0360] Plant-derived agents are a group of drugs that are derived from plants or modified based on the molecular structure of the agents. Examples of plant-derived agents include, but are not limited to, vinca alkaloids (e.g., vincristine, vinblastine, vindesine, vinzolidine and vinorelbine), podophyllotoxins (e.g., etoposide (VP-16) and teniposide (VM-26)), and

taxanes (e.g., paclitaxel and docetaxel). These plant-derived agents generally act as antimitotic agents that bind to tubulin and inhibit mitosis. Podophyllotoxins such as etoposide are believed to interfere with DNA synthesis by interacting with topoisomerase II, leading to DNA strand scission. Combination therapy including an inhibitor of the present invention and a plant-derived agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0361] Biologic agents are a group of biomolecules that elicit cancer/tumor regression when used alone or in combination with chemotherapy and/or radiotherapy. Examples of biologic agents include, but are not limited to, immuno-modulating proteins such as cytokines, monoclonal antibodies against tumor antigens, tumor suppressor genes, and cancer vaccines. Combination therapy including an inhibitor of the present invention and a biologic agent may have therapeutic synergistic effects on cancer, enhance the patient's immune responses to tumorigenic signals, and reduce potential sides affects associated with this chemotherapeutic agent.

[0362] Cytokines possess profound immunomodulatory activity. Some cytokines such as interleukin-2 (IL-2, aldesleukin) and interferon have demonstrated antitumor activity and have been approved for the treatment of patients with metastatic renal cell carcinoma and metastatic malignant melanoma. IL-2 is a T-cell growth factor that is central to T-cell-mediated immune responses. The selective antitumor effects of IL-2 on some patients are believed to be the result of a cell-mediated immune response that discriminate between self and nonself. Examples of interleukins that may be used in conjunction with inhibitors of the present invention include, but are not limited to, interleukin 2 (IL-2), and interleukin 4 (IL-4), interleukin 12 (IL-12).

[0363] Interferons include more than 23 related subtypes with overlapping activities, all of the IFN subtypes within the scope of the present invention. IFN has demonstrated activity against many solid and hematologic malignancies, the later appearing to be particularly sensitive.

[0364] Other cytokines that may be used in conjunction with the inhibitors of the present invention include those cytokines that exert profound effects on hematopoiesis and immune functions. Examples of such cytokines include, but are not limited to erythropoietin, granulocyte-CSF (filgrastin), and granulocyte, macrophage-CSF (sargramostim). These cytokines may be used in conjunction with an inhibitor of the present invention to reduce chemotherapy-induced myelopoietic toxicity.

[0365] Other immuno-modulating agents other than cytokines may also be used in conjunction with the inhibitors of the present invention to inhibit abnormal cell growth. Examples of such immuno-modulating agents include, but are not limited to bacillus Calmette-Guerin, levamisole, and octreotide, a long-acting octapeptide that mimics the effects of the naturally occurring hormone somatostatin.

[0366] Monoclonal antibodies against tumor antigens are antibodies elicited against antigens expressed by tumors, preferably tumor-specific antigens. For example, monoclonal antibody HERCEPTIN® (Trastruzumab) is raised against human epidermal growth factor receptor2 (HER2) that is overexpressed in some breast tumors including metastatic breast cancer. Overexpression of HER2 protein is associated with more aggressive disease and poorer prognosis in the clinic. HERCEPTIN® is used as a single agent for the treatment of patients with metastatic breast cancer whose tumors over express the HER2 protein. Combination therapy including an inhibitor of the present invention and HERCEPTIN® may have therapeutic synergistic effects on tumors, especially on metastatic cancers.

[0367] Another example of monoclonal antibodies against tumor antigens is RITUXAN® (Rituximab) that is raised against CD20 on lymphoma cells and selectively deplete normal and malignant $CD20^+$ pre-B and mature B cells. RITUXAN® is used as single agent for the treatment of patients with relapsed or refractory low-grade or follicular, CD20+, B cell non-Hodgkin's lymphoma. Combination therapy including an inhibitor of the present invention and RITUXAN® may have therapeutic synergistic effects not only on lymphoma, but also on other forms or types of malignant tumors.

[0368] Tumor suppressor genes are genes that function to inhibit the cell growth and division cycles, thus preventing the development of neoplasia. Mutations in tumor suppressor genes cause the cell to ignore one or more of the components of the network of inhibitory signals, overcoming the cell cycle check points and resulting in a higher rate of controlled cell growth—cancer. Examples of the tumor suppressor genes include, but are not limited to, DPC-4, NF-1, NF-2, RB, p53, WT1, BRCA1, and BRCA2.

[0369] DPC-4 is involved in pancreatic cancer and participates in a cytoplasmic pathway that inhibits cell division. NF-1 codes for a protein that inhibits Ras, a cytoplasmic inhibitory protein. NF-1 is involved in neurofibroma and pheochromocytomas of the nervous system and myeloid leukemia. NF-2 encodes a nuclear protein that is involved in meningioma, schwanoma, and ependymoma of the nervous system. RB codes for the pRB protein, a nuclear protein that is a major inhibitor of cell cycle. RB is involved in retinoblastoma as

well as bone, bladder, small cell lung and breast cancer. P53 codes for p53 protein that regulates cell division and can induce apoptosis. Mutation and/or inaction of p53 is found in a wide ranges of cancers. WT1 is involved in Wilms tumor of the kidneys. BRCA1 is involved in breast and ovarian cancer, and BRCA2 is involved in breast cancer. The tumor suppressor gene can be transferred into the tumor cells where it exerts its tumor suppressing functions. Combination therapy including an inhibitor of the present invention and a tumor suppressor may have therapeutic synergistic effects on patients suffering from various forms of cancers.

[0370] Cancer vaccines are a group of agents that induce the body's specific immune response to tumors. Most of cancer vaccines under research and development and clinical trials are tumor-associated antigens (TAAs). TAA are structures (i.e. proteins, enzymes or carbohydrates) which are present on tumor cells and relatively absent or diminished on normal cells. By virtue of being fairly unique to the tumor cell, TAAs provide targets for the immune system to recognize and cause their destruction. Example of TAAs include, but are not limited to gangliosides (GM2), prostate specific antigen (PSA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) (produced by colon cancers and other adenocarcinomas, e.g. breast, lung, gastric, and pancreas cancer s), melanoma associated antigens (MART-1, gp100, MAGE 1,3 tyrosinase), papillomavirus E6 and E7 fragments, whole cells or portions/lysates of antologous tumor cells and allogeneic tumor cells.

[0371] An adjuvant may be used to augment the immune response to TAAs. Examples of adjuvants include, but are not limited to, bacillus Calmette-Guerin (BCG), endotoxin lipopolysaccharides, keyhole limpet hemocyanin (GKLH), interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF) and cytoxan, a chemotherapeutic agent which is believe to reduce tumor-induced suppression when given in low doses.

EXAMPLES

Preparation of cMET Inhibitors

[0372] Various methods can be used 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.

[0373] 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.

[0374] 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).

[0375] 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.

[0376] 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).

[0377] 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.

[0378] 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.

[0379] 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).

[0380] 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.

[0381] 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.

[0382] 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).

[0383] 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.

[0384] 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.

[0385] ^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).

[0386] 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).

[0387] 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.

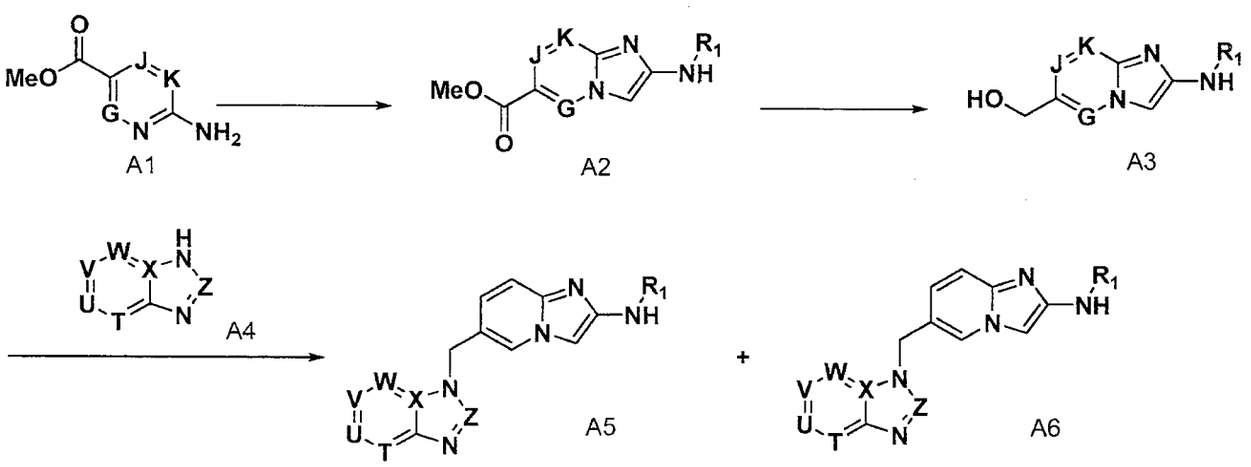
[0388] The entire disclosures of all documents cited throughout this application are incorporated herein by reference.

Synthetic Schemes for Compounds of the Present Invention

[0389] 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.

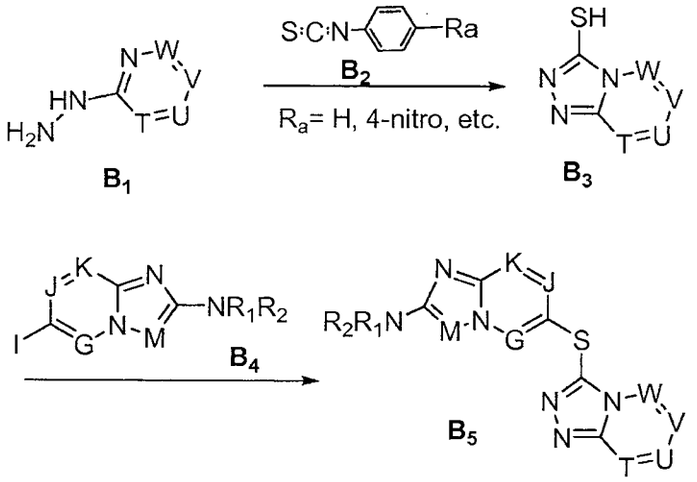
[0390] In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may 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.

Scheme A



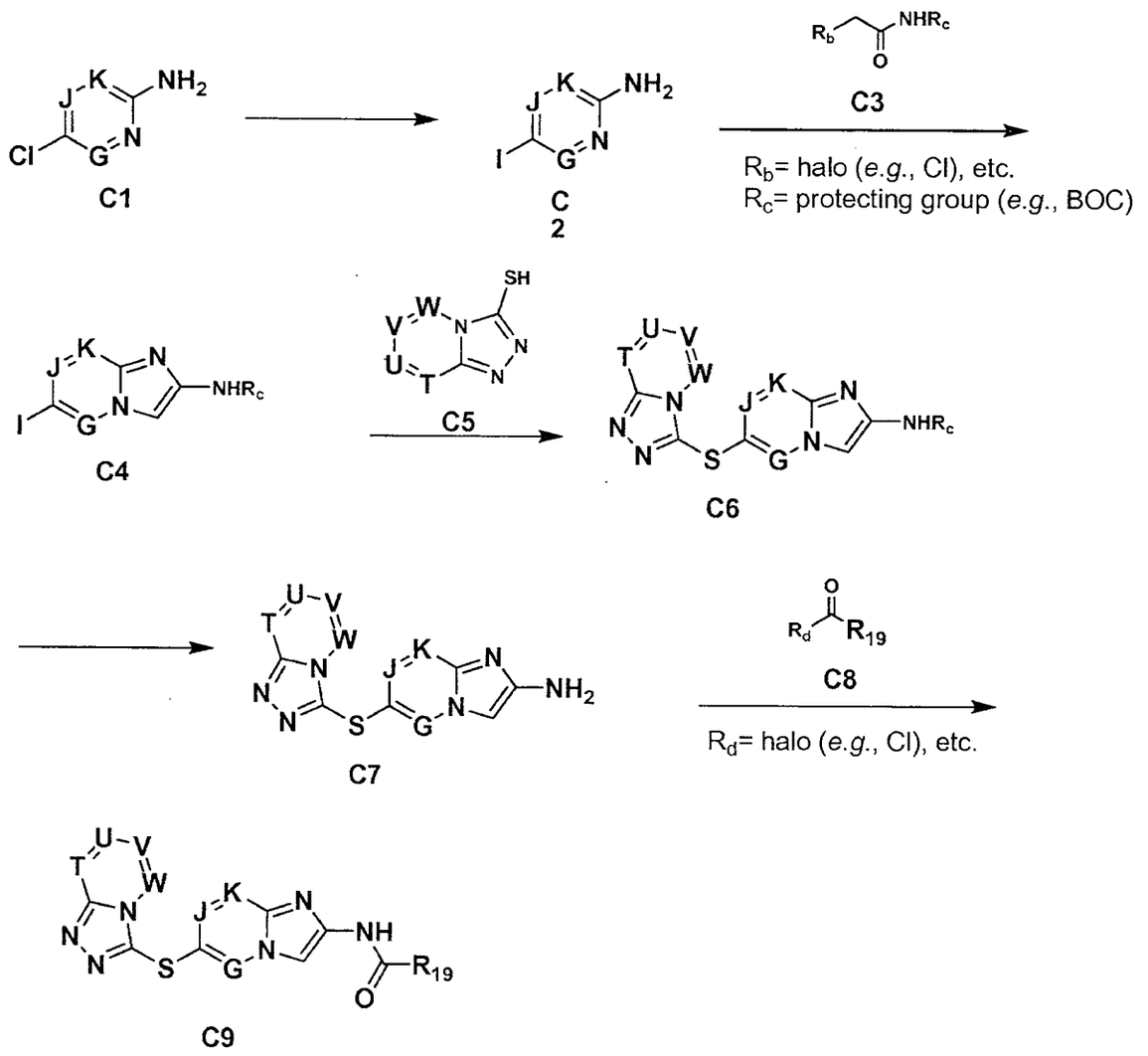
[0391] Compound **A2** can be prepared starting from compound **A1** in three steps following an analogous method to that described in US Patent No. 6,358, 971, which is incorporated by reference herein in its entirety. Reduction of the ester can be accomplished in the presence of a reducing agent such as LAH or $NaBH_4$ in THF or dioxane at 0 – 80 °C for 1 – 8 hrs to provide alcohol (A3). Standard Mitsunobu coupling of A3 and A4 in the presence of triphenylphosphine and an azodicarboxalate, such as DEAD or DIAD, at 0 – 80 °C for 1 – 24 hrs can be used to provide compounds A5 and A6. Compounds **A5** and **A6** can be separated using any of a variety of techniques known in the art including, for example, preparative LCMS.

Scheme B



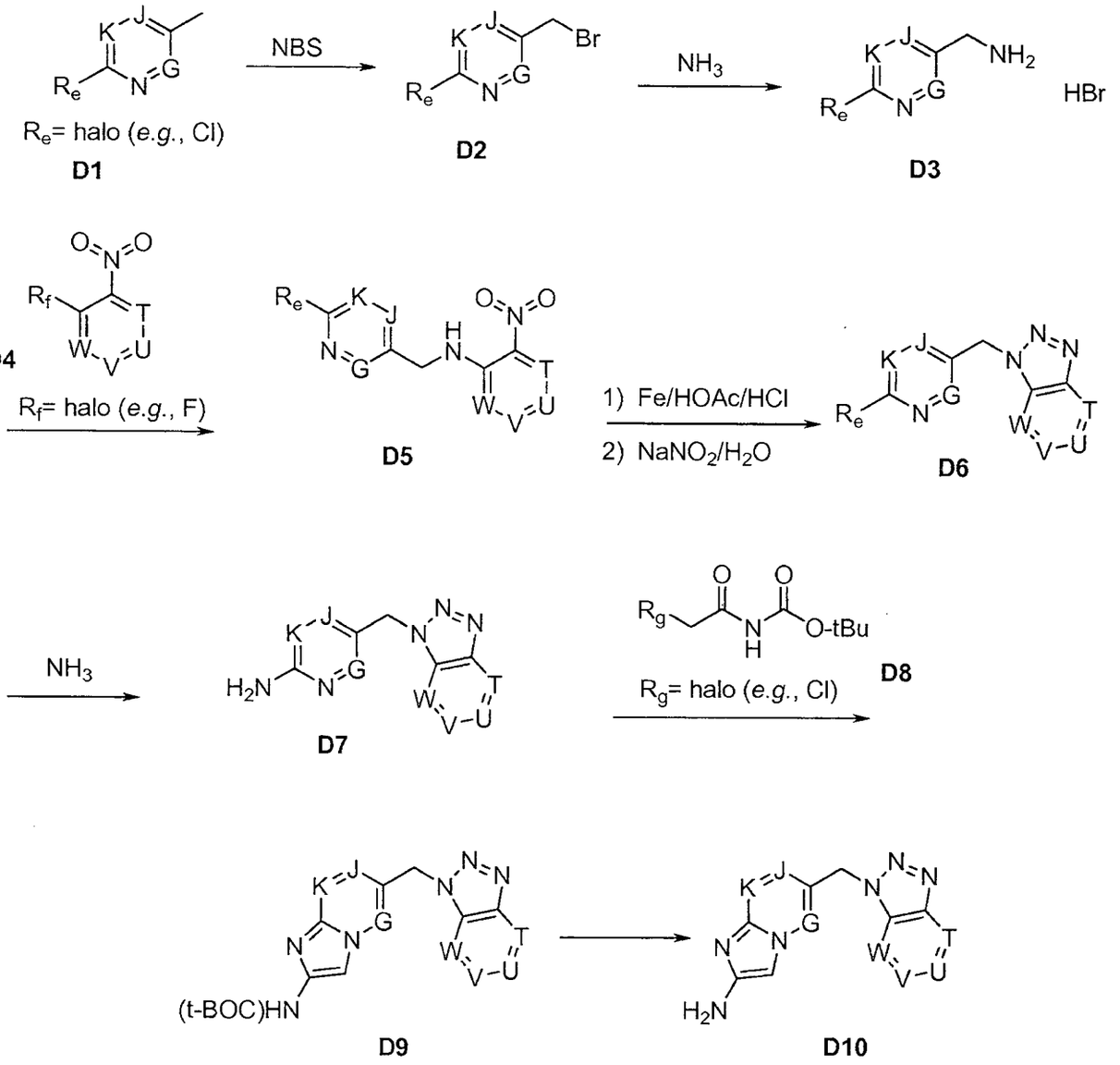
[0392] Compound **B1** is treated with compound **B2** (*e.g.*, phenylisothiocyanate or p-nitrophenylisothiocyanate) in DME at 100 – 120 °C in a microwave for 1 – 8 hrs to provide thiol (**B3**). A palladium mediated coupling of compound **B3** and **B4** in DME with $Pd_2(dba)_3$ and 4,5-bis(phenylphosphino)-9,9-dimethylxanthene at 100 – 120 °C in a microwave for 1 – 8 hrs can be used to provide compound **B5**.

Scheme C



[0393] Aniline (**C1**) is heated in HI at 100°C for 18 hrs to provide compound **C2**. Aniline (**C2**) is treated with acetamide (**C3**) and a base such as sodium hydrogen phosphate in a polar solvent (eg. DMA, DMF, or DMSO) and heated at 100 – 120 °C in a microwave for 1 – 8 hrs to afford cyclized product **C4**. Palladium mediated coupling of **C4** and **C5** can be accomplished in DME with $Pd_2(dba)_3$ and 4,5-bis(phenylphosphino)-9,9-dimethylxanthene at 100 – 120 °C in a microwave for 1 – 8 hrs to provide compound **C6**. Removal of the R_c group from **C6** can be accomplished in a solvent such as THF or dioxane or an alcohol such as MeOH, EtOH, or iPrOH in the presence of an acid such as HCl or TFA at 0 – 100 °C for 1 – 24 hrs to provide compound **C7**. Compound **C7** is treated with the appropriate acylchloride in a solvent (*e.g.*, DCM, THF, or $CHCl_3$) in the presence of a base (*e.g.*, TEA, DIEA, or pyridine) at 0 – 80 °C for 1 – 24 hrs to provide compound **C9**.

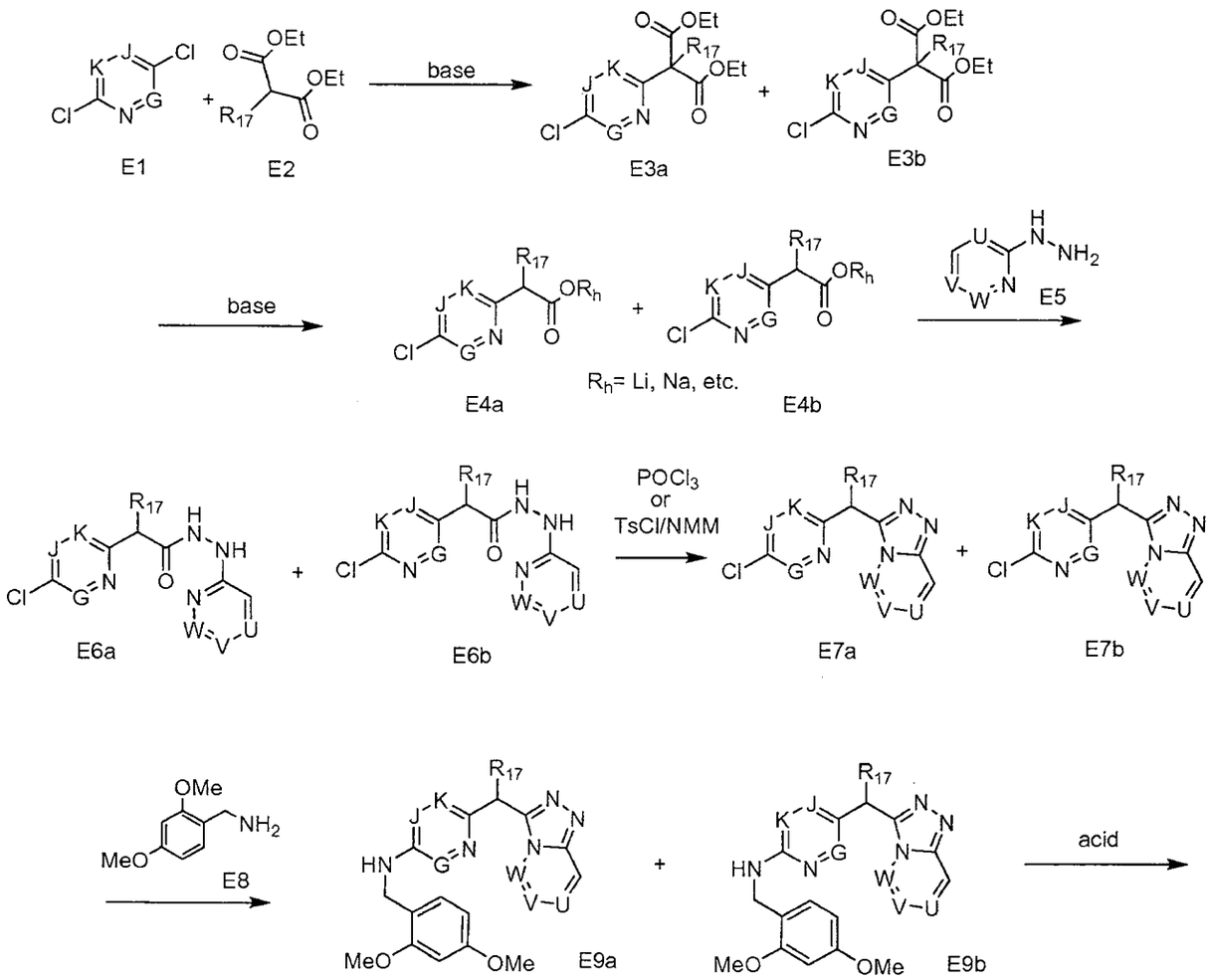
Scheme D

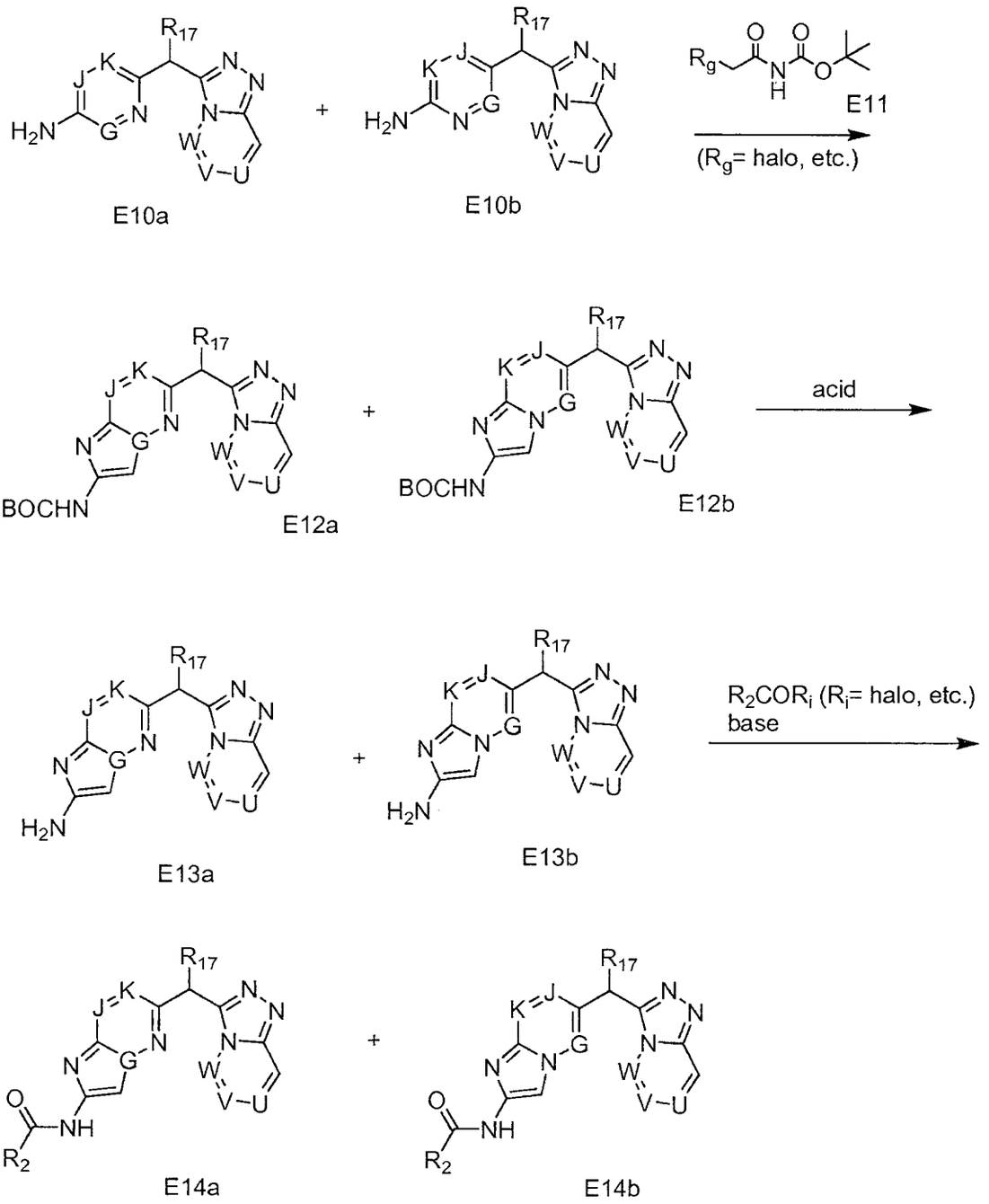


[0394] Compound **D1** is brominated under standard conditions such as NBS in the presence of a peroxide, AIBN, or 200 – 400 w light in CCl_4 at reflux (*e.g.*, for 1 – 8 hrs). Displacement of bromide (**D2**) with ammonia in an alcoholic solvent (*e.g.*, MeOH, EtOH, or i-PrOH) at 0 – 80 °C for 1 – 24 hrs provides compound **D3**. The substitution reaction with compounds **D3** and **D4** is accomplished in a solvent (*e.g.*, DMF, DMA, or EtOH) in the presence of a base (*e.g.*, TEA, DIEA, or pyridine) at 0 – 80 °C for 1 – 24 hrs to provide the arylnitro **D5**. Reduction of the arylnitro (**D5**) is accomplished under standard conditions using a palladium catalyst such as 10% Pd/C or metal (*e.g.*, Fe or Zn) in acidic medium. Subsequent ring closure of the resulting aniline to the triazole is accomplished in the presence of aqueous $NaNO_2$ to provide compound **D6**. Treatment of compound **D6** in ammonia saturated solvent (*e.g.*, EtOH or i-PrOH in a sealed vessel) at 100 – 150 °C for 1 – 4 days

provides aniline **D7**. Aniline (**D7**) is treated with acetamide (**D8**) and a base such as sodium hydrogen phosphate in a polar solvent (*e.g.*, DMA, DMF, or DMSO) and heated at 100 – 120 °C in a microwave for 1 – 8 hrs to afford cyclized product **D9**. Treatment of compound **D9** with acid (*e.g.*, HCl or TFA) provides compound **D10**.

Scheme E

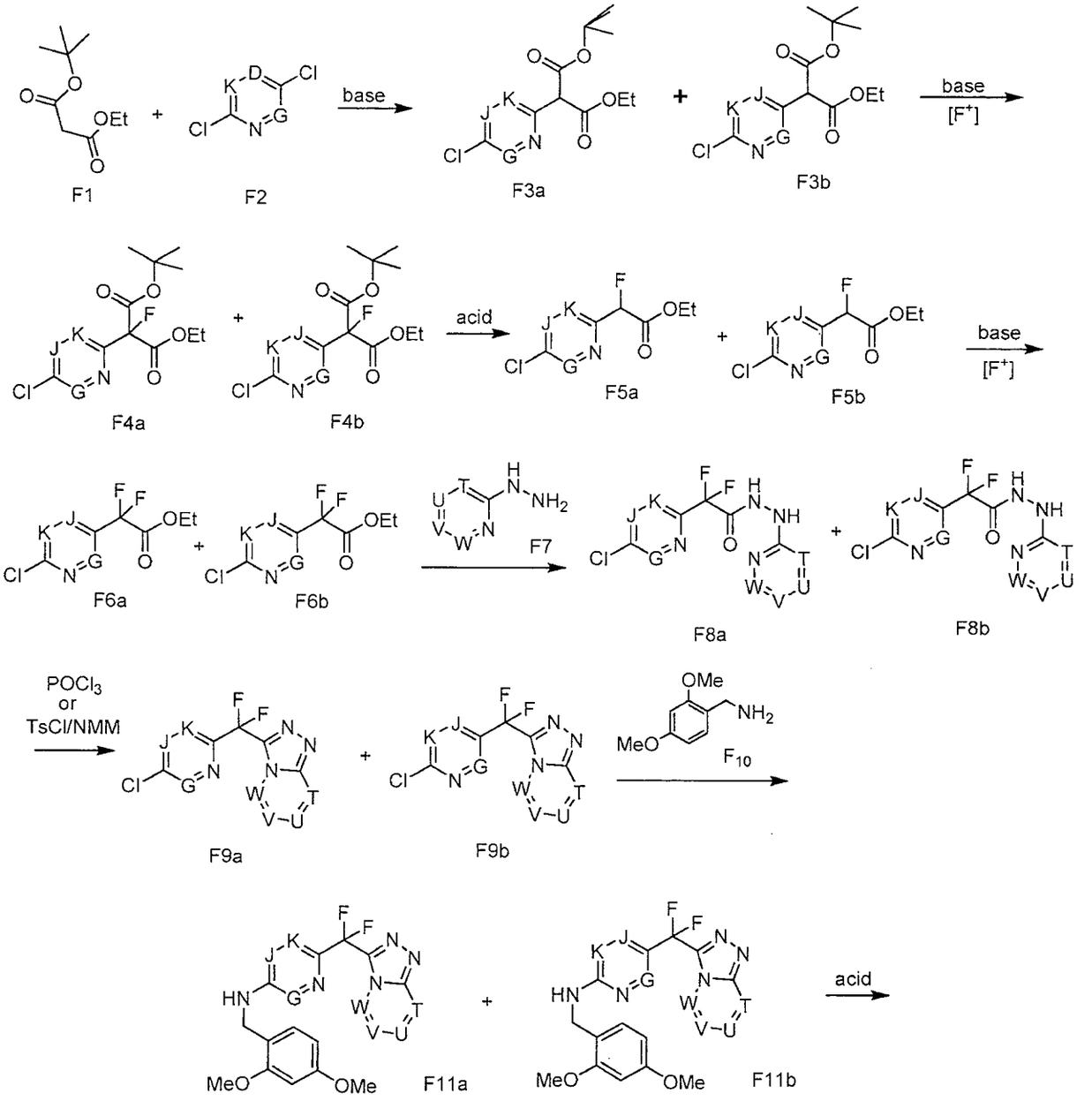


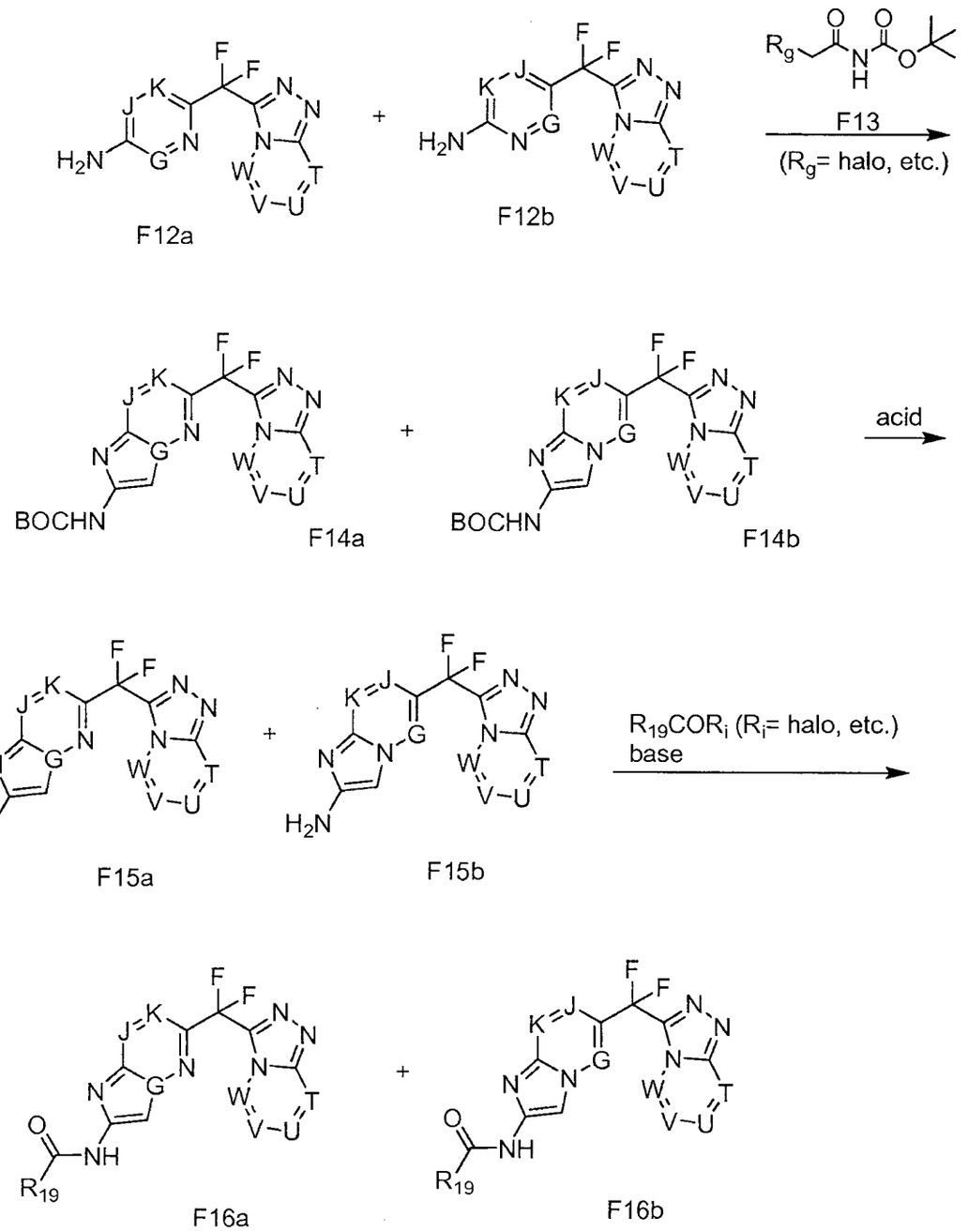


[0395] Compounds **E3a** and **E3b** can be prepared starting from compounds **E1** and **E2** by treating compound E2 with a base such as NaH in a solvent such as THF or dioxane at -78 - 0 °C and subsequent treatment with compound E1. Compound **E3a** and **E3b** are optionally separated prior to further use. Treatment of compound E3a and/or E3b with a base such as LiOH or NaOH at -20 – 75 °C for 1 – 8 hrs provides compounds E4a and/or E4b as the lithium or sodium salt, respectively. Treatment of compounds E4a and/or E4b with compound E5 in the presence of EDC or DCC for 1 – 24 hrs provides compounds E6a and/or E6b. Treatment of compounds E6a and/or E6b with $POCl_3$ at 80 – 160 °C provides

compounds E7a and/or E7b. Alternatively, compounds E7a and/or E7b can be prepared by treating compounds E6a and/or E6b with TsCl/N-methylmorpholine at ambient temperature to 100 °C for 30 min to 8 hrs. Coupling of compound E8 and compounds E7a and/or E7b is achieved in a solvent such as THF, Dioxane, or DMF at 25 – 100 °C for 2 – 24 hrs in the presence of a co-base such as DIEA or Et_3N. Removal of the dimethoxy benzyl group from compounds E9a and/or E9b is achieved by treating compounds E9a and/or E9b with an acid such as TFA at 25 – 75 °C for 2 – 24 hrs to provide compounds E10a and/or E10b. Treatment of compounds E10a and/or E10b with compound E11 in the presence of a base such as Na_2HPO_4 in a solvent such as DMA at 120 °C provides compounds E12a and/or E12b. Treatment of compounds E12a and/or E12b with an acid such as TFA or HCl provides compounds E13a and/or E13b. Treatment of compounds E13a and/or E13b with an acid halide in the presence of a co-base such as DIEA or Et_3N at 25 - 75 °C in a solvent such as DCM, THF, dioxane or DMF provides compounds E14a and/or E14b.

Scheme F

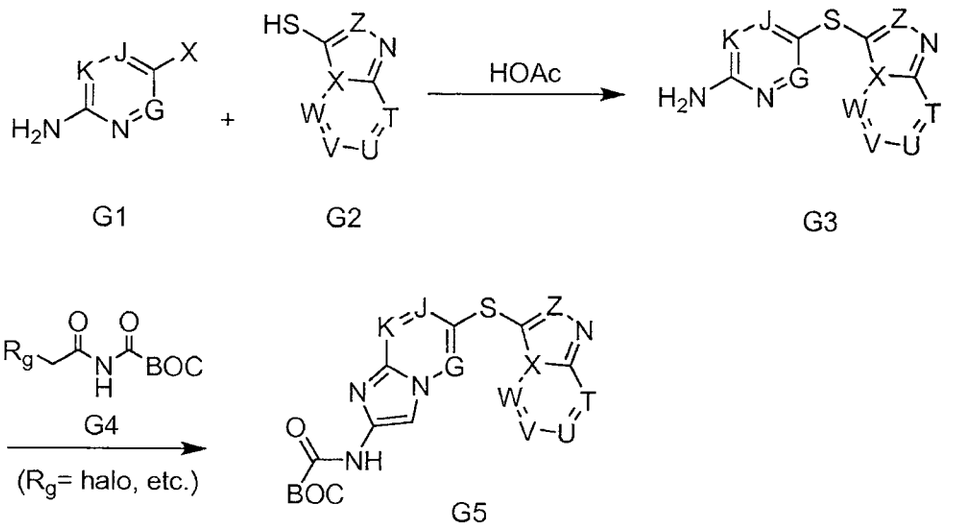

F1
F2
base
F3a
F3b
base
[F+]
F4a
F4b
acid
F5a
F5b
base
[F+]
F6a
F6b
F7
F8a
F8b
POCl3
or
TsCl/NMM
F9a
F9b
F10
F11a
F11b
acid



[0396] Compounds **F3a** and **F3b** can be prepared starting from compounds **F1** and **F2** by treating compound F1 with a base such as NaH in a solvent such as THF or dioxane at -78 - 0 °C and subsequent treatment with compound F2. Compound **F3a** and **F3b** are optionally separated prior to further use. Treatment of compounds F3a and/or F3b with a base such as NaH and a fluoride ion source provides compounds F4a and/or F4b. Subsequent treatment of compounds F4a and/or F4b with an acid such as TFA or HCl in a solvent such as THF, DCM, or dioxane at 0 – 75 °C for 1 – 8 hrs provides compounds F5a and/or F5b. Treatment of compounds F5a and/or F5b with a base such as NaH and a fluoride ion source provides compounds F6a and/or F6b. Treatment of compounds F6a and/or F6b with compound F7 in

the presence of base such as TEA or DIEA in solvents such as MeOH or EtOH for 1 – 24 hrs provides compounds F8a and/or F8b. Treatment of compounds F8a and/or F8b with $POCl_3$ at 80-160 °C provides compounds F9a and/or F9b. Alternatively, compounds F9a and/or F9b can be prepared by treating compounds F8a and/or F8b with TsCl/N-methylmorpholine at ambient temperature to 100 °C for 30 min to 8 hrs. Coupling of compounds F9a and/orF9b with compound F10 is achieved in a solvent such as THF, Dioxane, or DMF at 25 – 100 °C for 2 – 24 hrs in the presence of a co-base such as DIEA or Et_3N. Removal of the dimethoxy benzyl group from compounds F11a and/or F11b is achieved by treating compounds F11a and/or F11b with an acid such as TFA at 25 – 75 °C for 2 – 24 hrs to provide compounds F12a and/or F12b. Treatment of compounds F12a and/or F12b with compound F13 in the presence of a base such as Na_2HPO_4 in a solvent such as DMA at 120 °C provides compounds F14a and/or F14b. Treatment of compounds F14a and/or F14b with an acid such as TFA or HCl provides compounds F15a and/or F15b. Treatment of compounds F15a and/or F15b with an acid halide in the presence of a co-base such as DIEA or Et_3N at 25 - 75 °C in a solvent such as DCM, THF, dioxane or DMF provides compounds F16a and/or F16b.

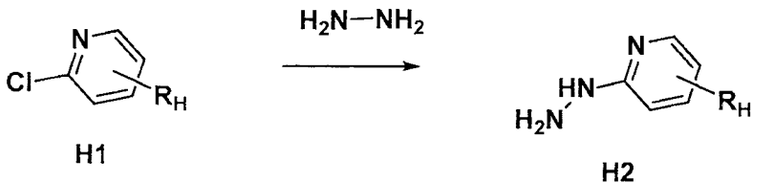
Scheme G



G5

[0397] Heating compound G1 and G2 in HOAc at 50 – 100 °C for 2 – 24 hrs provides compound G3. Treatment of compound G3 with compound G4 in the presence of a base such as Na_2HPO_4 in a solvent such as DMA at 120 °C provides compound G5.

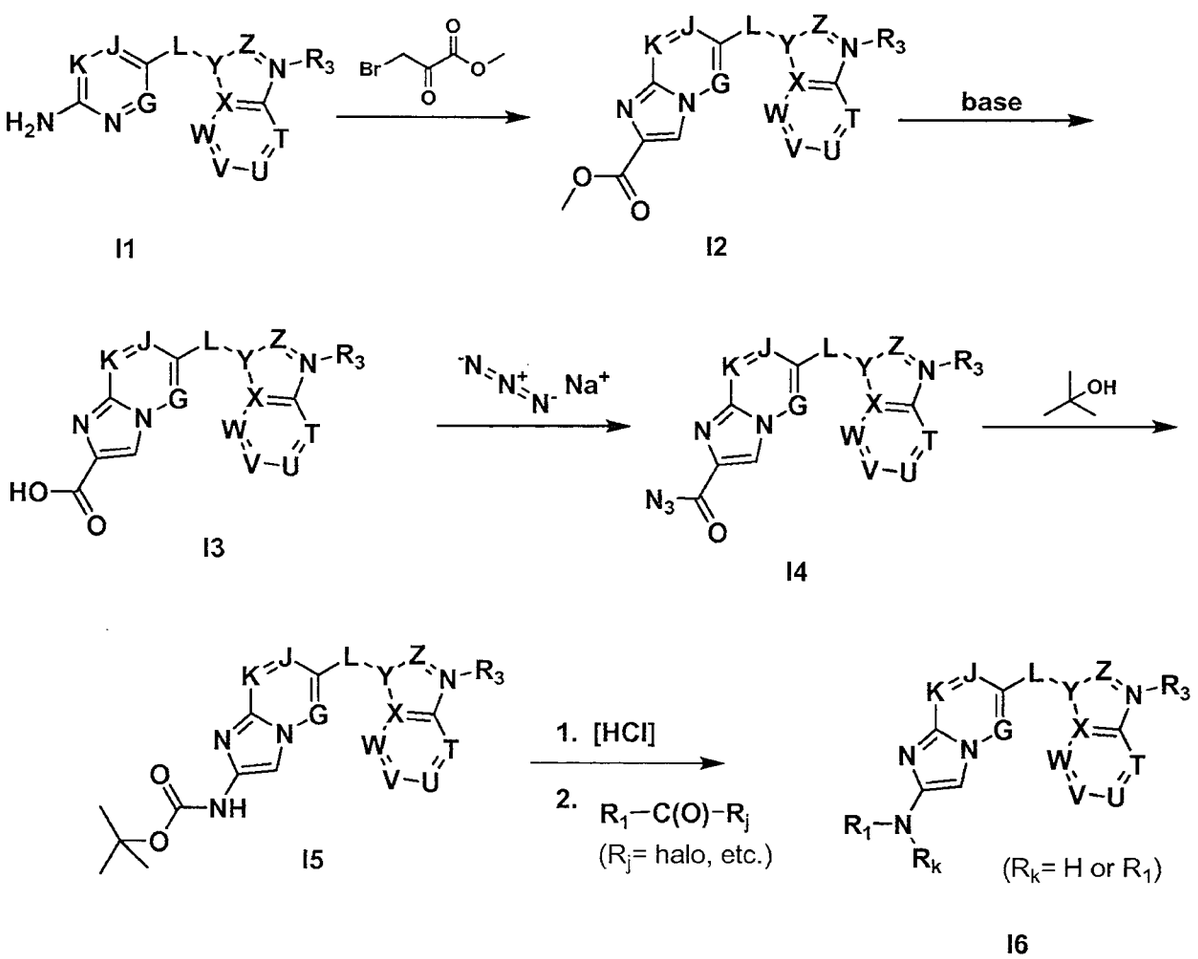
Scheme H



H1 H2

[0398] A solution of H1 (5 mmol; wherein R_H is R_8, R_9, R_{10} or R_{11}) and hydrazine (30 mmol) in isopropanol or EtOH (5mL) is heated under microwave conditions at 60-160 °C for 2-5 h dependent on substrates. The solid product is filtered, washed with water and dried under high vacuum. Excess hydrazine can optionally be removed by concentrating the mixture and co-evaporating it with MeOH and Et_3N. The product can be suspended in ether, filtered and dried under high vacuum (*e.g.*, overnight).

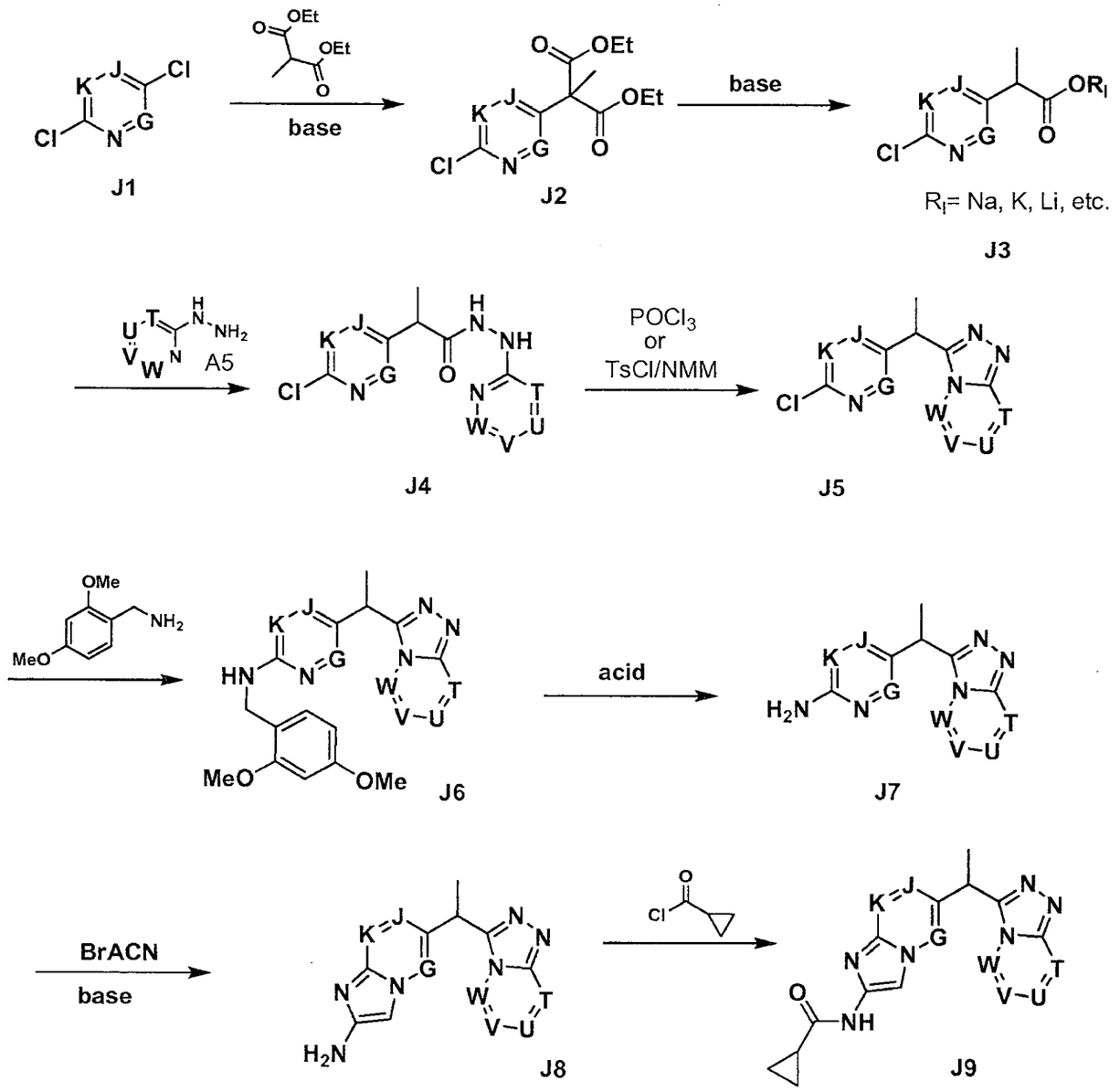
Scheme I



[0399] Compound I1 is treated with methyl 3-bromo-2-oxopropanoate in the presence of a base such as $NaHCO_3$, Na_2CO_3, sodium phosphate (mono, di, or tri -basic), or K_2CO_3 in a

solvent such as dioxane or THF and heated at 50 – 100°C for 1 – 18 hrs to provide compound of structure I2. Compound I2 is saponified with a base such as NaOH, KOH, or LiOH in a solvent such as MeOH, EtOH, or alcohol water mixtures with stirring for 1 - 18 hrs at 25 – 100°C to provide compound of structure I3. Compound I3 can be treated with sodium azide and PyBOB in the presence of a base such as TEA, DIEA, or pyridine in an anhydrous solvent such as DMA or DMF and stirred for 1 – 18 hrs at ambient temperature to provide compound I4. Compound I4 is stirred in t-butanol for 1 – 18 hrs at 25 – 120°C to provide compound I5. Compound I5 is treated with an acid such as TFA or HCl in a solvent such as DCM or dioxane and stirred for 1 – 18 hrs at 25 – 100°C. This deprotected product is then treated with an acylchloride in the presence of a base such as TEA, DIEA, or pyridine (which gives rise to a bis acylated product) or without a base (which gives rise to a mono acylated product) in a solvent such as DCM, THF, dioxane, or DMF and stirred for 1 – 18 hrs at 25 – 100°C to yield compounds of structure I6.

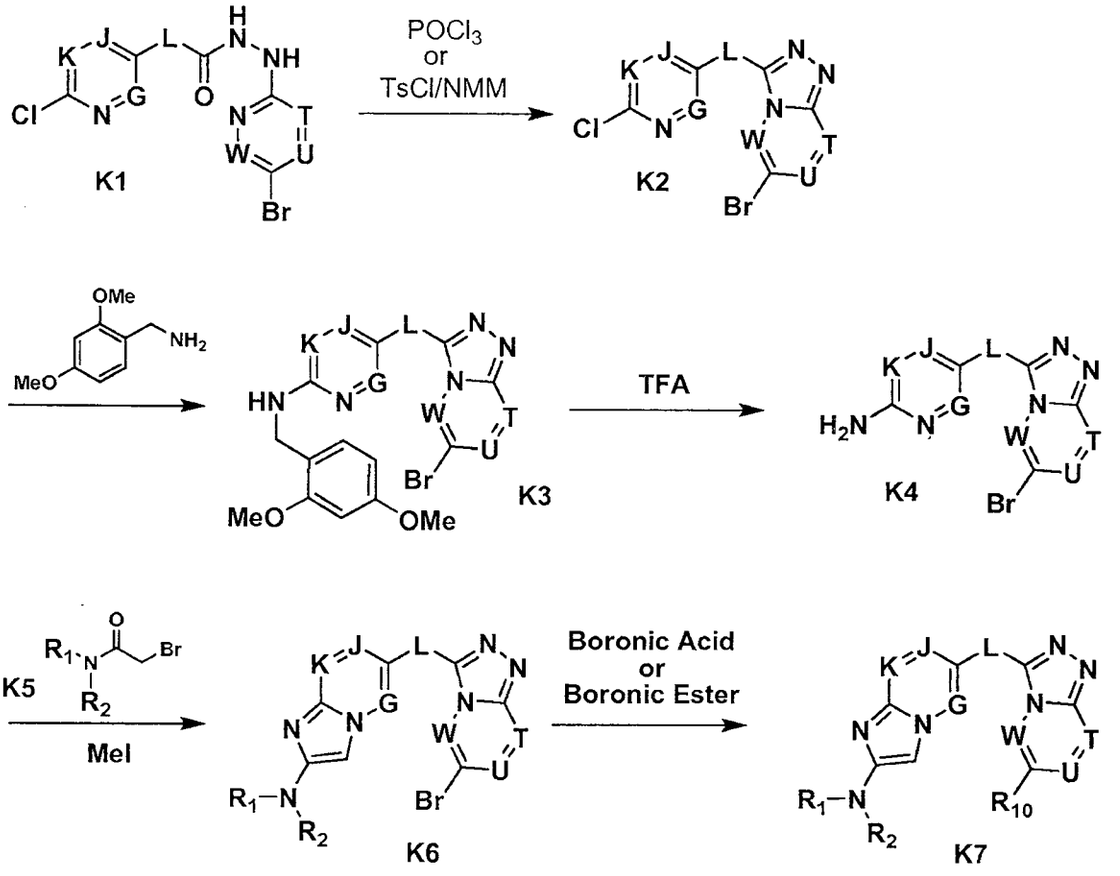
Scheme J



[0400] To a mixture of a base such as NaH or potassium t-butoxide in a solvent such as dioxane or THF is added diethyl 2-methylmalonate at -78 – 0°C. The mixture is allowed to warm to ambient temperature over 1 – 4 hrs. To this is added J1 portion-wise and the reaction is then stirred for 1 – 18 hrs at 25 - 100°C to give compounds of structure J2. Compound J2 is saponified with a base such as NaOH, KOH, or LiOH in a solvent such as MeOH, EtOH, or alcohol water mixtures with stirring for 1 - 18 hrs at 25 – 100°C to provide compound of structure J3 as the appropriate salt. Compound J3 and A5 in the presence of coupling reagents such as EDCI and HoBT or PyBOB in a solvent such as DMF or DMA are stirred for 1 – 8 hrs at 25 - 100°C to provide compounds of structure J4. Compound J4 is heated in phosphorous oxychloride for 1 – 18 hrs at 80-160 °C to give compounds of

structure J5. Alternatively, compound J5 can be prepared by treating compound J4 with TsCl/N-methylmorpholine at ambient temperature to 100 °C for 30 min to 8 hrs. Compound J5 is treated with 2,4-dimethoxybenzylamine in the presence of a base such as $NaHCO_3$, Na_2CO_3, sodium phosphate (mono, di, or tri -basic), or K_2CO_3 and in a solvent such as IPA and is heated in a microwave for 1- 24 hrs at 75 - 150°C to give compounds of structure J6. Compound J6 is treated with an acid such as TFA or HCl in a solvent such as DCM or dioxane for 1 – 18 hrs at 25 - 100°C to give compounds of structure J7. Compound J7 is treated with bromoacetonitrile in the presence of a base such as $NaHCO_3$, Na_2CO_3, sodium phosphate (mono, di, or tri -basic), or K_2CO_3 and in a solvent such as IPA for 1 – 18 hrs at 100°C in a sealed tube to provide compounds of structure J8. Compound J8 is treated with cyclopropanecarbonyl chloride in the presence of a base such as TEA, DIEA, or pyridine or in the absence of a base and in a solvent such as DCM, THF, or dioxane for 1 – 8 hrs at ambient temperature to provide compounds of structure J9.

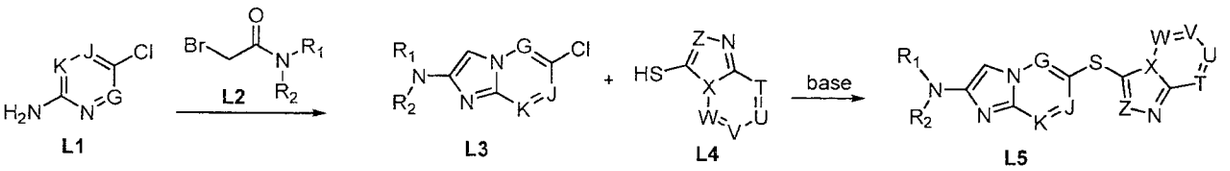
Scheme K



[0401] Compound K1 is heated in phosphorous oxychloride for 1 – 18 hrs at 80-160 °C to give compounds of structure K2. Alternatively, compound K2 can be prepared by treating

compound K1 with TsCl/N-methylmorpholine at ambient temperature to 100 °C for 30 min to 8 hrs. Compound K2 is treated with 2,4-dimethoxybenzylamine in the presence of a base such as $NaHCO_3$, Na_2CO_3, sodium phosphate (mono, di, or tri -basic), or K_2CO_3 and in a solvent such as IPA and is heated in a microwave for 1- 24 hrs at 75 - 150°C to give compounds of structure K3. Compound K3 is treated with an acid such as TFA or HCl in a solvent such as DCM or dioxane for 1 – 18 hrs at 25 - 100°C to give compounds of structure K4. Compounds of structure K4 is heated with compounds of structure K5 in the presence of KI and a base such as sodium hydrogenphosphate and in a solvent such as DMA or DME for 1 – 24 hrs at 50 - 120°C to provide compounds of structure K6. Compound K6 is treated with the appropriate boronic acid or boronic ester in the presence of a catalyst such as tetrakis(triphenylphosphine)palladium(0) and a base such as Cs_2CO_3 (aq) or K_2CO_3 (aq) in a solvent such as dioxane, THF, or DME for 15 min – 8 hrs at 50 - 120°C to give compounds of structure K7.

Scheme L



[0402] Compound L1 is treated with compound L2 and a base (eg., K_2HPO_4) in a polar solvent (eg., DMA, DMF or DMSO) and heated at 65 – 85°C to provide compound L3. Compound L3 was reacted with Compound L4 and a base (eg., K_2CO_3) in a polar solvent (eg., DMA, DMF or DMSO) at 130 - 160°C and atmospheric pressure to 125 psi N_2 to provide compound L5.

[0403] Chiral components can be separated and purified using any of a variety of techniques known to those skilled in the art. For example, chiral components can be purified using supercritical fluid chromatography (SFC). In one particular variation, chiral analytical SFC/MS analyses are conducted using a Berger analytical SFC system (AutoChem, Newark, DE) which consists of a Berger SFC dual pump fluid control module with a Berger FCM 1100/1200 supercritical fluid pump and FCM 1200 modifier fluid pump, a Berger TCM 2000 oven, and an Alcott 718 autosampler. The integrated system can be controlled by BI-SFC Chemstation software version 3.4. Detection can be accomplished with a Watrers ZQ 2000

detector operated in positive mode with an ESI interface and a scan range from 200-800 Da with 0.5 second per scan. Chromatographic separations can be performed on a ChiralPak AD-H, ChiralPak AS-H, ChiralCel OD-H, or ChiralCel OJ-H column (5μ, 4.6 x 250 mm; Chiral Technologies, Inc. West Chester, PA) with 10 to 40% methanol as the modifier and with or without ammonium acetate (10 mM). Any of a variety of flow rates can be utilized including, for example, 1.5 or 3.5 mL/min with an inlet pressure set at 100 bar. Additionally, a variety of sample injection conditions can be used including, for example, sample injections of either 5 or 10μL in methanol at 0.1 mg/mL in concentration.

[0404] In another variation, preparative chiral separations are performed using a Berger MultiGram II SFC purification system. For example, samples can be loaded onto a ChiralPak AD column (21 x 250 mm, 10μ). In particular variations, the flow rate for separation can be 70 mL/min, the injection volume up to 2 mL, and the inlet pressure set at 130 bar. Stacked injections can be applied to increase the efficiency.

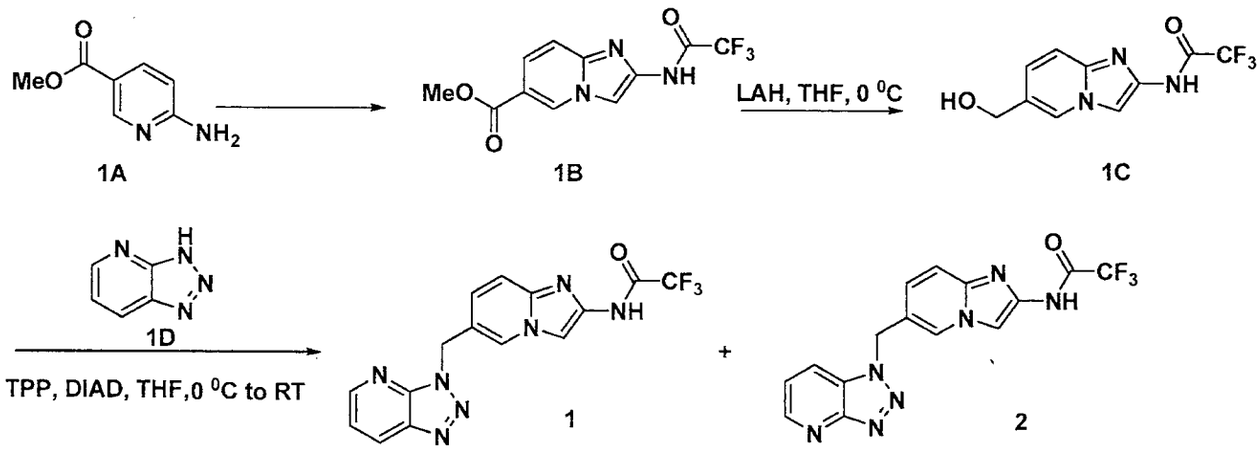
[0405] In each of the above reaction procedures or schemes, the various substituents may be selected from among the various substituents otherwise taught herein.

[0406] Descriptions of the syntheses of particular compounds according to the present invention based on the above reaction scheme are set forth herein.

Examples of cMET Inhibitors

[0407] The present invention is further exemplified, but not limited by, the following examples that describe the synthesis of particular compounds according to the invention.

Compounds 1 and 2: N-(6-((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)methyl)imidazo[1,2-a]pyridin-2-yl)-2,2,2-trifluoroacetamide and N-(6-((1H-[1,2,3]triazolo[4,5-b]pyridin-1-yl)methyl)imidazo-[1,2-a]pyridin-2-yl)-2,2,2-trifluoroacetamide



[0408] Methyl 2-(2,2,2-trifluoroacetamido)imidazo[1,2-a]pyridine-6-carboxylate (1B): Compound **1B** was prepared starting from compound **1A** in three steps following an analogous method to that described in US Patent No. 6,358, 971, which is incorporated by reference herein in its entirety. Specifically, a mixture of methyl 6-aminonicotinate (**1A**, 3 g, 19.7 mmol) and tosylchloride (4.5 g, 23.6 mmol) in pyridine (40 mL) was heated at 80 °C for 16 hrs. The reaction was cooled to room temperature and pyridine was removed in vacuo. The resulting residue was diluted with water and allowed to stir for 10 min. The resulting solid was filtered and dried under vacuum to provide methyl 6-(4-methylphenylsulfonamido)nicotinate which was used without further purification. To a suspension of methyl 6-(4-methylphenylsulfonamido) nicotinate (5.3 g, 17.3 mmol) in anhydrous DMF was sequentially added DIEA (3.31 mL, 19.03 mmol) and then 2-bromoacetamide (2.63 g, 19.03 mmol). The reaction was stirred at ambient temperature for 24 hrs and then poured into water. The resulting solid was filtered and dried under vacuum to provide methyl 1-(2-amino-2-oxoethyl)-6-(4-methylphenylsulfonamido)-1,6-dihydropyridine-3-carboxylate which was used without further purification. To a suspension of methyl 1-(2-amino-2-oxoethyl)-6-(4-methylphenylsulfonamido)-1,6-dihydropyridine-3-carboxylate (1.0 g, 2.8 mmol) in DCM (20 mL) was added TFAA (8.0 mL, 57.5 mmol) dropwise at ambient temperature. The reaction was refluxed for 2 hrs, cooled to ambient temperature, and then concentrated in vacuo. The resulting residue was suspended in saturated sodium bicarbonate and stirred for 15 min. The resulting solid was filtered and

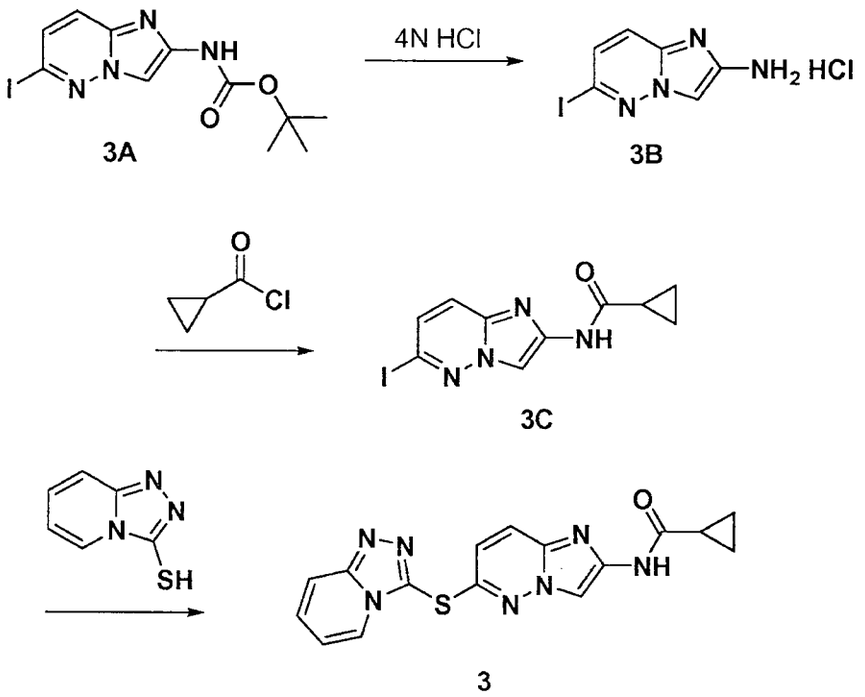
dried under vacuum to provide methyl 2-(2,2,2-trifluoroacetamido)imidazo[1,2-a]pyridine-6-carboxylate (**1B**) which was used without further purification.

[0409] 2,2,2-Trifluoro-N-(6-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)acetamide (1C): To a stirred solution of compound **1B** (470 mg, 1.64 mmol) in anhydrous THF (20 mL) were portion wise added lithium aluminum hydride (155 mg, 4.09 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the reaction was quenched with 0.16 mL of water, followed by 0.16 mL of 15% NaOH and 0.48 mL of water. The heterogenous reaction mixture was stirred for 0.5 h at room temperature and then filtered through celite. Residue was washed with THF. Filtrate and washings were concentrated and the crude residue was purified by column chromatography to furnish compound **1C** (220 mg, 52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.41 (s, 1H), 8.52 (s, 1H), 8.21 (s, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.25 (d, J = 9.6 Hz, 1H), 5.36 (t, *J*=5.6 Hz, 1 H) 4.48 (d, *J*=5.6 Hz, 2 H) ESI-MS:m/z 260.2 $(M+H)^+$..

[0410] N-(6-((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)methyl)imidazo[1,2-a]pyridin-2-yl)-2,2,2-trifluoroacetamide and N-(6-((1H-[1,2,3]triazolo[4,5-b]pyridin-1-yl)methyl)imidazo-[1,2-a]pyridin-2-yl)-2,2,2-trifluoroacetamide (1 and 2): To a stirred solution of compound **1C** (30 mg, 0.12 mmol) in anhydrous THF (3.0 mL) were sequentially added compound **1D** (28 mg, 0.23 mmol) and triphenyl phosphine (61 mg, 0.23 mmol). The reaction mixture was cooled to 0°C, and to it diisopropyl-azodicarboxylate (0.05 mL, 0.23 mmol) was added in drop wise manner. After the addition was over, stirring continued for another 0.5 h at 0°C and then for 12 h at room temperature. Solvents were removed in vacuum and the residue was purified by preparative HPLC to provide compounds 1 and 2 as TFA salts. ESI-MS for both compounds:m/z 362.1 $(M+H)^+$.

Compound 3: N-(6-([1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclo-propanecarboxamide

Method A



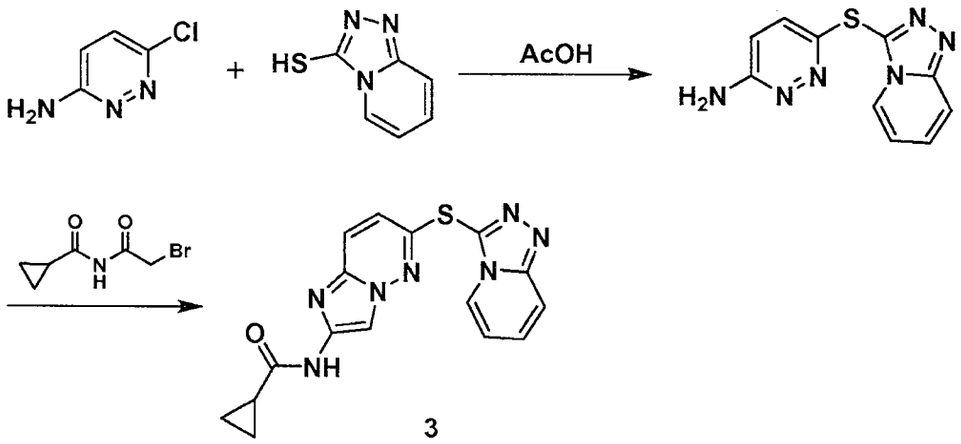
[0411] 6-iodoimidazo[1,2-*b*]pyridazin-2-amine hydrochloride (3B): Compound **3B** was synthesized according to a procedure analogous to that described in International Patent Publication No. WO 2008/06192 (Takeda Pharmaceutical Company Limited), which is incorporated by reference herein in its entirety. Specifically, tert-butyl 6-iodoimidazo[1,2-b]pyridazin-2-ylcarbamate (**3A**, 5.9 g, 16.38 mmol) was dissolved in 4N HCl in dioxane (60 mL) and stirred at ambient temperature for 4 hours. Ether (140 mL) was added to the reaction and a brown precipitate formed. The precipitate was filtered and washed with ether to give 6-iodoimidazo[1,2-b]pyridazin-2-amine hydrochloride in quantitative yield. This material was used without purification. ESI-MS:m/z 261.0 $(M+H)^+$.

[0412] N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (3C): Compound **3C** was synthesized according to a procedure analogous to that described in International Patent Publication No. WO 2008/06192 (Takeda Pharmaceutical Company Limited), which is incorporated by reference herein in its entirety. 6-Iodoimidazo[1,2-b]pyridazin-2-amine hydrochloride (4.45 g, 17.11 mmol) and cyclopropanecarbonyl chloride (1.35 mL, 18.82 mmol) were dissolved in DMA (85 mL) and stirred for 3 hours at ambient temperature. The reaction mixture was then poured into water (400 mL) resulting in the formation of a brown precipitate. The solid was filtered and dried under vacuum to give N-

(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (4.2 g, 77%). ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.21 (s, 1 H), 8.26 - 8.17 (m, 1 H), 7.74 (d, *J* = 9.3 Hz, 1 H), 7.49 (d, *J* = 9.1 Hz, 1 H), 2.07 - 1.87 (m, 1 H), 0.97 - 0.77 (m, 4 H) ESI-MS:m/z 329.1 $(M+H)^+$.

[0413] ***N*-(6-([1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-yl)cyclopropanecarboxamide (3):** N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (0.5 g, 1.52 mmol), [1,2,4]triazolo[4,3-*a*]pyridine-3-thiol (0.23 g, 1.52 mmol), Tris(dibenzylideneacetone)dipalladium(0) (84 mg, 0.09 mmol), 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (106 mg g, 0.18 mmol), and DIEA (0.531 mL, 3.05 mmol) were dissolved in DME (15.2 mL) and heated in a microwave at 120°C for 30 min. The reaction mixture was concentrated to dryness, reconstituted in DMSO, and purified by preparative LCMS to give *N*-(6-([1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-yl)cyclopropanecarboxamide (1 g, 43 %) as a TFA salt. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.17 (s, 1 H), 8.57 - 8.44 (m, 1 H), 8.03 - 7.94 (m, 1 H), 7.96 - 7.88 (m, 2 H), 7.59 (ddd, *J* = 1.0, 6.6, 9.3 Hz, 1 H), 7.22 - 7.11 (m, 1 H), 7.11 - 7.03 (m, 1 H), 1.97 - 1.84 (m, 1 H), 0.83 - 0.73 (m, 4 H) ESI-MS:m/z 352.3 $(M+H)^+$. MP 193-195°C.

Method B



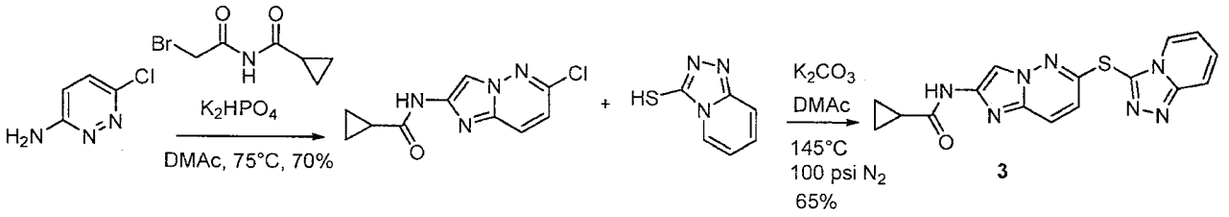
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[0414] ***6-([1,2,4]Triazolo[4,3-a]pyridin-3-ylsulfanyl)-pyridazin-3-ylamine***: A reaction mixture of [1,2,4]triazolo[4,3-a]pyridine-3-thiol (8.49 g, 55.0 mmol) and 6-chloropyridazin-3-amine (6.82 g, 50 mmol) in acetic acid (100 mL) was heated at 80°C for 20 hrs. The reaction was stripped to dryness via rotary evaporation and the resulting material was suspended in H_2O (100 mL). To this suspension, solid Na_2CO_3 was added in portions until pH 10 was achieved and then the mixture was sonicated. The resulting solid was collected by filtration and rinsed thoroughly with water followed by ethyl ether. The solid was dried in

vacuum over P_2O_5 to provide the title compound, 6-([1,2,4]Triazolo[4,3-a]pyridin-3-ylsulfanyl)-pyridazin-3-ylamine, as a white power (11.0 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.15 - 7.25 (m, 1 H) 7.53 - 7.58 (m, 1 H) 7.61 (ddd, *J*=9.22, 6.69, 1.26 Hz, 1 H) 7.84 - 7.90 (m, 1 H) 7.99 (dt, *J*=9.09, 1.01 Hz, 1 H) 8.51 (dt, *J*=7.01, 1.04 Hz, 1 H) 8.79 (br. s., 2 H). ESI-MS:m/z 553.2 $(M+H)^+$.

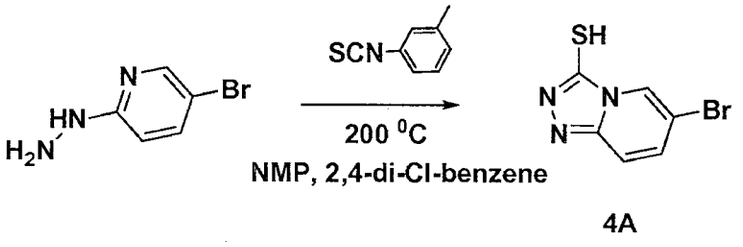
[0415] ***N-(6-([1,2,4]Triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide***: A mixture of 6-([1,2,4]triazolo[4,3-a]pyridin-3-ylthio)pyridazin-3-amine (2.443 g, 10 mmol), N-(2-bromoacetyl)cyclopropanecarboxamide (3.09 g, 15.00 mmol), potassium hydrogenphosphate (5.23 g, 30.0 mmol) and potassium iodide (0.830 g, 5.00 mmol) in DMA (100 mL) was stirred at 120°C for 2 hrs. Additional amounts of N-(2-bromoacetyl)cyclopropanecarboxamide (2.06 g, 10 mmol) and potassium hydrogenphosphate (1.74g, 10 mmol) were added to the mixture and the reaction was stirred at 120°C for another 2 hrs. The reaction was then stirred at room temperature overnight. The reaction mixture was again stirred at 140°C for 3 hrs and then cooled to room temperature. The resulting solid was filtered off and rinsed with DMA. The filtrate was concentrated to 100 mL and then poured into water (300 mL). The resulting precipitate was collected by filtration and rinsed thoroughly with water. The solid material was re-suspended in 10%MeOH/CH2Cl2 (100 mL), sonicated, refluxed for 30 min and cooled to room temperature. The MeOH/CH2Cl2 solution was filtered through a silica plug, rinsed with 10% MeOH/CH2Cl2 (200 mL). To above organic solution, activated charcoal (0.5g) was added, the solution was refluxed for 30 min, and then stirred at room temperature overnight. The charcoal was filtered through Celite, and the filtrate was concentrated to dryness to provide an off white solid. This solid was refluxed in MeOH (10 mL) for 30 min. and cooled to room temperature. The resulting off white solid was collected by filtration, rinsed with MeOH (2 mL) and dried in vacuum to provide the title compound, N-(6-([1,2,4]Triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (1.2 g). ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.17 (s, 1 H), 8.57 - 8.44 (m, 1 H), 8.03 - 7.94 (m, 1 H), 7.96 - 7.88 (m, 2 H), 7.59 (ddd, *J* = 1.0, 6.6, 9.3 Hz, 1 H), 7.22 - 7.11 (m, 1 H), 7.11 - 7.03 (m, 1 H), 1.97 - 1.84 (m, 1 H), 0.83 - 0.73 (m, 4 H) ESI-MS:m/z 352.3 $(M+H)^+$. MP 193-195°C.

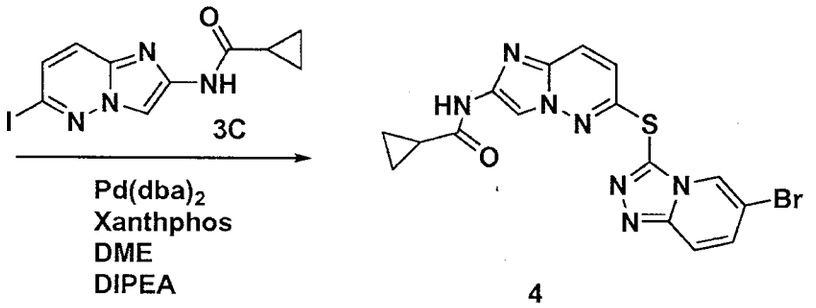
Method C



[0416] 6-Chloropyridazin-3-amine, N-(2-bromoacetyl)cyclopropanecarboxamide, and potassium hydrogenphosphate were mixed in DMA at 75°C to provide N-(6-chloroimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide. N-(6-chloroimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide was reacted with [1,2,4]triazolo[4,3-a]pyridine-3-thiol and K_2CO_3 in DMA at 145 °C and 100 psi N_2 to provide N-(6-([1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclo-propanecarboxamide.

Compound 4: N-(6-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

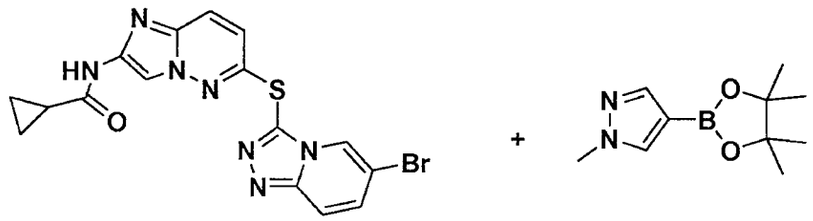




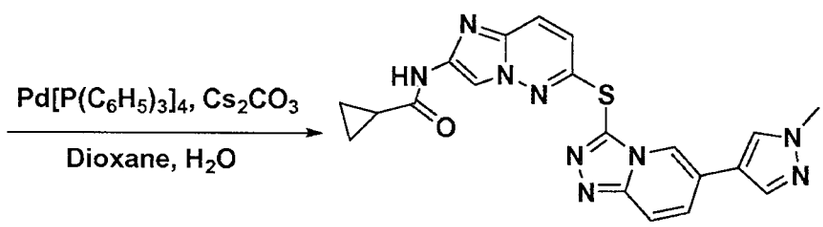
[0417] **6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-thiol (4A):** To the suspended solution of 5-Bromo-2-hydrazinylpyridine (1.85g, 10mmol) in a mixture of 1,4-dichlorobenzene and NMP (5:1, 10 ml) was added isothiocyanato-3-methylbenzene (1.5g 10mmol). The mixture was stirred at rt for 5 min, 70 °C for 15 min, and then heated under microwave condition at 200 °C for 1.5 h. The mixture was poured into Ether (20 mL). Solid was filtered and the washed with ether to give title product.

[0418] N-(6-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (4): To a sealed tube packed with N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (100 mg, 0.3 mmol), compound **4A**, $Pd(dba)_2$ (3%/mol), xanthphos (5%/mol) and DIPEA (1.5 mmol) was added DME (2mL). After degas under vacuum, the mixture was heated under microwave condition at 125 °C for 30 min. The mixture was purified by LCMS to give the title compound as a TFA salt. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ ppm 8.5 (s, 1 H), 8.1 (s, 1 H), 7.8 (d, *J*=9.8 Hz, 1 H), 7.7 (d, *J*=9.2 Hz, 2 H), 7.60 (d, *J*=9.6 Hz, 1 H), 7.1 (d, *J*=9.36 Hz, 1 H), 1.7 (m, 1 H), 1.05 (m, 2 H), 0.90 (m, 2H) ESI-MS:m/z 430.2 $(M+H)^+$.

Compound 5: N-(6-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)-imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



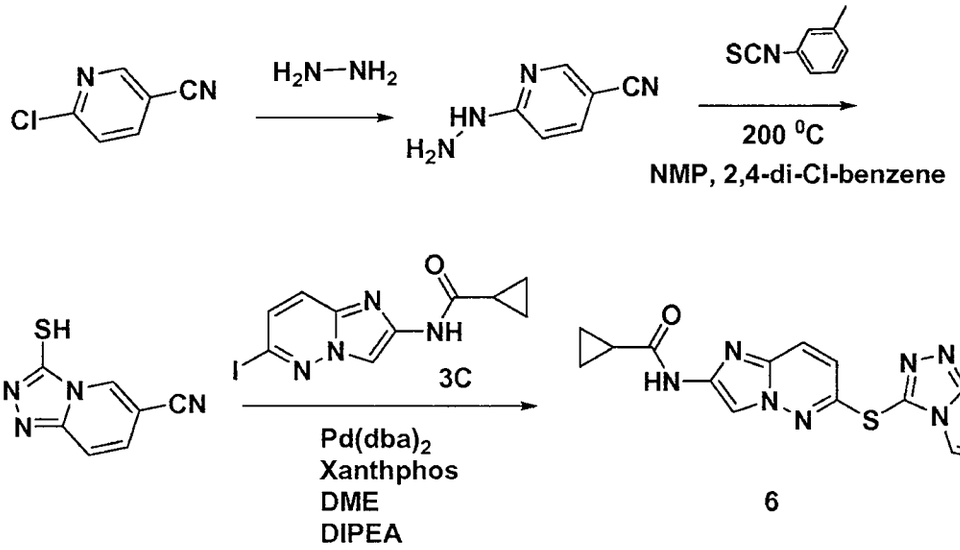
4



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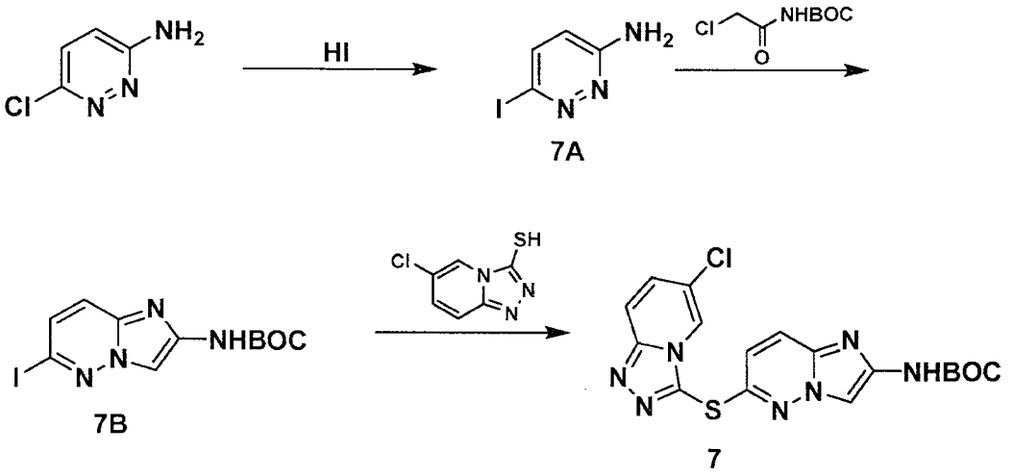
[0419] A of mixture Compound **4** (15mg, 0.35 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (11mg, 0.52mmol), Cs_2CO_3 (350mg), and tetrakis(triphenylphosphine)palladium(0) (*i.e.*, $Pd[P(C_6H_5)_3]_4$) (1%/mol) in dioxane-H_2O (20:1, 1.5 mL) was heated under micro wave condition at 140 °C for 30min. The mixture was purified by LCMS to give title compound as a TFA salt. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ ppm 8.33 (s, 1 H), 8.14(s, 1 H), 7.75 (s, 1H), 7.70 (s, 1H), 7.67 (d, *J*=9.5 Hz, 1 H), 7.56 (dd, *J*=9.4 and 1.6 Hz, 1 H), 7.06 (d, *J*=9.4 Hz, 1 H), 3.96 (s, 3 H), 1.67 (m, 1 H), 1.06 (m, 2 H), 0.90 (m, 2H) ESI-MS:m/z 432.2 $(M+H)^+$.

Compound 6: N-(6-(6-cyano-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0420] To a suspended mixture of 6-chloronicotinonitrile (7g, 50.8 mmol) in EtOH(50 mL), was added NH_2NH_2 (10g, 310.2mmol). The mixture was stirred at room temperature for 10 min, and then 60 °C for 5h. The mixture was cooled to room temperature. The solids were filtered out, washed with water and dried under high vacuum to give 6-hydrazinylnicotinonitrile (3.5g). Compound **6** was prepared from 6-hydrazinylnicotinonitrile following the procedure of the synthesis of compound **4**. ^{1}H NMR (400 MHz, CDCl3-CD3OD 10:1) δ ppm 11.37 (s, 1H), 8.70 (t, *J*= 1.2 Hz, 1 H), 8.14 (s, 1H), 8.11(dd, *J*= 1.04 and 9.52 Hz, 1 H), 7.96 (dd, *J*= 1.12 and 9.52 Hz, 1 H), 7.61 (dd, *J*= 1.52 and 9.48 Hz, 1 H), 7.38 (d, *J*=9.0 Hz, 1 H), 1.77 (m, 1 H), 1.06 (m, 2 H), 0.90 (m, 2H) ESI-MS:m/z 377.2 $(M+H)^+$.

Compound 7: *tert*-butyl 6-(6-chloro-[1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-ylcarbamate

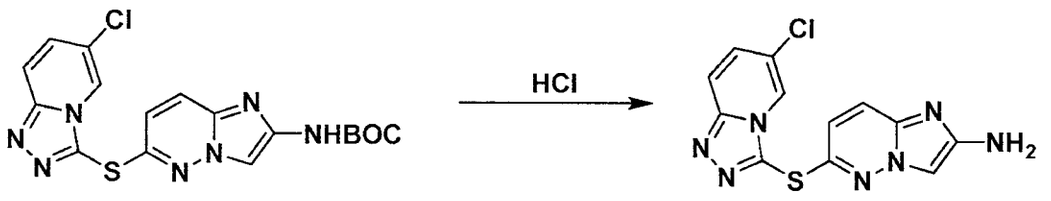


[0421] **6-iodopyridazin-3-amine (7A):** Compound **7A** was synthesized according to a procedure analogous to that described in International Patent Publication No. WO 2007/30366 (Smithkline Beecham Corporation), which is incorporated by reference herein in its entirety. Specifically, 6-chloropyridazin-3-amine (10.0 g, 77.2 mmol) was mixed with hydroiodic acid (78 mL, aqueous 57%) and heated to 100 °C overnight. Ethyl acetate (50mL) was added after the reaction was cooled to room temperature. The resulting mixture was sonicated and filtered. The filter cake was washed with copious amounts of ethyl acetate. The crude material was then dried under high vacuum to give 6-iodopyridazin-3-amine (**7A**; 24 g, 89 %) as bright yellow solid, which was used without further purification. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 8.36 - 8.08 (m, 1 H), 7.95 (d, J = 9.6 Hz, 1 H), 7.12 - 7.03 (m, 1 H). ESI-MS:m/z 221.9 $(M+H)^+$.

[0422] ***Tert*-butyl 6-iodoimidazo[1,2-*b*]pyridazin-2-ylcarbamate (7B):** A mixture containing compound **7A** (2.5 g, 11.3 mmol), *tert*-butyl 2-chloroacetylcarbamate (2.4 g, 12.4 mmol), sodium hydrogen phosphate (3.2 g, 22.6 mmol) and DMA (23 mL) was heated at 120°C for two hours. The mixture was cooled to room temperature, poured into a flask containing 400 mL of water and sonicated. The solids were filtered, rinsed with water then dried under vacuum. The solids were then taken up in 600 mL ethyl acetate and filtered over short plug of silica gel. The filtrate was concentrated down to give compound **7B** (1.6 g, 39 %), as a dark green solid, which was used without further purification. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 10.21 (br. s., 1 H), 8.06 - 8.00 (m, 1 H), 7.69 (d, J = 9.9 Hz, 1 H), 7.46 (d, J = 9.3 Hz, 1 H), 1.48 (s, 9 H) ESI-MS:m/z 361.1 $(M+H)^+$.

[0423] ***Tert*-butyl 6-(6-chloro-[1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-ylcarbamate (7):** Combined compound **7B** (50 mg, 0.14 mmol), 6-chloro-[1,2,4]triazolo[4,3-a]pyridine-3-thiol (28 mg, 0.15 mmol), Tris(dibenzylideneacetone)dipalladium(0) (11 mg, 0.01 mmol), 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (14 mg, 0.025 mmol), DIEA (48 uL, 0.28 mmol) and DME (1.4 mL) and heated in a microwave unit at high absorbance, 120°C for 30 min. The resulting crude material was purified by silica gel using 5% MeOH in DCM. The cleanest fractions were concentrated to give compound **7** (0.06 g; quantitative yield). ^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 10.18 (br. s., 1 H), 8.86 - 8.82 (m, 1 H), 8.11 - 8.05 (m, 1 H), 7.89 (d, J = 9.3 Hz, 1 H), 7.73 (s, 1 H), 7.66 (dd, J = 1.9, 9.7 Hz, 1 H), 7.09 (d, J = 9.6 Hz, 1 H), 1.48 - 1.41 (m, 9 H) ESI-MS:m/z 418.2.0 $(M+H)^+$.

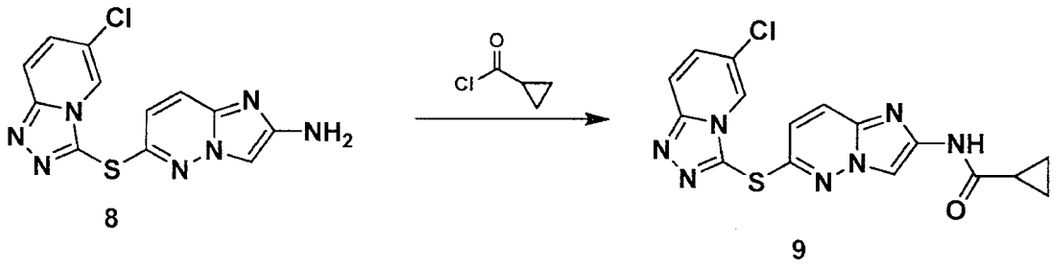
Compound 8: 6-(6-chloro-[1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-amine



7 8

[0424] Compound **7** (0.15 g, 0.42 mmol) and 4N HCl in dioxane (2 mL) was combined and stirred at RT for 2 hours to yield compound **8**. The crude reaction mixture was concentrated and used without purification. ESI-MS:m/z 318.2 $(M+H)^+$.

Compound 9: *N*-(6-(6-chloro-[1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-yl)cyclopropanecarboxamide

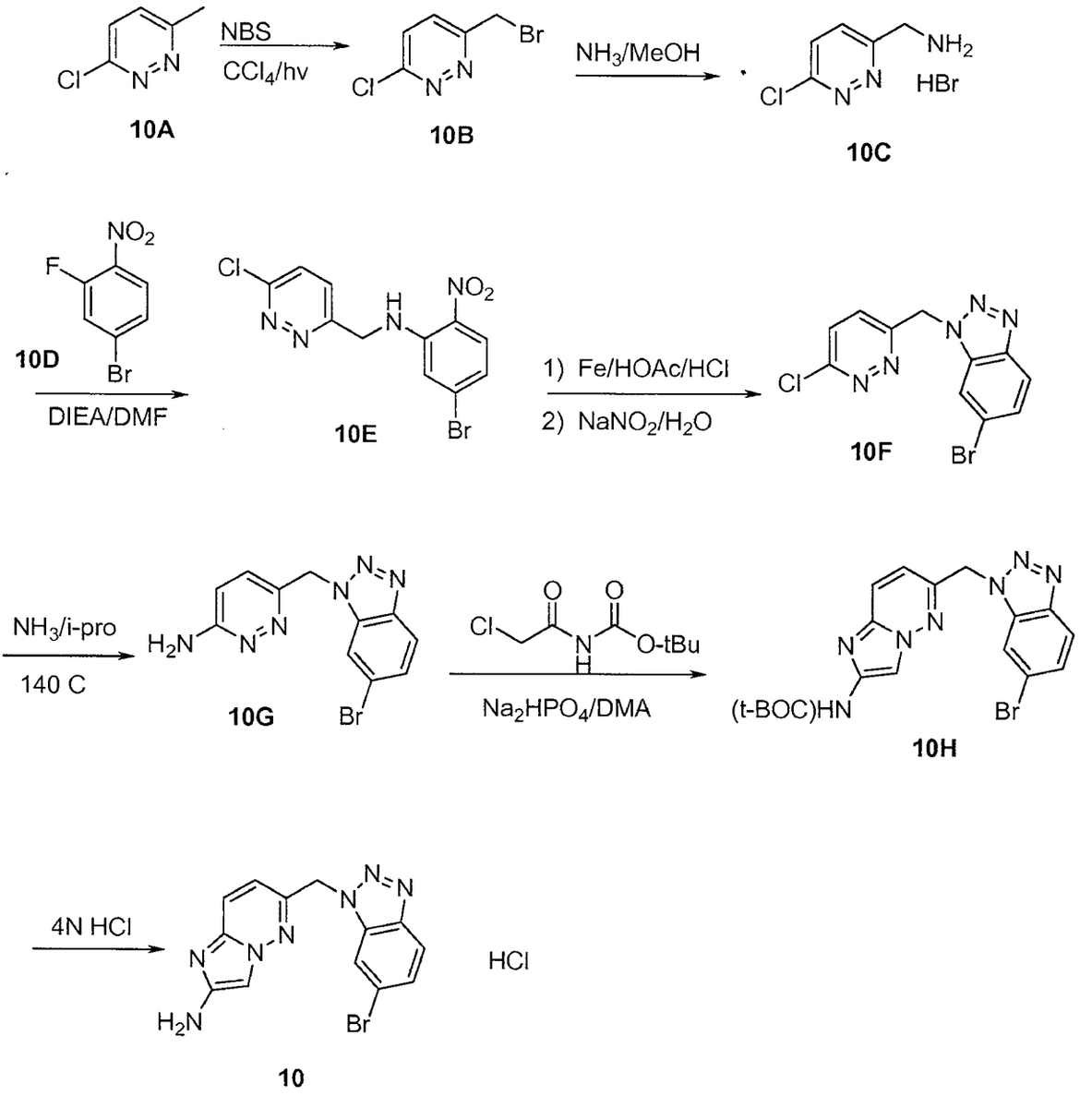


8 9

[0425] Compound **8** (0.13 g, 0.41 mmol), cyclopropanecarbonyl chloride (112 uL, 1.23 mmol), triethylamine (690 mL, 4.9 mmol) and DCE (2 mL) were combined and stirred for 2

hours to yield compound **9**. The reaction mixture was concentrated and purified by preparative LC. ESI-MS:m/z 386.3 $(M+H)^+$.

Compound 10: 6-(6-Bromo-benzotriazol-1-ylmethyl)-imidazo[1,2-b]pyridazin-2-ylamine hydrochloride



[0426] 3-Bromomethyl-6-chloro-pyridazine (10B): A solution of 3-Chloro-6-methyl-pyridazine **10A** (5.12 g, 40 mmol) and NBS (8.90g, 50 mmol) in CCl_4 (300 mL) was refluxed under light (200 w) for 4 hours. The reaction mixture was cooled to room temperature and filtered. The solid residue was washed thoroughly with Cl_4C and filtered. The filtrates was combined, concentrated to small volume and loaded on to a silica gel column. The column

was eluted with 50% hexane/ ethyl acetate to give 2.2g of desired product (**10B)** which was dried in vacuum and used immediately in next step. ESI-MS:m/z 206.9 $(M+H)^+$.

[0427] **C-(6-Chloro-pyridazin-3-yl)-methylamine Hydrobromide (10C):** A solution of compound **10B** (2.08g, 10 mmol) in methanol (50 mL) was added into a pre-saturated ammonia/methanol solution (200 mL) at 0 °C. The reaction solution was sealed and stirred at room temperature overnight. The methanol solution was concentrated and dried in vacuum to give 2.2 g of crude product (**10C**) as hydrobromide salt, which was used in next step without further purification. ESI-MS:m/z 144.1 $(M+H)^+$.

[0428] **(5-Bromo-2-nitro-phenyl)-(6-chloro-pyridazin-3-ylmethyl)-amine (10E):** A solution of compound **10C** (1.00 g, 4.46 mmol) and 4-bromo-2-fluoro-1-nitro-benzene (**10D**) (0.97g, 4.40 mmol) in DMF (50 mL) with DIEA (1.30 g, 10 mmol) was stirred at 65 °C for two hours. The reaction was poured into ice/water and the solid precipitate was collected by filtration, washed with water and dried in vacuum over P_2O_5 overnight to give 1.5 g of desired product (**10E**). ESI-MS:m/z 342.9 $(M+H)^+$.

[0429] **6-Bromo-1-(6-chloro-pyridazin-3-ylmethyl)-1H-benzotriazole (10F):** To a solution of compound **10E** (1.40 g, 4.08 mmol) in HOAc/HCl (50/5 mL) was added iron power (2.2 g, 40 mmol). The reaction mixture was stirred at 50 °C for 30 minutes, then cooled to room temperature and filtered. A solution of $NaNO_2$ (0.35 g, 5 mmol) in water (2 mL) was then added drop wise into above acid solution at 0 °C. The reaction solution was stirred for one hour and concentrated to dryness under reduced pressure. The resulting residue was sonicated in ethyl acetate/$NaHCO_3$ solution and the precipitate was filtered off and rinsed thoroughly with ethyl acetate. The organic solution was separated and dried with $MgSO_4$, filtered and concentrated to give 1.2 g of desired product (**10F**). ESI-MS:m/z 323.9 $(M+H)^+$.

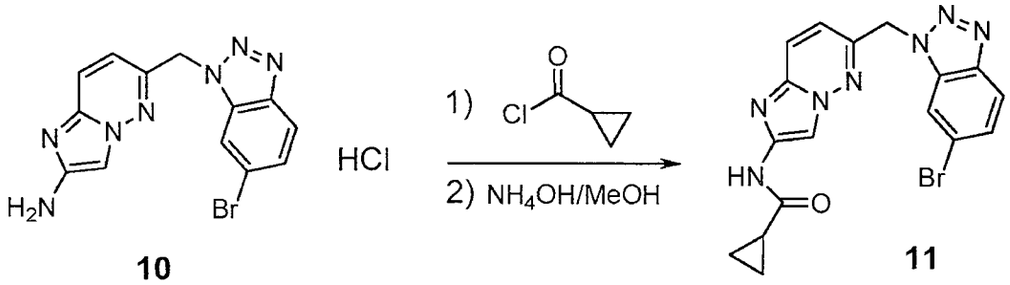
[0430] **6-(6-Bromo-benzotriazol-1-ylmethyl)-pyridazin-3-ylamine (10G):** To a suspension of compound **10F** (1.2g, 3.7 mmole) in isopropanol (15 mL) in a stainless pressure tube, an ammonia gas was bubbled through at -78 °C for 5 minutes. The pressure tube was sealed and heated in an oil bath at 140 °C for three days. The reaction solution was then re-cooled, transferred to a round bottle, concentrated and dried in vacuum to give 1.3 g of crude product (**10G**), which was used in next step without further purification. ESI-MS:m/z 305.1 $(M+H)^+$.

[0431] **[6-(6-Bromo-benzotriazol-1-ylmethyl)-imidazo[1,2-b]pyridazin-2-yl]-carbamic acid tert-butyl ester (10H):** A mixture of compound **10G** (1.0 g, 3.28 mmol), (2-chloro-

acetyl)-carbamic acid *tert*-butyl ester (1.0g, 5.0 mmol) and Na_2HPO_4 (1.4g, 10 mmol) in DMA (50 mL) was stirred at 135 °C for four hours. Solvent was removed under reduced pressure. The residue was sonicated in ethyl acetate/water, and the precipitate was filtered off. Ethyl acetate solution was separated and concentrated and loaded on silica gel. The silica column was eluted with hexane/ethyl acetate (1/2) to give 0.45 g of desired product (**10H**). ESI-MS:m/z 444.1 $(M+H)^+$.

[0432] 6-(6-Bromo-benzotriazol-1-ylmethyl)-imidazo[1,2-b]pyridazin-2-ylamine Hydrochloride (10): A solution of compound **10H** (0.44g, 1.0 mmol) in 4N HCl/dioxane (10mL) was stirred at room temperature for 60 minutes, concentrated and dried in vacuum to give 0.3 g of product (**10**) as a hydrochloride salt. ESI-MS:m/z 344.1 $(M+H)^+$.

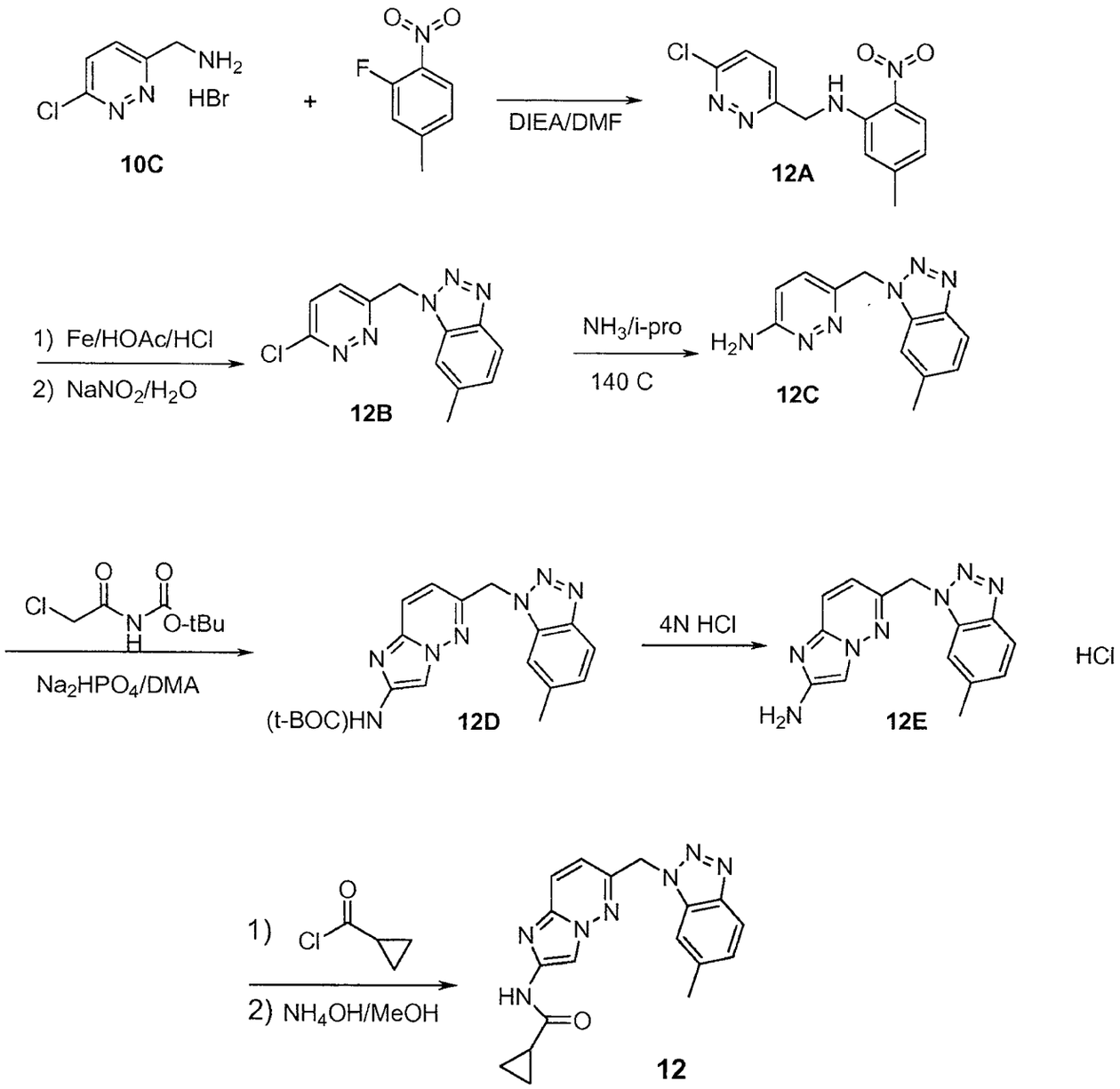
Compound 11: Cyclopropanecarboxylic acid [6-(6-bromo-benzotriazol-1-ylmethyl)-imidazo[1,2-b]pyridazin-2-yl]-amide



10 **11**

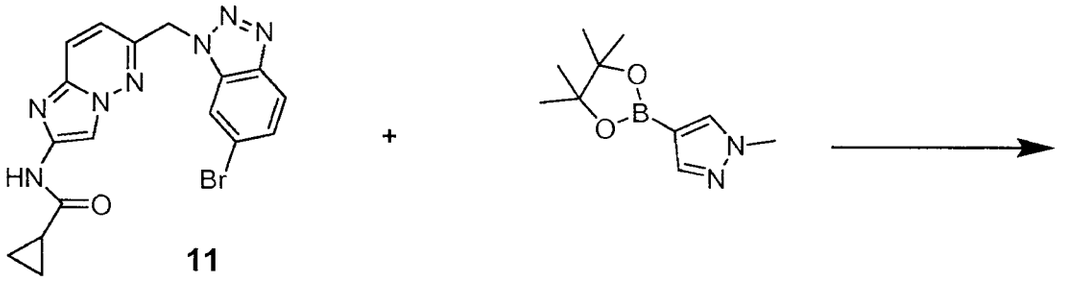
[0433] To a solution of compound **10** (0.34 g, 1 mmol) in CH_2Cl_2 (25 mL) was added DIEA (0.31g, 3 mmol), followed by cyclopropanecarbonyl chloride (0.23g, 2.2 mmol). The reaction solution was stirred at room temperature for 60 minutes and concentrated. The residue was re-dissolved in methanol (10 mL) and ammonium hydroxide (0.5 mL) was added. The reaction solution was stirred for 30 minutes and concentrated. The residue was dissolved in ethyl acetate and washed with 5% citric acid and then saturated $NaHCO_3$. The organic phase was dried with $MgSO_4$ and concentrated to give 0.25 g of desired product (**11**). ESI-MS:m/z 412.1 $(M+H)^+$.

Compound 12: N-(6-((6-methyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

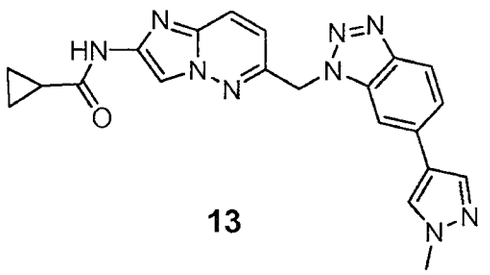


[0434] Compound **12E** was prepared using a similar procedure to that described in connection with compound **10**, except that 2-fluoro-4-methyl-1-nitro-benzene was used in place of compound **10D**. Compound **12** was then prepared from compound **12E** using the method described in connection with compound **11**. ^{1}H NMR (DMSO-d_6): δ ppm 11.20 (s, 1H), 8.20 (s,1H), 7.96 (m, 2H), 7.68 (s, 1H), 7.28 (d, 1H), 7.10 (d, 1H), 6.14 (s, 2H), 2.46 (s, 3H), 1.94 (m, 1H), 0.80 (m, 4H).

Compound 13: Cyclopropanecarboxylic acid {6-[6-(1-methyl-1H-pyrazol-4-yl)-benzotriazol-1-ylmethyl]-imidazo[1,2-b]pyridazin-2-yl}-amide



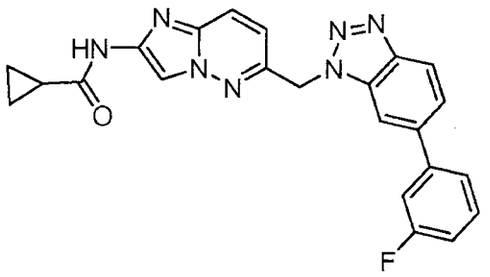
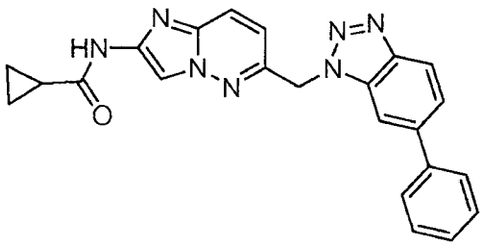
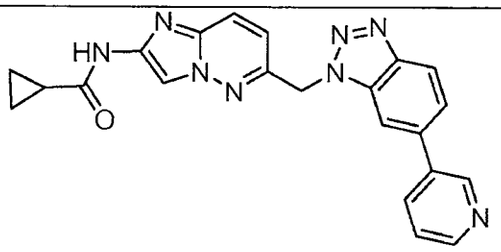
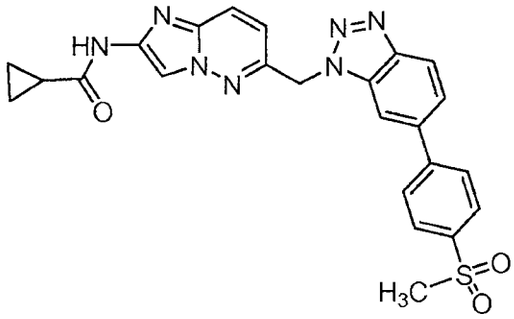
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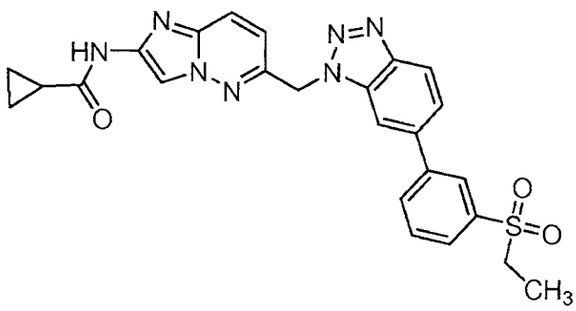
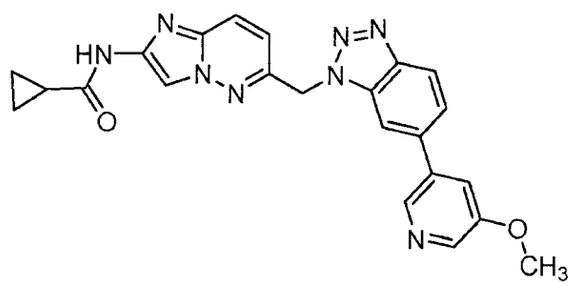
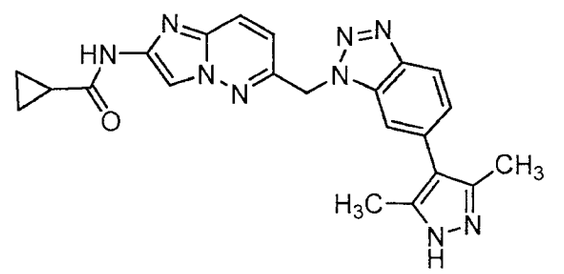


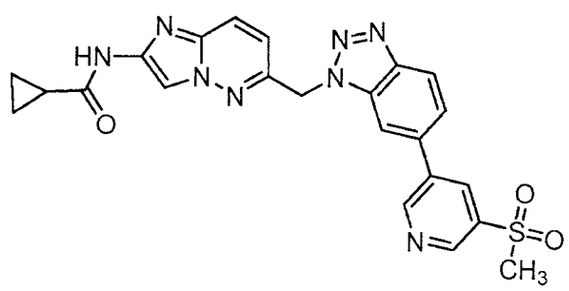
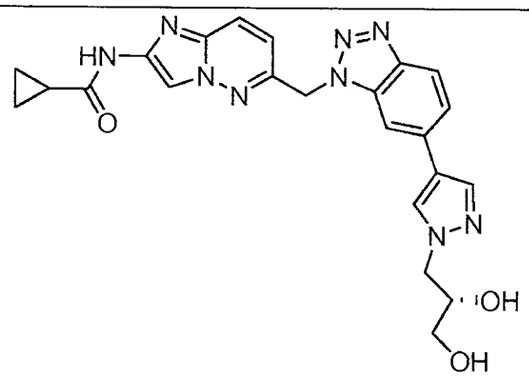
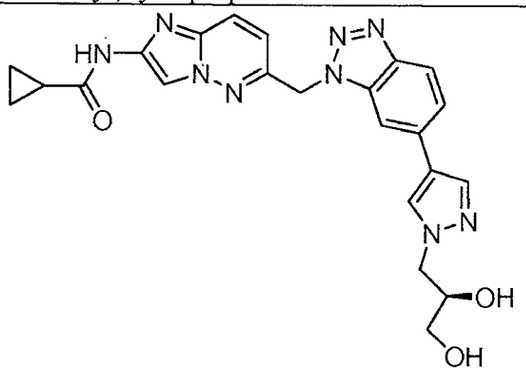
13

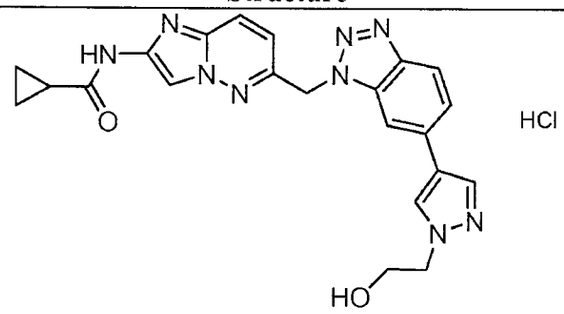
[0435] A mixture of compound **11** (20 mg, 0.05 mmol), 1-methylpyrazole-4-boronic acid pinacol ester (20 mg, 0.1 mmol) and catalytic amount of $Pd(dppf)Cl_2$ in a $NaHCO_3$ saturated dioxane/H2O (2/1) solution (0.5 mL) was heated using a microwave oven at 120 °C for 30 minutes. After preparative LCMS purification, 11 mg of the desired product was obtained as the TFA salt. ^1H NMR (DMSO-d_6): δ ppm 11.40 (s, 1H), 8.32 (s, 1H), 8.16 (s, 1H), 8.08 (s, 1H), 8.04 (d, 1H), 7.96 (m, 2H), 7.64 (m, 1H), 7.14 (d, 1H), 6.16 (s, 2H), 3.90 (s, 3H), 1.94 (m, 1H), 0.80 (m, 4H) ESI-MS:m/z 414.2 $(M+H)^+$.

[0436] In a similar manner as compound **13**, compounds **14-24** were synthesized and purified from compound **11** and the corresponding boronic acid or ester.

Compound	Structure	LC/MS	NMR
14	 N-(6-((6-(3-fluorophenyl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	427	^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.17 (s, 1 H), 8.40 - 8.28 (m, 1 H), 8.21 - 8.11 (m, 1 H), 7.97 (d, J = 9.3 Hz, 1 H), 7.86 - 7.78 (m, 1 H), 7.69 - 7.45 (m, 4 H), 7.31 - 7.21 (m, 1 H), 7.16 (d, J = 9.3 Hz, 1 H), 6.30 - 6.17 (m, 2 H), 1.92 (quin, J = 6.1 Hz, 1 H), 0.86 - 0.75 (m, 4 H)
15	 N-(6-((6-phenyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	409	^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.18 (s, 1 H), 8.24 (s, 1 H), 8.19 - 8.13 (m, 2 H), 7.97 (d, J = 9.3 Hz, 1 H), 7.81 - 7.73 (m, 3 H), 7.52 (t, J = 7.6 Hz, 2 H), 7.45 - 7.38 (m, 1 H), 7.16 (d, J = 9.1 Hz, 1 H), 6.28 - 6.19 (m, 2 H), 1.92 (quin, J = 6.1 Hz, 1 H), 0.85 - 0.78 (m, 4 H)
16	 N-(6-((6-(pyridin-3-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	410	---
17	 N-(6-((6-(4-(methylsulfonyl)phenyl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	487	^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.18 (s, 1 H), 8.39 (s, 1 H), 8.25 - 8.20 (m, 1 H), 8.14 (s, 1 H), 8.09 - 8.03 (m, 4 H), 7.98 (d, J = 9.9 Hz, 1 H), 7.86 - 7.80 (m, 1 H), 7.17 (d, J = 9.3 Hz, 1 H), 6.27 (s, 2 H), 3.28 (s, 3 H), 1.98 - 1.85 (m, 1 H), 0.85 - 0.77 (m, 4 H)

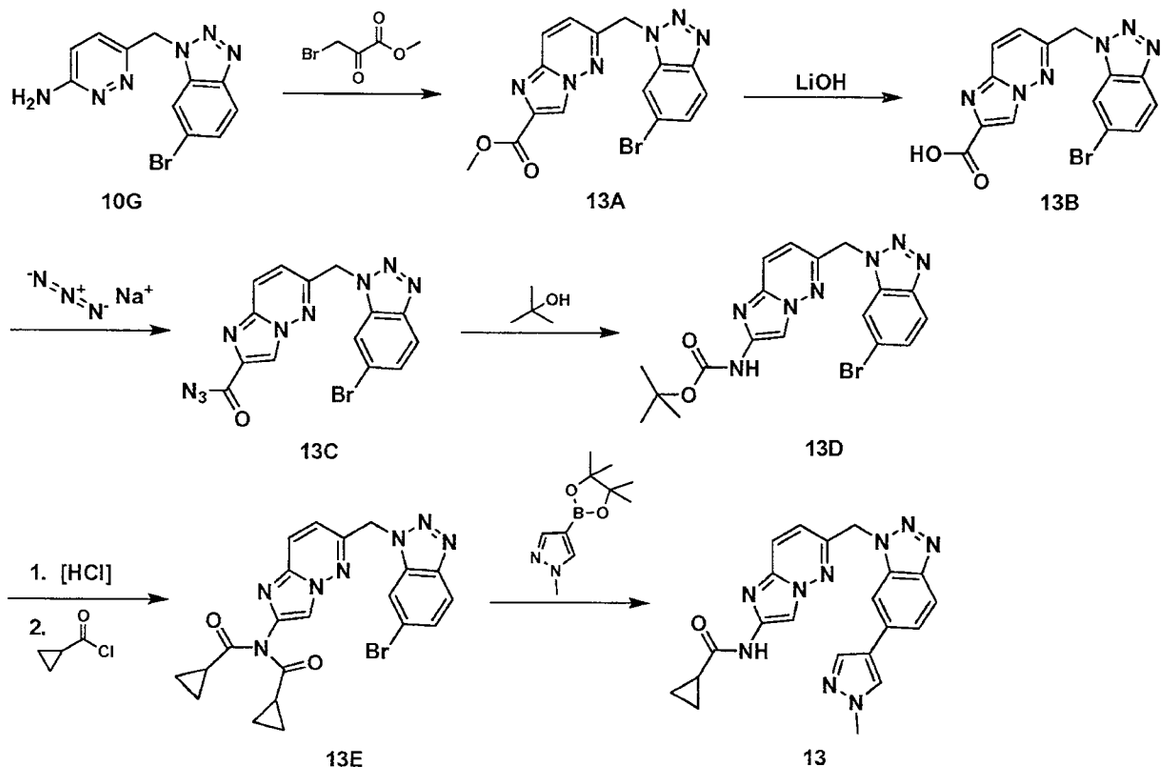
Compound	Structure	LC/MS	NMR
18	 N-(6-((6-(3-(ethylsulfonyl)phenyl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	501	^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.17 (s, 1 H), 8.39 (s, 1 H), 8.28 - 8.20 (m, 2 H), 8.13 (s, 2 H), 7.95 (dd, *J* = 8.7, 14.8 Hz, 3 H), 7.90 - 7.79 (m, 2 H), 7.15 (d, *J* = 9.3 Hz, 1 H), 6.28 (s, 2 H), 1.92 (d, *J* = 5.3 Hz, 1 H), 1.14 (t, *J* = 7.2 Hz, 4 H), 0.88 - 0.76 (m, 4 H)
19	 N-(6-((6-(5-methoxypyridin-3-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	440	^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.18 (s, 1 H), 8.64 (d, *J* = 1.8 Hz, 1 H), 8.47 - 8.36 (m, 2 H), 8.21 (d, *J* = 8.8 Hz, 1 H), 8.14 (s, 1 H), 7.98 (d, *J* = 9.3 Hz, 1 H), 7.91 - 7.79 (m, 2 H), 7.17 (d, *J* = 9.3 Hz, 1 H), 6.26 (s, 2 H), 3.97 - 3.93 (m, 3 H), 2.02 - 1.86 (m, 1 H), 0.83 - 0.78 (m, 4 H)
20	 N-(6-((6-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	427	^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.20 (s, 1 H), 8.17 (s, 1 H), 8.08 (d, *J* = 8.6 Hz, 1 H), 7.99 (d, *J* = 9.3 Hz, 1 H), 7.71 (s, 1 H), 7.44 - 7.35 (m, 1 H), 7.17 (d, *J* = 9.3 Hz, 1 H), 6.20 (s, 2 H), 2.26 - 2.16 (m, 6 H), 2.02 - 1.88 (m, 1 H), 0.90 - 0.77 (m, 4 H)

Compound	Structure	LC/MS	NMR
21	 N-(6-((6-(5-(methylsulfonyl)pyridin-3-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	488	^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.17 (s, 1 H), 9.35 (d, J = 2.0 Hz, 1 H), 9.19 - 9.04 (m, 1 H), 8.70 - 8.65 (m, 1 H), 8.54 (s, 1 H), 8.30 - 8.25 (m, 1 H), 8.18 - 8.10 (m, 1 H), 8.00 - 7.91 (m, 2 H), 7.17 (d, J = 9.3 Hz, 1 H), 6.29 (s, 2 H), 3.42 (s, 3 H), 1.96 - 1.86 (m, 1 H), 0.85 - 0.77 (m, 4 H)
22	 (S)-N-(6-((6-(1-(2,3-dihydroxypropyl)-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	474	^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.18 (s, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 8.14 (d, 2H), 8.00 (m, 3H), 7.70 (d, 1H), 7.20 (d, 1H), 6.16 (s, 2H), 4.26 (m, 1H), 4.10 (m, 1H), 3.34 (m,1H),1.94 (m, 1H), 0.83 (m, 4H).
23	 (R)-N-(6-((6-(1-(2,3-dihydroxypropyl)-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	474	^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.18 (s, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 8.14 (d, 2H), 8.00 (m, 3H), 7.70 (d, 1H), 7.20 (d, 1H), 6.16 (s, 2H), 4.26 (m, 1H), 4.10 (m, 1H), 3.34 (m,1H),1.94 (m, 1H), 0.83 (m, 4H)

Compound	Structure	LC/MS	NMR
24 [a]	 N-(6-((6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide hydrochloride	444	^{1}H NMR (DMSO-d_6): δ 11.21 (s, 1H), 8.30 (s, 1H), 8.20 (s, 1H), 8.12 (s, 1H), 8.02 (m, 3H), 7.70 (d, 1H), 7.14 (d, 1H), 6.16 (s, 2H), 4.17 (t, 2H), 3.77 (m, 2H), 1.94 (m, 1H), 0.83 (m, 4H)

a Melting point: > 200 °C.

Compound 13: N-(6-((6-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0437] Ethyl 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazine-2-carboxylate: A mixture of 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)pyridazin-3-amine **10G** (4.8 g, 15.73 mmol), ethyl 3-bromo-2-oxopropanoate (4.60 g, 23.60 mmol) and $NaHCO_3$ (4.0 g) in dioxane was heated at 60°C for 1 hr. Additional ethyl 3-bromo-2-oxopropanoate (1.5 g, 7.87 mmol, 0.5 eq) was added and stirred at 60°C for an additional hour. The reaction mixture was filtered and rinsed with dioxane. 4-

Methylbenzenesulfonic acid (2.71 g, 15.73 mmol) was added to the filtrate, and the reaction was heated at 75°C for 2 hrs. The reaction was evaporated to dryness via rotary evaporation and the resulting residue was dissolved in EtOAc. The organic phase was washed with saturated $NaHCO_3$ followed by 0.1 N NaOH (3x 150 mL). The solution was dried with $MgSO_4$, filtered, concentrated to dryness and purified by MPLC (10% MeOH/CH_2Cl_2) to provide the title compound, ethyl 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazine-2-carboxylate **13A** (4.7g, 11.6 mmol, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, *J*=7.07 Hz, 3 H) 4.30 (q, *J*=7.07 Hz, 2 H) 6.26 (s, 2 H) 7.33 (d, *J*=9.60 Hz, 1 H) 7.59 (dd, *J*=8.72, 1.64 Hz, 1 H) 8.08 (d, *J*=8.84 Hz, 1 H) 8.23 (d, *J*=9.60 Hz, 1 H) 8.31 (d, *J*=1.26 Hz, 1 H) 8.77 (s, 1 H). MS:m/z 401.2 $(M+H)^+$.

[0438] 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazine-2-carboxylic acid: To a solution of ethyl 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazine-2-carboxylate **13A** (5 g, 12.46 mmol) in 10% H_2O/MeOH (200 mL), LiOH (0.597 g, 24.92 mmol) was added. The reaction was stirred at ambient temperature for 18 hrs and then concentrated to remove the MeOH. H_2O (100 mL) was added and the pH was adjusted to 4 with concentrated HCl. The resulting solid was collected by filtration, rinsed with water followed by EtOAc, and dried in vacuum over P_2O_5 to provide the title compound, 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazine-2-carboxylic acid **13B** (3.6 g 9.65mmol, 77%). The filtrate was extracted with EtOAc (3 x 150 mL) and the organics were combined, dried with $MgSO_4$, filtered and concentrated to dryness to give an additional 0.6 g of product. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.24 (s, 2 H) 7.24 (d, *J*=9.35 Hz, 1 H) 7.58 (dd, *J*=8.84, 1.77 Hz, 1 H) 8.04 - 8.14 (m, 2 H) 8.32 (d, *J*=1.01 Hz, 1 H) 8.47 (s, 1 H). MS:m/z 373.2 $(M+H)^+$.

[0439] 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazine-2-carbonyl azide: To a stirred solution of 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazine-2-carboxylic acid **13B** (3.6 g, 9.65 mmol), N-ethyl-N-isopropylpropan-2-amine (7.48 g, 57.9 mmol) and sodium azide (6.27 g, 96 mmol) in anhydrous DMF (60 mL), PyBOP (6.02 g, 11.58 mmol) was added in portions at ambient temperature over 5 min. The reaction was stirred for another 30 min and then poured into a EtOAc/H_2O (100/300 mL) mixture and shaken well. The resulting precipitate was filtered, rinsed with H_2O followed by EtOAc, and dried in vacuum over P_2O_5 for 18 hrs to provide the title compound, 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-

b]pyridazine-2-carbonyl azide **13C** (2.1g, 5.28 mmol, 55%). The EtOAc solution washed with 5% citric acid (2 x100 mL), $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated to dryness to give additional crude product (1.6 g of 80% pure material). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.28 (s, 2 H) 7.37 (d, *J*=9.60 Hz, 1 H) 7.59 (dd, *J*=8.84, 1.77 Hz, 1 H) 8.09 (d, *J*=8.84 Hz, 1 H) 8.26 (d, *J*=10.10 Hz, 1 H) 8.32 (d, *J*=1.26 Hz, 1 H) 8.92 (s, 1 H). MS:m/z 398.2 $(M+H)^+$.

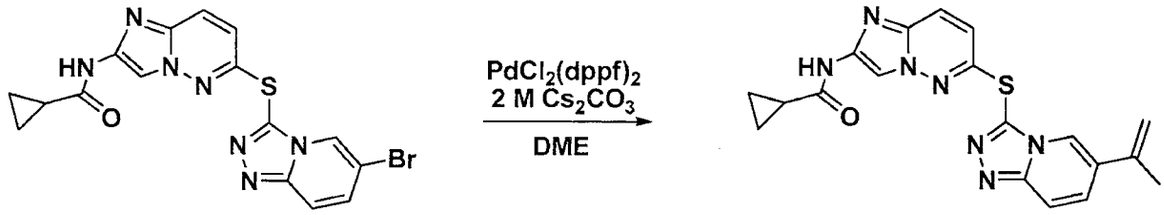
[0440] tert-Butyl 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-ylcarbamate: A suspension of 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazine-2-carbonyl azide **13C** (1 g, 2.51 mmol) in 2-methylpropan-2-ol (50mL, 753 mmol) was heated at 100°C in a microwave for 3 hrs. The reaction was repeated once. The reactions were combined and the solvent was removed via rotary evaporation. The resulting residue was suspended in EtOAc/H_2O and sonicated. The resulting solid was collected by filtration, rinsed with H_2O followed by EtOAc, and dried in vacuum over P_2O_5 to provide the title compound, tert-Butyl 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-ylcarbamate **13D** (1.7g, 3.83 mmol, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.47 (s, 9 H) 6.18 (s, 2 H) 7.13 (d, *J*=9.35 Hz, 1 H) 7.58 (dd, *J*=8.72, 1.64 Hz, 1 H) 7.94 (d, *J*=9.85 Hz, 2 H) 8.07 (d, *J*=8.84 Hz, 1 H) 8.31 (d, *J*=1.77 Hz, 1 H) 10.24 (br, 1 H). MS:m/z 444.2 $(M+H)^+$.

[0441] N-(6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)-N-(cyclopropanecarbonyl)cyclopropanecarboxamide: A mixture of tert-butyl 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-ylcarbamate **13D** (1.7 g, 3.83 mmol) in 4N HCl/dioxane (30 mL) was stirred at ambient temperature for 2 hrs. The solvent was removed via rotary evaporation, and the resulting residue was dried in vacuum for 18 hrs to yield the 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-amine as an HCl salt. This material was used without further purification. To a solution of 6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-amine HCl (1.8 g, 5.23 mmol) in CH_2Cl_2 was added N-ethyl-N-isopropylpropan-2-amine (2.70 g, 20.92 mmol) followed by cyclopropanecarbonyl chloride (1.640 g, 15.69 mmol) at 0°C. The reaction was stirred at ambient temperature for 2 hrs. The reaction was then washed with 5% citric acid solution followed by saturated $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated to dryness. The resulting residue was purified by MPLC (5% MeOH/CH_2Cl_2) to provide the title compound, N-(6-((6-bromo-1H-

benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)-N-(cyclopropanecarbonyl)cyclopropanecarboxamide **13E** (2.0 g, 4.1 mmol, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.75 - 0.86 (m, 8 H) 1.93 (m, 2 H) 6.19 (s, 2 H) 7.16 (d, J=9.35 Hz, 1 H) 7.51 - 7.64 (m, 1 H) 7.99 (d, J=9.35 Hz, 1 H) 8.01 - 8.10 (m, 1 H) 8.13 (s, 1 H) 8.31 (d, J=1.77 Hz, 1 H). MS:m/z 480.2 $(M+H)^+$.

[0442] N-(6-((6-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: A mixture of N-(6-((6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)-N-(cyclopropanecarbonyl)cyclopropanecarboxamide **13E** (0.7 g, 1.457 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.303 g, 1.457 mmol) and $PdCl_2$(dppf)- CH_2Cl_2 (0.06 g, 0.075 mmol) in Na_2CO_3 (2N, 6 mL)/dioxane (12 mL) was heated in a microwave at 110°C for 45 min. The reaction was filtered and rinsed with EtOAc. This reaction was repeated twice. The organic solutions were combined and washed with 5% citric acid followed by $NaHCO_3$, dried with $MgSO_4$, and filtered. MeOH was added to the EtOAc solution to give 5% MeOH (v/v), and the resulting solution was filtered through a short silica column and rinsed thoroughly with 5% MeOH/EtOAc. Activated charcoal (1 g) was added to the eluent and stirred at ambient temperature for 1 hr. The solution was filtered through Celite and concentrated to dryness via rotary evaporation. The resulting material was suspended in EtOAc (50 mL) and sonicated. The resulting solid was collected by filtration and rinsed with EtOAc to provide the title compound, N-(6-((6-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide **13** (820 mg, 1.98 mmol, 45%). The filtrate was concentrated and reconstituted in 10% MeOH/EtOAc, loaded on a short silica column and eluted with 10% MeOH/EA to give provide additional product (190 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.86 (m, 4 H) 1.88 - 1.97 (m, 1 H) 3.88 (s, 3 H) 6.15 (s, 2 H) 7.12 (d, J=9.35 Hz, 1 H) 7.66 (dd, J=8.72, 1.39 Hz, 1 H) 7.93 - 8.01 (m, 2 H) 8.04 (d, J=8.84 Hz, 1 H) 8.10 (s, 1 H) 8.17 (s, 1 H) 8.26 (s, 1 H) 11.18 (s, 1 H). MS:m/z 414.2 $(M+H)^+$. MP 250.2 - 251.6°C.

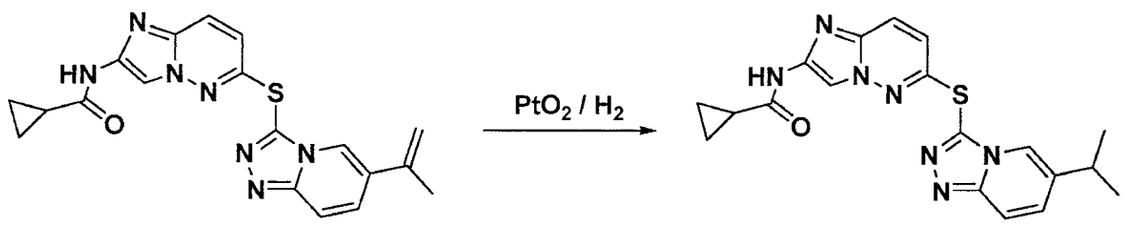
Compound 25: N-(6-(6-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



4 25

[0443] A of mixture Compound **4** (50 mg, 0.10 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (71 mg, 0.43 mmol), Cs_2CO_3 (3 M; 0.11 mL, 0.30 mmol), and $PdCl_2(dppf)_2$ (4.0 mg, 0.0005 mmol) in DME (1.0 mL) was heated in a microwave at 100 °C for 1 hr. The reaction mixture was then concentrated to dryness via rotary evaporation. The resulting crude material was reconstituted in DMSO (1.0 mL) and purified via preparative mass trigger LCMS using a gradient eluant of 25-50% ACN:0.05% TFA (aq). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting mixture was lyophilized to provide the TFA salt of the title compound. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.17 (s, 1 H) 8.31 (s, 1 H) 8.14(s, 1 H) 7.95 (s, 1H) 7.91 (d, *J*=9.5 Hz, 1 H) 7.64 (dd, *J*=9.4 and 1.6 Hz, 1 H) 7.05 (d, *J*=9.4 Hz, 1 H) 5.67 (s, 1 H) 5.29 (s, 1 H) 2.08 (m, 3 H) 1.89 (m, 1 H) 1.06 (m, 2 H) 0.90 (m, 2H) ESI-MS:m/z 391.1 $(M+H)^+$.

Compound 26: N-(6-(6-isopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

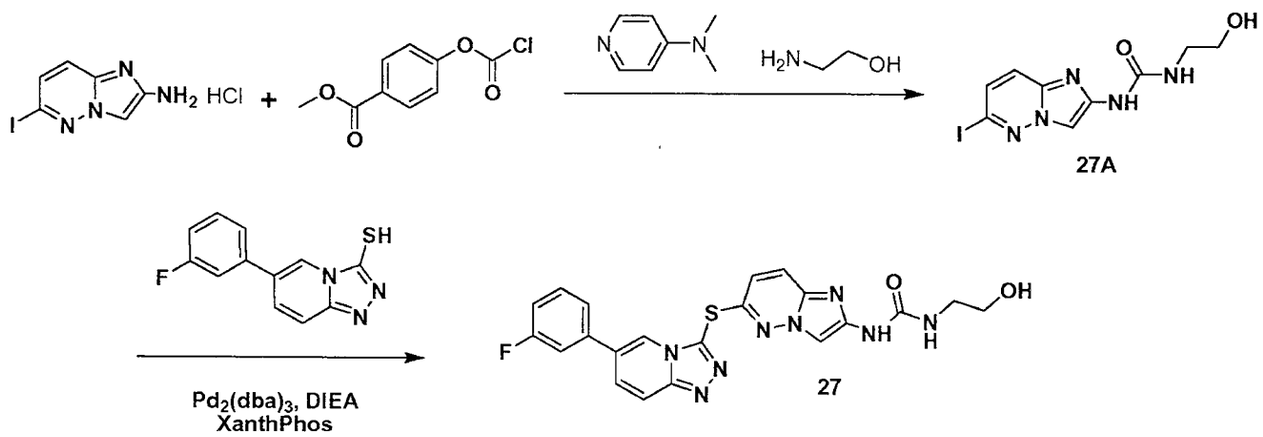


25 26

[0444] To a solution of N-(6-(6-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (150 mg, 0.383 mmol) in ethanol (20 mL) was added platinum (IV) oxide (4.35 mg, 0.019 mmol). The reaction was stirred for 24 hr at 25°C under 10 psi of H_2. The reaction mixture was then filtered through Celite and the filtrate was concentrated to dryness via rotary evaporation. The resulting crude material was reconstituted in DMSO (1.0 mL) and purified via preparative mass trigger

LCMS using a gradient eluant of 25-50% ACN:0.05% TFA (aq). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting mixture was lyophilized to provide the TFA salt of the title compound (6.0 mg, 0.015 mmol, 3.98 % yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 0.71 - 0.87 (m, 4 H) 1.19 (d, J=6.82 Hz, 6 H) 1.79 - 1.98 (m, 1 H) 3.02 (dt, J=13.71, 6.92 Hz, 1 H) 7.03 (d, J=9.35 Hz, 1 H) 7.62 (dd, J=9.47, 1.64 Hz, 1 H) 7.90 - 7.97 (m, 3 H) 8.26 (s, 1 H) 11.17 (s, 1 H). ESI-MS:m/z 394.3 $(M+H)^+$.

Compound 27: 1-(6-(6-(3-fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)-3-(2-hydroxyethyl)urea

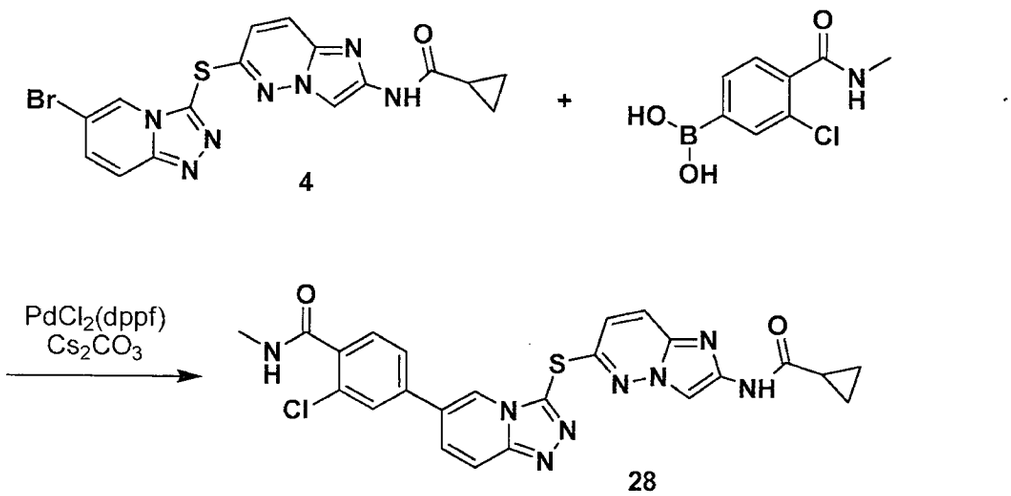


[0445] 1-(2-Hydroxyethyl)-3-(6-iodoimidazo[1,2-b]pyridazin-2-yl)urea: To a solution of 6-iodoimidazo[1,2-b]pyridazin-2-amine hydrochloride (250 mg, 0.843 mmol) and DMAP (227 mg, 1.855 mmol) in DCM (Volume: 5.0 mL) was added methyl 4-(chlorocarbonyloxy)benzoate (199 mg, 0.927 mmol) at 25°C. The reaction was stirred at 25°C for 1 hr to provide a dark green heterogeneous mixture which was filtered. The solid was resuspended in DCM (Volume: 5.0 mL), treated with ethanolamine (2M in MeOH, 0.843 mL, 1.686 mmol) at room temperature, and then stirred for an additional 1 hr. The reaction was then evaporated to dryness via rotary evaporation, and the resulting residue was suspended in EtOAc (Volume: 10.0 mL). The mixture was filtered, and the resulting black solid was dried under high vacuum and used without further purification.

[0446] 1-(6-(6-(3-Fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)-3-(2-hydroxyethyl)urea : A mixture of 1-(2-hydroxyethyl)-3-(6-iodoimidazo[1,2-b]pyridazin-2-yl)urea (125 mg, 0.360 mmol), 6-(3-fluorophenyl)-

[1,2,4]triazolo[4,3-a]pyridine-3-thiol (88 mg, 0.360 mmol), $Pd_2(dba)_3$ (19.79 mg, 0.022 mmol), XANTPHOS (25.00 mg, 0.043 mmol), and DIEA (0.126 mL, 0.720 mmol) in DME (Volume: 2.0 mL) was heated in the microwave on high absorbance for 30 min at 120°C. The reaction mixture was then concentrated to dryness via rotary evaporation. The resulting crude material was reconstituted in DMSO (Volume: 1.0 mL) and purified via preparative mass trigger LCMS using a gradient eluant of 20-45% ACN:0.05% TFA (aq). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting mixture was lyophilized and reconstituted in water:ACN (1:10, 5.0 mL) Two drops of [HCl] were added and the resulting solution was lyophilized to provide the HCl salt of the title compound (20 mg, 0.043 mmol, 11.96 % yield) as a brown solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 3.14 (q, J=5.47 Hz, 2 H), 341 (m, 2 H), 6.61 (br. s., 1 H) 6.97 - 7.07 (m, 2 H) 7.21 - 7.32 (m, 1 H) 7.53 (td, J=7.96, 6.06 Hz, 1 H) 7.62 (d, J=8.34 Hz, 1 H) 7.65 - 7.72 (m, 1 H) 7.83 (d, J=9.35 Hz, 1 H) 7.99 (dd, J=9.60, 1.77 Hz, 1 H) 8.11 (dd, J=9.60, 1.01 Hz, 1 H) 8.69 - 8.93 (m, 1 H) 9.17 (s, 1 H). ESI-MS:m/z 465.3 $(M+H)^+$.

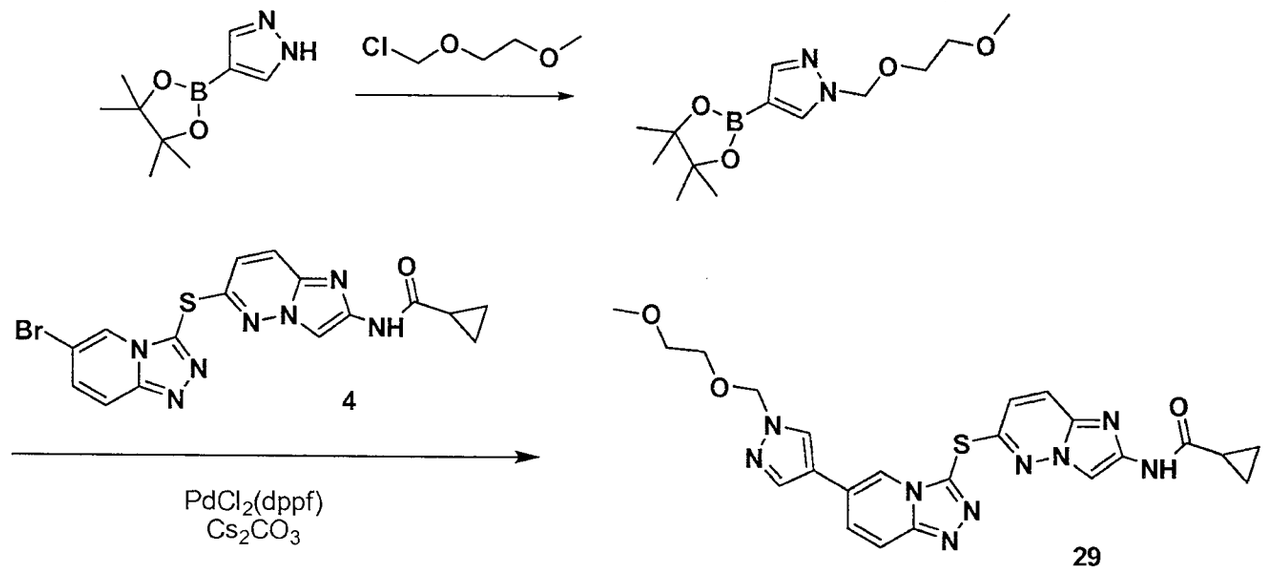
Compound 28: 2-chloro-4-(3-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-ylthio)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-N-methylbenzamide



[0447] A mixture of N-(6-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (150 mg, 0.349 mmol), 3-chloro-4-(methylcarbamoyl)phenylboronic acid (112 mg, 0.523 mmol), $PdCl_2(dppf)$ (12.75 mg, 0.017 mmol), and cesium carbonate (0.349 mL, 1.046 mmol) in DME (Volume: 1.0 mL) was heated in a microwave on high absorbance for 1 hr at 100°C. The reaction mixture was then concentrated to dryness via rotary evaporation. The resulting crude material was

reconstituted in DMSO (Volume: 1.0 mL) and purified via preparative mass trigger LCMS using a gradient eluant of 20-45% ACN:0.05% TFA (aq). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting mixture was lyophilized to provide the TFA salt of the titled compound (6.0 mg, 0.012 mmol, 3.32 % yield) as a pale yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 0.69 - 0.85 (m, 4 H) 1.81 - 1.96 (m, 1 H) 2.75 (d, J=4.55 Hz, 3 H) 7.07 (d, J=9.60 Hz, 1 H) 7.51 (d, J=8.08 Hz, 1 H) 7.79 (dd, J=7.83, 1.77 Hz, 1 H) 7.87 - 7.97 (m, 3 H) 8.00 (dd, J=9.60, 1.77 Hz, 1 H) 8.11 (dd, J=9.60, 1.01 Hz, 1 H) 8.39 (d, J=4.80 Hz, 1 H) 8.86 (d, J=1.52 Hz, 1 H) 11.15 (s, 1 H). ESI-MS:m/z 419.2 $(M+H)^+$.

Compound 29: N-(6-(6-(1-((2-methoxyethoxy)methyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

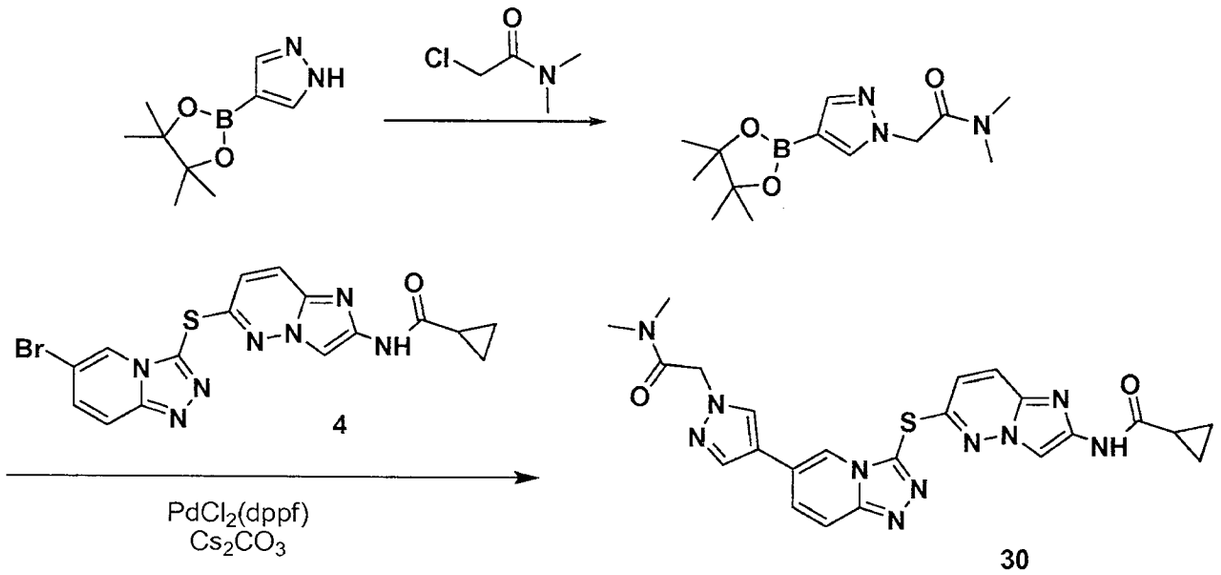


[0448] A solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.8 g, 4.1 mmol), cesium carbonate (2.0 g, 6.2 mmol), and 1-(chloromethoxy)-2-methoxyethane (0.59 mL, 5.2 mmol) in DMF (14 mL) was heated in a microwave at 90°C for 1 hr. After the initial heating, additional 1-(chloromethoxy)-2-methoxyethane (0.59 mL) and cesium carbonate (2 g) was added. Heating was repeated for an additional 1 hr. The crude reaction mixtures were then diluted with water (250 mL) and extracted with ethyl acetate (3 x 50 mL). The title compound was purified by silica gel column using DCM/EtOAc/MeOH (8/1.5/0.5)

as eluent to give 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.6 g) as a light yellow oil. ESI-MS:m/z 283.2 $(M+H)^+$.

[0449] A mixture of N-(6-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (100 mg, 0.232 mmol), 1-((2-methoxyethoxy)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (328 mg, 1.162 mmol), pdcl2(dppf) (8.50 mg, 0.012 mmol), and cesium carbonate (0.232 mL, 0.697 mmol) in Dioxane (Volume: 1.0 mL) was heated in a microwave on high absorbance for 1 hr at 100°C. The reaction mixture was then concentrated to dryness via rotary evaporation. The resulting crude material was reconstituted in DMSO (Volume: 1.0 mL) and purified via preparative mass trigger LCMS using a gradient eluant of 15-40% ACN:0.05% TFA (aq). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting mixture was lyophilized to provide the TFA salt of the title compound (8.0 mg, 0.016 mmol, 6.81 % yield) as a pale yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 0.72 - 0.78 (m, 4 H) 1.90 (m, 1 H) 3.20 (m, 3 H) 3.38 - 3.42 (m, 2 H) 3.54 - 3.58 (m, 2 H) 5.45 (m, 2 H) 7.00 (m, 1 H) 7.67 (m, 1 H) 7.91 - 7.96 (m, 3 H) 8.04 (m, 1 H) 8.59 (m, 1 H), 8.76 (m, 1 H) 11.16 (s, 1 H). ESI-MS:m/z 506.3 $(M+H)^+$.

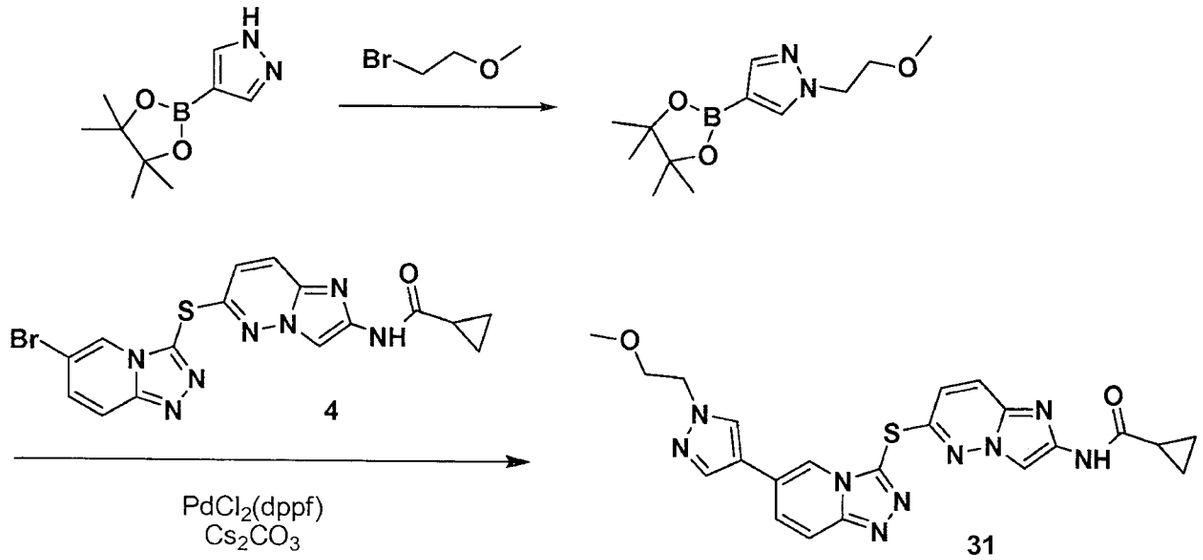
Compound 30: N-(6-(6-(1-(2-(dimethylamino)-2-oxoethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0450] A solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.8 g, 4.1 mmol), cesium carbonate (2.0 g, 6.2 mmol), and 2-chloro-N,N-dimethylacetamide (0.47 mL, 4.5 mmol) in DMF (14 mL) was heated in a microwave at 90°C for 1 hr. The crude reaction mixtures were then diluted with water (300 mL) and extracted with ethyl acetate (3 x 50 mL). Product was purified by silica gel column using DCM/EtOAc/MeOH (8/1.5/0.5) as eluent to provide N,N-dimethyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetamide (1.3 g) as a light yellow oil. ESI-MS:m/z 280.3 $(M+H)^+$.

[0451] A mixture of N-(6-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (100 mg, 0.232 mmol), N,N-dimethyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetamide (324 mg, 1.162 mmol), pdcl2(dppf) (8.50 mg, 0.012 mmol), and cesium carbonate (0.232 mL, 0.697 mmol) in Dioxane (Volume: 1.0 mL) was heated in a microwave on high absorbance for 1 hr at 100°C. The reaction mixture was then concentrated to dryness via rotary evaporation. The resulting crude material was reconstituted in DMSO (Volume: 1.0 mL) and purified via preparative mass trigger LCMS using a gradient eluant of 15-40% ACN:0.05% TFA (aq). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting mixture was lyophilized to provide the TFA salt of the title compound (4.8 mg, 9.55 μmol, 4.11 % yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 0.79 (d, J=6.06 Hz, 4 H) 1.90 (d, J=6.57 Hz, 1 H) 2.84 (s, 3 H) 3.03 (s, 3 H) 5.12 (s, 2 H) 7.00 (d, J=9.35 Hz, 1 H) 7.87 - 7.97 (m, 3 H) 8.01 - 8.08 (m, 2 H) 8.31 (s, 1 H) 8.71 (s, 1 H) 11.16 (s, 1 H). ESI-MS:m/z 503.3 $(M+H)^+$.

Compound 31: N-(6-(6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

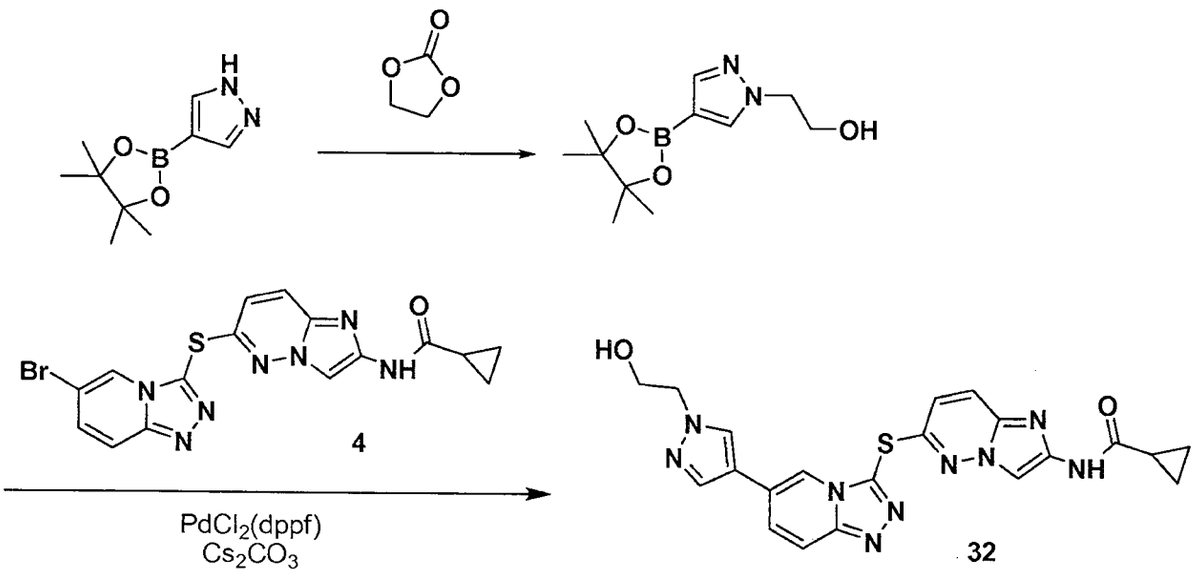


[0452] A solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.8 g, 4.1 mmol), cesium carbonate (2.0 g, 6.2 mmol), and 1-bromo-2-methoxyethane (0.41 mL, 4.3 mmol) in DMF (14 mL) was heated in a microwave at 90°C for 1 hr. After the initial heating, additional 1-bromo-2-methoxyethane (0.41 mL) was added to the reaction. Heating was repeated for an additional 1 hr. The crude reaction mixtures were then diluted with water (250 mL) and extracted with ethyl acetate (3 x 50 mL). Product was purified by silica gel column using DCM/EtOAc/MeOH (8/1.5/0.5) as eluent to give 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.2 g) as a light yellow oil. ESI-MS:m/z 253.2 $(M+H)^+$.

[0453] A mixture of N-(6-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (100 mg, 0.232 mmol), 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (410 mg, 1.627 mmol), pdcl2(dppf) (8.50 mg, 0.012 mmol), and cesium carbonate (0.232 mL, 0.697 mmol) in Dioxane (Volume: 1.0 mL) was heated in a microwave on high absorbance for 1 hr at 100°C. The reaction mixture was then concentrated to dryness via rotary evaporation. The resulting crude material was reconstituted in DMSO (Volume: 1.0 mL) and purified via preparative mass trigger LCMS using a gradient eluant of 15-40% ACN:0.05% TFA (aq). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting mixture was lyophilized to provide the TFA salt of the title compound (6.0 mg, 0.013 mmol, 5.43 % yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 0.69 - 0.86 (m, 4 H)

1.90 (m, 1 H) 3.20 (m, 3 H) 3.63 - 3.70 (m, 2 H) 4.22 - 4.27 (m, 2 H) 7.00 (m, 1 H) 7.57 (m, 1 H) 7.86 - 7.95 (m, 3 H) 8.04 (m, 1 H) 8.08 (m, 1 H) 8.37 (m, 1 H), 11.16 (s, 1 H). ESI-MS:m/z 476.3 $(M+H)^+$.

Compound 32: N-(6-(6-(1-(2-hydroxyoxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

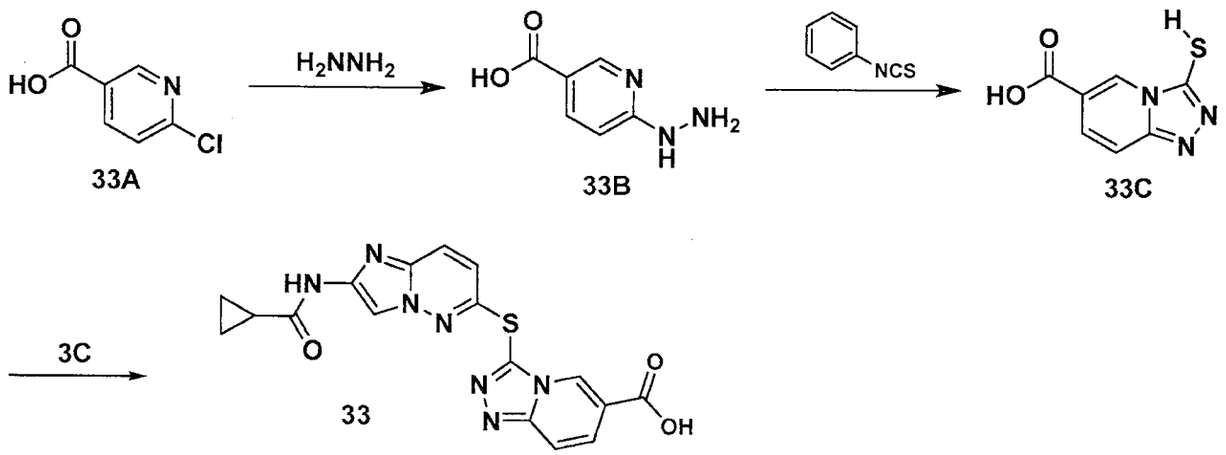


[0454] 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethanol was synthesized according to the procedure in PCT Publication No. WO 2008/44022, which is incorporated herein in its entirety. Specifically, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (5.0 g, 25.8 mmol), 1,3-dioxolan-2-one (2.5 g, 28.3 mmol), and sodium hydroxide (pellets, 1.0 g, 25.8 mmol) were dissolved in DMF (206 mL). The reaction mixture was heated to reflux for 2 hours. Activated charcoal was added after reaction was cooled to ambient temperature and the reaction was stirred for 1 hr and then filtered through Celite. The filter cake was then rinsed with DMF (120 mL), and the filtrate was concentrated to provide 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethanol as a yellow oil (6 g). The resulting material was used without further purification. ESI-MS:m/z 239.3 $(M+H)^+$.

[0455] A mixture of *N*-(6-(6-bromo-[1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-yl)cyclopropanecarboxamide (500 mg, 1.2 mmol), 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethanol (1.4 g, 5.8 mmol), cesium carbonate (1.14 mL, 3 M solution), and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (85 mg, 0.12 mmol) in DME (5 mL) was heated in a microwave for 30 min at 100°C. The reaction

mixture was then concentrated to dryness via rotary evaporation. The resulting crude material was reconstituted in DMSO (Volume: 1.0 mL) and purified via preparative mass trigger LCMS using a gradient eluant of 10-35% ACN:0.05% TFA (aq). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting mixture was lyophilized and reconstituted in water:ACN (1:10, 5.0 mL) Two drops of concentrated HCl were added and the resulting solution was lyophilized to provide the HCl salt of the title compound ^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 11.16 (s, 1 H) 8.69 (s, 1 H) 8.38 (s, 1 H) 8.04 - 8.08 (m, 1 H) 8.02 (d, *J*=1.01 Hz, 1 H) 7.91 - 7.95 (m, 1 H) 7.88 - 7.91 (m, 2 H) 6.99 - 7.05 (m, 1 H) 4.10 - 4.16 (m, 2 H) 3.73 (t, *J*=5.56 Hz, 2 H) 1.90 (quin, *J*=6.19 Hz, 1 H) 0.74 - 0.84 (m, 4 H) ESI-MS:m/z 462.3 $(M+H)^+$. MP 182 - 184°C.

Compound 33: 3-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-ylthio)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid

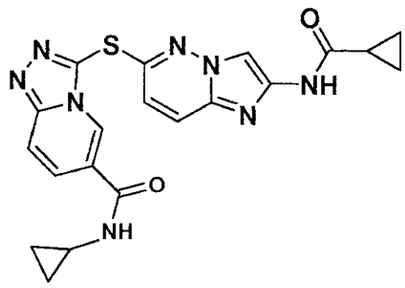


[0456] 3-Mercapto-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid: 6-chloronicotinic acid (1.6 g) in MeOH (10mL) was treated with NH_2NH_2 (2 g) at 140 ^{0}C for 2h. After cooling to -20 ^{0}C, the solid was filtered to give 560mg of compound **33B**. Compound **33B** was treated with isothiocyanatobenzene (141 mg) in 1,2-dichlorobenzene (5 mL) at 100 ^{0}C for 10 min, and then 180 ^{0}C for 1h. The product was purified by LCMS to give 3-mercapto-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (450mg). ESI-MS:m/z 196.1 $(M+H)^+$.

[0457] 3-(2-(Cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-ylthio)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid: Compound **33** was prepared from 3-mercapto-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid following the procedure described in the synthesis of compound **4**. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ ppm 9.03 (bs, 1

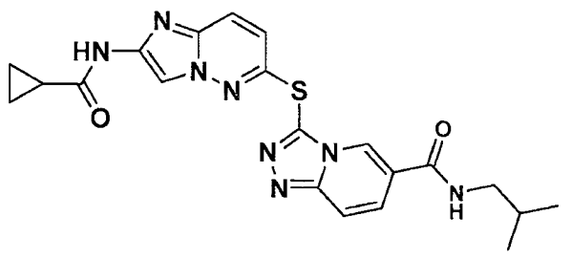
H), 8.01 (d, *J*=9.1 Hz, 1 H), 7.87 (d, *J*=9.6 Hz, 1 H), 7.68 (d, *J*=9.4 Hz, 1 H), 7.36 (m, 1H), 7.09 (d, *J*=9.3 Hz, 1 H), 2.84 (m, 1H), 1.72 (m, 1 H), 0.97 (m, 2 H), 0.84 (m, 2H) ESI-MS:m/z 396.1 $(M+H)^+$.

Compound 34: 3-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-ylthio)-N-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide



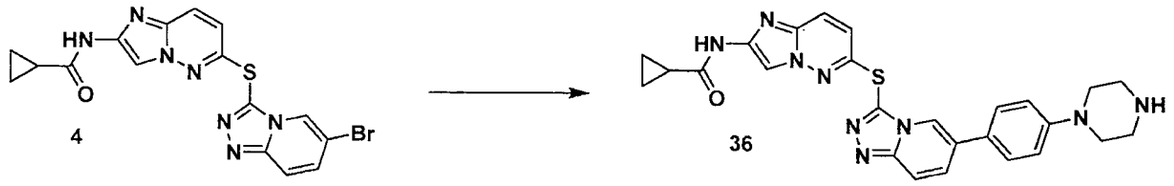
[0458] To a solution of compound **33** (10 mg), cyclopropanamine (30 mg) and DIEPA (100uL) in DMF (1mL) was added HATU (20 mg). The mixture was stirred at rt for 0.5h and 60 ^{0}C for 5h. The title compound was isolated by preparative LCMS. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ ppm 8.95 (bs, 1 H), 8.06 (dd, *J*=9.4, 1.6 Hz, 1 H), 7.98 (dd, *J*=9.6, 1.0 Hz, 1 H), 7.93 (s, 1 H), 7.87 (d, *J*=9.4 Hz, 1 H), 7.29 (d, *J*=9.3 Hz, 1 H), 1.77 (m, 1 H), 1.04 (m, 1 H), 0.95 (m, 2H). 0.89 (m, 2H). 0.80 (m, 2H). 0.63 (m, 2H). ESI-MS:m/z 435.1 $(M+H)^+$.

Compound 35: 3-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-ylthio)-N-isobutyl-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide



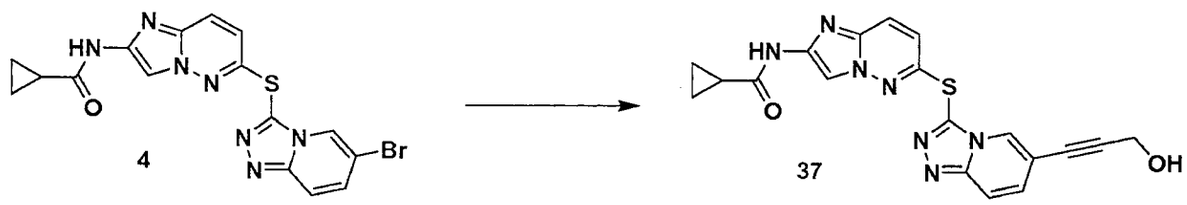
[0459] Compound **35** was prepared from 2-methylpropan-1-amine following the procedure described in the synthesis of compound **34**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.88 (bs, 1 H), 8.72 (bs, 1 H), 7.95-7.88 (m, 3H), 7.15 (bs, 1 H), 3.08 (t, *J*=6.0 Hz, 2H), 1.78 (m, 1H), 1.3-1.15 (m, 3H), 0.85 (m, 2H), 0.82 (d, *J*=6.8 Hz, 6H) ESI-MS:m/z 451.1 $(M+H)^+$.

Compound 36: N-(6-(6-(4-(piperazin-1-yl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



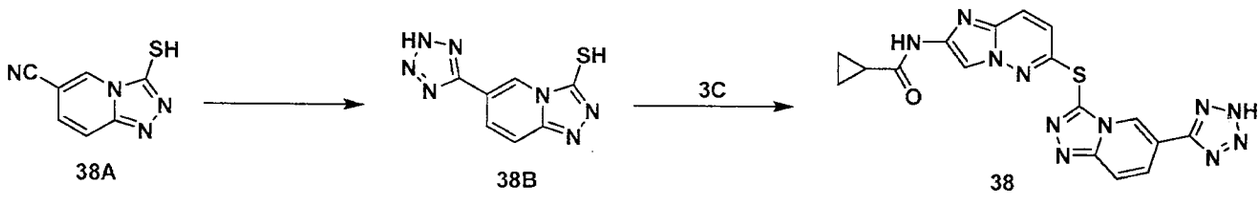
[0460] Compound **36** was prepared from N-(6-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide and tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate following an analogous procedure to that described in conection with the synthesis of compound **5**. The crude product was treated with 4 M HCl-dioxane at 80 ^{0}C for 1 h. Purification of the mixture by LCMS gave the title compound as a TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.61 (bs, 1 H), 7.92-8.0 (m, 2H), 7.8 (bs, 1 H), 7.6 (m, 1H), 7.57, (d, *J*=8.9Hz, 2H), 7.21 (bs, 1H), 7.08, (d, *J*=8.8Hz, 2H), 3.47 (m, 4H), 3.36 (m, 4H), 1.82 (m, 1H), 1.3-1.15 (m, 2H), 0.85 (m, 2H). ESI-MS:m/z 512.2 $(M+H)^+$.

Compound 37: N-(6-(6-(3-hydroxyprop-1-ynyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0461] A mixture of N-(6-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (43mg), prop-2-yn-1-ol (10mg), Ph_3P (1.1mg) and tetrakis(triphenylphosphine)palladium(0) (*i.e.*, $Pd[P(C_6H_5)_3]_4$) (4mg) in THF (1.5 mL), was stirred at rt for 10 min under N_2, and then CuI (1mg) was added. The mixture was heated at 60 ^{0}C overnight. Purification of the mixture by LCMS gave the title compound as a TFA salt. ^{1}H NMR (400 MHz, DMSO) δ ppm 11.16 (s, 1H), 8.67 (t, *J*=1.0Hz, 1H), 8.00 (dd, *J*=9.4 and 1.0 Hz,1 H), 7.93 (dd, *J*=9.3 and 0.7 Hz, 1 H), 7.91 (s, 1H), 7.53 (dd, *J*=9.4 and 1.5 Hz, 1 H), 7.12 (d, *J*=9.4 Hz, 1 H), 1.91 (m, 1 H), 1.24 (m, 2 H), 0.80 (m, 2H). ESI-MS:m/z 406.2 $(M+H)^+$.

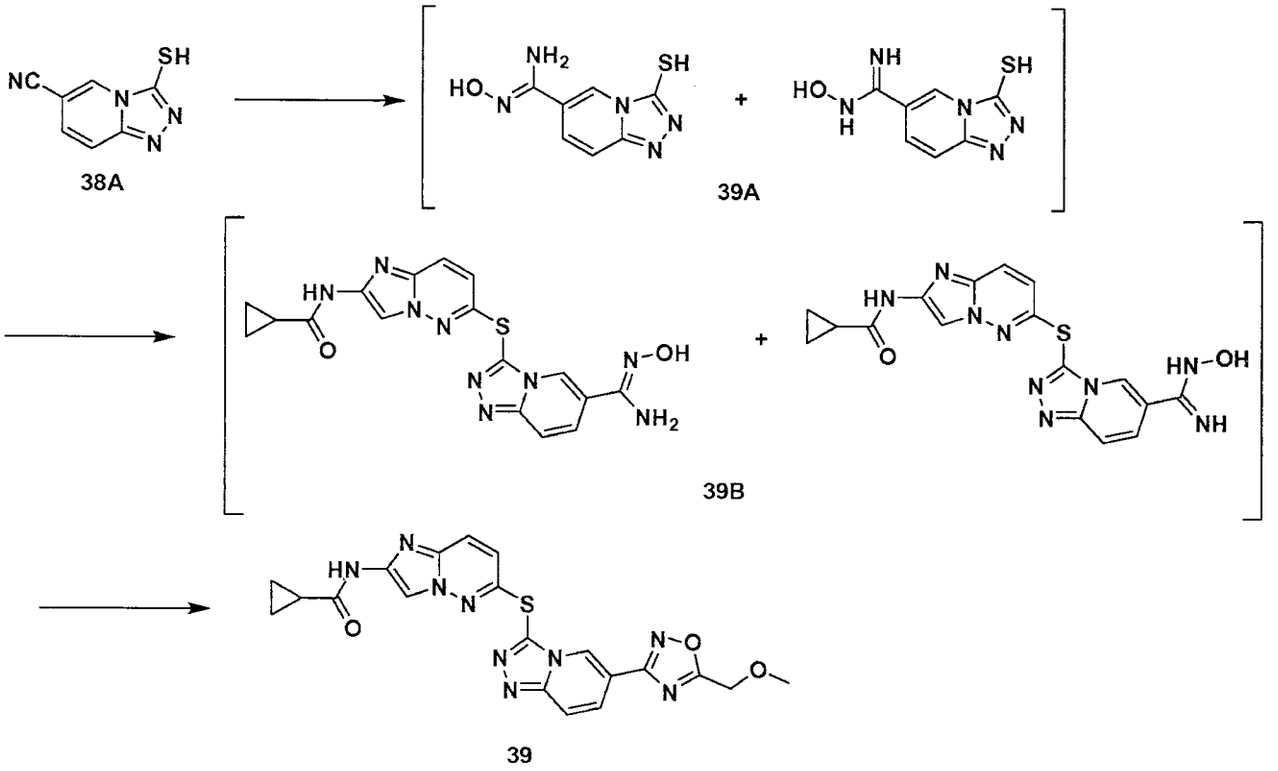
Compound 38: N-(6-(6-(2H-tetrazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0462] **6-(2H-tetrazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-thiol:** A mixture of 3-mercapto-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile (360mg, 2 mmol), NaN_3 and NH_4Cl in DMF (10mL) was heated at 140 ^{0}C for 10 h under microwave condition. The product was purified by LCMS to give compound **38B** (320mg). ESI-MS:m/z 220.1 $(M+H)^+$.

[0463] **3-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-ylthio)-N-isobutyl-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide:** Compound **38** was prepared from compound **38B** following the procedure described in the synthesis of compound **4**. ^{1}H NMR (400 MHz, DMSO) δ ppm 11.16 (s, 1H), 9.14 (t, *J*=1.5Hz, 1H), 8.22 (dd, *J*=9.6 and 1.0 Hz,1 H), 8.14 (dd, *J*=9.6 and 0.7 Hz, 1 H), 7.95 (s, 1H), 7.94 (d, *J*=9.4 Hz, 1 H), 7.18 (d, *J*=9.6 Hz, 1 H), 1.90 (m, 1 H), 0.78 (bd, J=5.8Hz, 2H). ESI-MS:m/z 419.1 $(M+H)^+$.

Compound 39: N-(6-(6-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



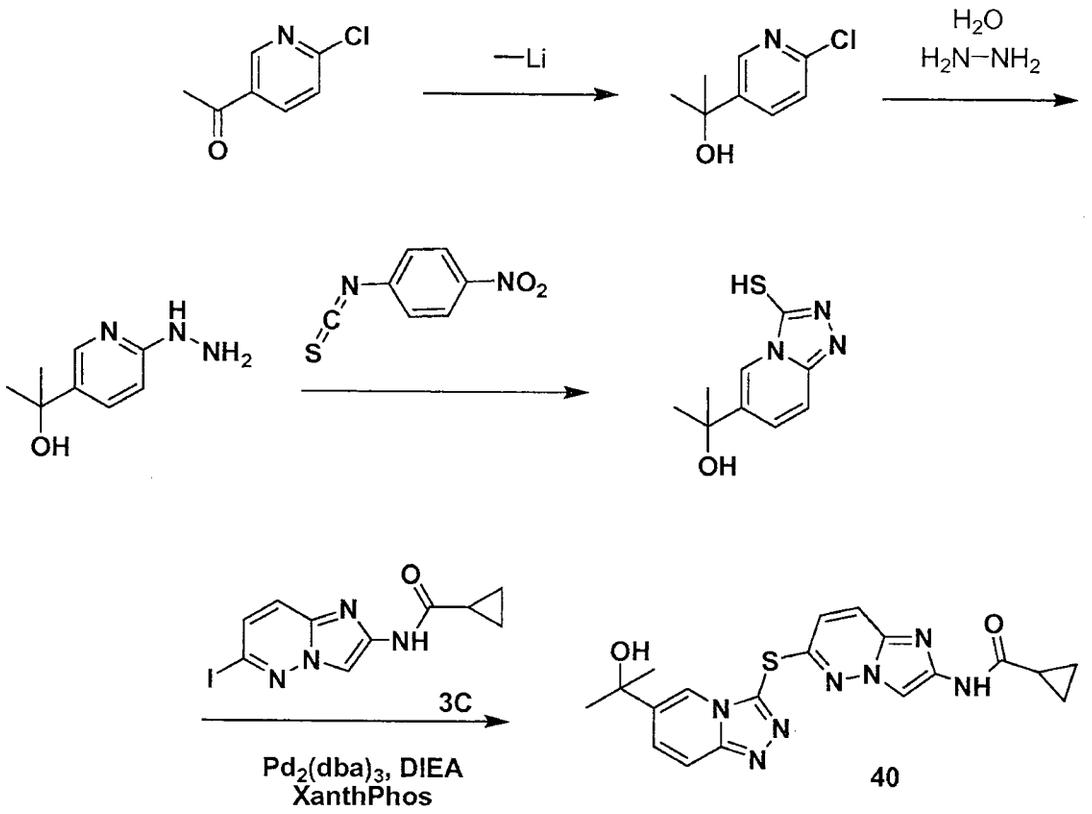
[0464] (Z)-N-hydroxy-3-mercapto-[1,2,4]triazolo[4,3-a]pyridine-6-carboximidamide: A mixture of 3-mercapto-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile (390mg, 2 mmol) and hydroxylamine (50 %wt in water, 420 mg) in EtOH (4mL) was heated at 120 ^{0}C for 10 h under microwave condition. The product was purified by LCMS to give compound **39A** and its tautomer (128mg). ESI-MS:m/z 210.0 $(M+H)^+$.

[0465] (Z)-N-(6-(6-(N'-hydroxycarbamimidoyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: Compound **39B** and its tautomer were prepared from compound **39A** and its tautomer following the procedure described in the synthesis of compound **4**. ESI-MS:m/z 410.1 $(M+H)^+$.

[0466] N-(6-(6-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: To a cooled (-10 ^{0}C) mixture of compound **39B** (30mg) and DIEPA (200mL) in THF-DME (1-1, 1.5 mL) was added a solution of 2-methoxyacetyl chloride (11mg) in THF (0.5mL). The mixture was stirred at this temperature for 5min, and then rt for 1h. The mixture was heated at 140 ^{0}C under microwave condition for 30 min, and purified by LCMS to give the title compound as a TFA salt. ^{1}H NMR (400 MHz, DMSO) δ ppm 11.49 (s, 1H), 9.09 (bs, 1H), 8.19 (dd, *J*=9.6

and 1.6 Hz,1 H), 8.11-8.12 (m, 2H), 7.92 (d, *J*=9.3 Hz, 1 H), 7.37 (d, *J*=9.4 Hz, 1 H), 4.77 (s, 1H), 3.56 (s, 3H), 1.77 (m, 1 H), 1.06 (m, 2H), 0.93 (m, 2H). ESI-MS:m/z 463.1 $(M+H)^+$.

Compound 40: N-(6-(6-(2-hydroxypropan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0467] **2-(6-Chloropyridin-3-yl)propan-2-ol:** To a solution of 1-(6-chloropyridin-3-yl)ethanone (2.0 g, 12.85 mmol) in THF (Volume: 25 mL) was added methyllithium (16.07 mL, 25.7 mmol) at 0°C. The reaction was stirred for 1 hr and allowed to warm to room temperature. The resulting deep red solution was quenched with water (Volume: 50 mL), extracted with EtOAc (1 x 50 mL), and the organic layer was dried over $MgSO_4$. The organic phase was filtered and the filtrate was evaporated to dryness via rotary evaporation. The resulting material was purified via MPLC (DCM: MeOH, 95:5) to provide 2-(6-chloropyridin-3-yl)propan-2-ol (.985 g, 5.74 mmol, 44.6 % yield) as a dark red solid. ^1H NMR (400MHz, DMSO-d_6) δ ppm 1.44 (s, 5 H) 5.32 (s, 1 H) 7.44 (d, J=8.34 Hz, 1 H) 7.90 (dd, J=8.34, 2.53 Hz, 1 H) 8.49 (d, J=2.53 Hz, 1 H). ESI-MS:m/z 172.0 $(M+H)^+$.

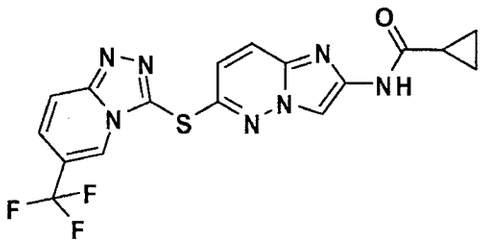
[0468] **2-(6-Hydrazinylpyridin-3-yl)propan-2-ol:** A mixture of 2-(6-chloropyridin-3-yl)propan-2-ol (975 mg, 5.68 mmol), and hydrazine hydrate (5512 µl, 114 mmol) was heated

in a microwave on high absorbance for 10 hr at 110°C. The mixture was cooled to room temperature and the hydrazine was removed via rotary evaporation. The resulting yellow residue was used without further work-up.

[0469] 2-(3-Mercapto-[1,2,4]triazolo[4,3-a]pyridin-6-yl)propan-2-ol: A mixture of 2-(6-hydrazinylpyridin-3-yl)propan-2-ol (250 mg, 1.495 mmol) and 1-isothiocyanato-4-nitrobenzene (269 mg, 1.495 mmol) in ACN (Volume: 2.0 mL) was stirred at room temperature for 1 hr. The reaction was diluted with Et_2O (Volume: 5.0 mL), and the resulting solid was filtered. Minimal product was present in the solid. On standing for 1 hr, the filtrate had formed a precipitate. This was filtered to provide 2-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-N-(4-nitrophenyl)hydrazinecarbothioamide (175 mg, 0.504 mmol, 33.7 % yield) as an orange solid. A solution of 2-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-N-(4-nitrophenyl)hydrazinecarbothioamide (275 mg, 0.792 mmol) in DME (Volume: 2.0 mL) was heated in a microwave on high absorbance for 3 hr at 110°C. The reaction was stripped to dryness onto silica gel via rotary evaporation and purified compound by MPLC with DCM:MeOH (98:2) to provide 2-(3-mercapto-[1,2,4]triazolo[4,3-a]pyridin-6-yl)propan-2-ol.

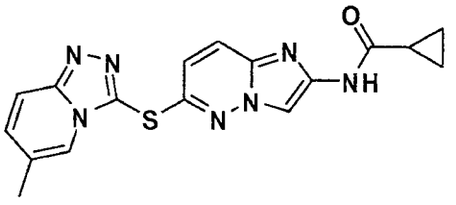
[0470] N-(6-(6-(2-hydroxypropan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (62.7 mg, 0.191 mmol), $Pd_2(dba)_3$ (10.50 mg, 0.011 mmol), XANTPHOS (13.27 mg, 0.023 mmol), DIEA (0.067 mL, 0.382 mmol), and 2-(3-mercapto-[1,2,4]triazolo[4,3-a]pyridin-6-yl)propan-2-ol (40 mg, 0.191 mmol) in DME (Volume: 1.5 mL) was heated in a microwave on high absorbance for 30 min at 120°C. The reaction mixture was then concentrated to dryness via rotary evaporation. The resulting crude material was reconstituted in DMSO (Volume: 1.0 mL) and purified via preparative mass trigger LCMS using a gradient eluant of 20-45% ACN:0.05% TFA (aq). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting mixture was lyophilized to provide the TFA salt of the title compound (3.3 mg, 8.06 μmol, 4.22 % yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.85 (m, 3 H) 1.43 (s, 4 H) 1.91 (m, 1 H) 7.04 (d, J=9.35 Hz, 1 H) 7.70 (dd, J=9.60, 1.77 Hz, 1 H) 7.87 - 8.00 (m, 2 H) 8.32 (d, J=1.52 Hz, 1 H) 11.18 (s, 1 H). ESI-MS:m/z 410.3 $(M+H)^+$.

Compound 41: *N*-(6-(6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



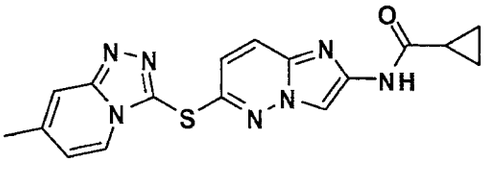
[0471] The title compound was prepared using an analogous procedure to that described in connection with compound **6**. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.16 (s, 1 H), 9.03 (d, *J* = 1.3 Hz, 1 H), 8.25 - 8.17 (m, 1 H), 7.96 - 7.90 (m, 2 H), 7.83 (dd, *J* = 1.5, 9.6 Hz, 1 H), 7.17 (d, *J* = 9.6 Hz, 1 H), 1.91 (quin, *J* = 6.3 Hz, 1 H), 0.84 - 0.76 (m, 4 H) ESI-MS:m/z 420.3 $(M+H)^+$.

Compound 42: *N*-(6-(6-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-yl)cyclopropanecarboxamide



[0472] The title compound was prepared using an analogous procedure to that described in connection with compound **6**. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.17 (s, 1 H), 8.35 (d, *J* = 1.3 Hz, 1 H), 7.96 - 7.87 (m, 3 H), 7.46 (dd, *J* = 1.5, 9.3 Hz, 1 H), 7.00 (d, *J* = 9.3 Hz, 1 H), 2.34 - 2.27 (m, 3 H), 1.95 - 1.86 (m, 1 H), 0.82 - 0.75 (m, 4 H) ESI-MS:m/z 366.3 $(M+H)^+$.

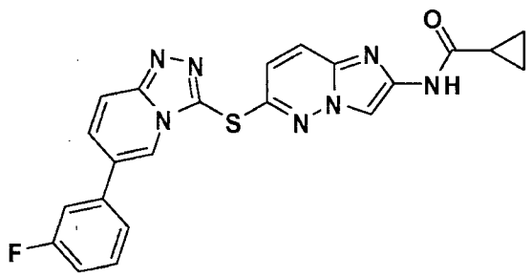
Compound 43: *N*-(6-(7-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-yl)cyclopropanecarboxamide



[0473] The title compound was prepared using an analogous procedure to that described in connection with compound **6**. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.17 (s, 1 H), 8.38 (d,

J = 7.1 Hz, 1 H), 7.96 - 7.88 (m, 2 H), 7.76 (d, J = 1.3 Hz, 1 H), 7.06 (d, J = 9.3 Hz, 1 H), 7.00 (dd, J = 1.5, 7.1 Hz, 1 H), 2.44 (s, 3 H), 1.95 - 1.86 (m, 1 H), 0.83 - 0.73 (m, 4 H)ESI-MS:m/z 366.3 $(M+H)^+$.

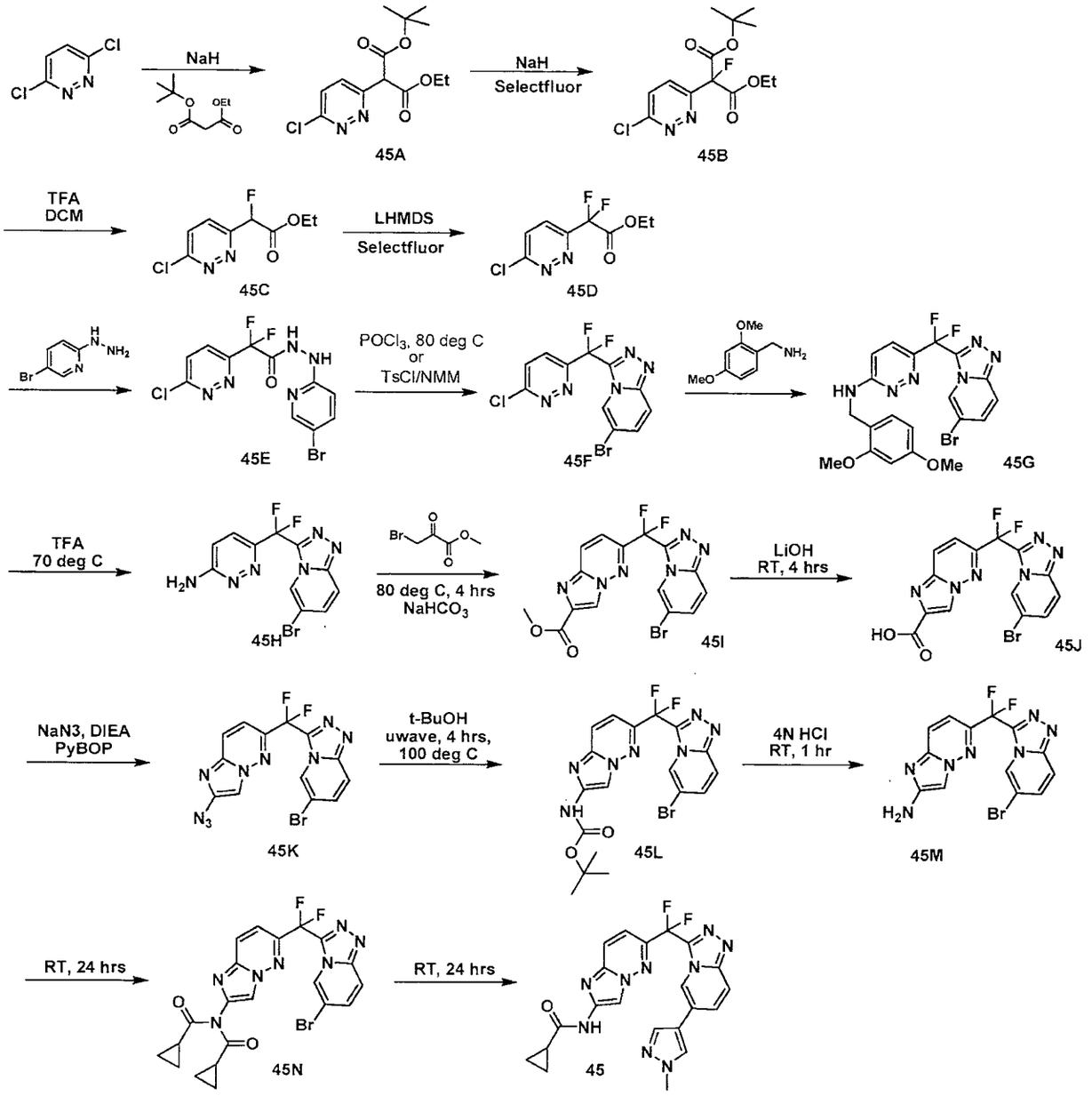
Compound 44: *N*-(6-(6-(3-fluorophenyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-yl)cyclopropanecarboxamide



[0474] The title compound was prepared using an analogous procedure to that described in connection with compound **6**. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.15 (s, 1 H), 8.81 (d, J = 1.5 Hz, 1 H), 8.11 (dd, J = 1.0, 9.6 Hz, 1 H), 7.99 (dd, J = 1.6, 9.5 Hz, 1 H), 7.95 - 7.89 (m, 1 H), 7.68 (dt, J = 2.1, 10.4 Hz, 2 H), 7.62 (d, J = 7.8 Hz, 1 H), 7.53 (td, J = 6.2, 8.0 Hz, 1 H), 7.27 (td, J = 2.1, 8.3 Hz, 1 H), 7.07 (d, J = 9.6 Hz, 1 H), 1.89 (quin, J = 6.3 Hz, 1 H), 0.86 - 0.74 (m, 4 H) ESI-MS:m/z 446.3 $(M+H)^+$.

Compound 45: N-(6-(difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

Method A



[0475] 1-tert-Butyl 3-ethyl 2-(6-chloropyridazin-3-yl)malonate: *tert*-Butyl ethyl malonate (41.3 ml, 211 mmol) was added drop-wise to a suspension of sodium hydride (19.33 g, 483 mmol) in dioxane (1000 mL) at 0°C. The reaction was stirred at 0°C for 1 hr and then allowed to warm to ambient temperature. 3,6-dichloropyridazine (30 g, 201 mmol) was then added portion wise at 25°C. The reaction was stirred at reflux for 2 hrs and then solvent was removed via rotary evaporation. The resulting residue was dissolved in EtOAc

(400 mL), and the organic phase was washed with saturated $NaHCO_3$ (400 mL), dried over $MgSO_4$, filtered, and concentrated to dryness via rotary evaporation. This reaction was repeated. The combined crude residues from both batches was purified via MPLC (Hex:EtOAc, 8:2) to provide the title compound, 1-*tert*-butyl 3-ethyl 2-(6-chloropyridazin-3-yl)malonate (86.5g, 288 mmol, 71.3 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 - 1.23 (m, 3 H) 1.36 - 1.52 (m, 9 H) 4.20 (m, *J*=10.71, 7.22, 7.22, 3.85, 3.85 Hz, 2 H) 5.29 (s, 1 H) 7.85 (d, *J*=8.84 Hz, 1 H) 7.99 (d, *J*=8.84 Hz, 1 H). ESI-MS:m/z 301.2 $(M+H)^+$.

[0476] **1-tert-Butyl 3-ethyl 2-(6-chloropyridazin-3-yl)-2-fluoromalonate**: To a solution of 1-*tert*-butyl 3-ethyl 2-(6-chloropyridazin-3-yl)malonate **45A** (86.5 g, 288 mmol) in THF (2400 mL) was added NaH (12.65 g, 316 mmol). The reaction was stirred at 0°C for 15 min. A cloudy solution of Selectfluor (112 g, 316 mmol) in DMF (dry, 800 mL) was added drop-wise at 0°C and then the reaction was allowed to warm to ambient temperature over a 2 hrs. The reaction was then quenched with saturated NH_4Cl (250 mL) and reduced in volume to about 1500 mL. To this mixture, Et_2O (300 mL) and water (50 mL) were added. Layers were separated, and the aqueous layer was extracted with Et_2O (3 x 300 mL). The combined organic layers were then washed with saturated $NaHCO_3$ solution (3 x 150 mL), dried with $MgSO_4$, filtered, and concentrated to dryness via rotary evaporation. The residue was purified via MPLC (Hex:EtOAc, 8:2) to provide 1-*tert*-butyl 3-ethyl 2-(6-chloropyridazin-3-yl)-2-fluoromalonate **45B** (70.2 g, 220 mmol, 77 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (t, *J*=7.20 Hz, 3 H) 1.46 (s, 9 H) 4.28 - 4.43 (m, 2 H) 8.14 (s, 2 H). ESI-MS:m/z 319.2 $(M+H)^+$.

[0477] **Ethyl 2-(6-chloropyridazin-3-yl)-2-fluoroacetate**: A solution of 1-*tert*-butyl 3-ethyl 2-(6-chloropyridazin-3-yl)-2-fluoromalonate **45B** (60.2 g, 189 mmol) in 300 mL TFA/DCM (1:1) was stirred at 25°C for 2 hrs and then concentrated to dryness via rotary evaporation. The resulting residue was dissolved in EtOAc (300 mL), washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and then concentrated to dryness to give the title compound, ethyl 2-(6-chloropyridazin-3-yl)-2-fluoroacetate **45C** (36.6 g, 167 mmol, 89%). The material was used immediately without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (t, *J*=7.20 Hz, 3 H) 4.23 (qd, *J*=7.12, 4.42 Hz, 2 H) 6.43 - 6.62 (m, 1 H) 8.00 - 8.12 (m, 2 H). ESI-MS:m/z 219.0 $(M+H)^+$.

[0478] Ethyl 2-(6-chloropyridazin-3-yl)-2,2-difluoroacetate: To a solution of ethyl 2-(6-chloropyridazin-3-yl)-2-fluoroacetate (36.6 g, 167 mmol) in anhydrous THF (500 mL) was added lithium hexamethyldisilazide (201 ml, 201 mmol) drop-wise at -78 °C. After 15 minutes, a solution of Selectfluor (71.2 g, 201 mmol) in DMF (183 mL) was added drop-wise. Upon complete addition, the reaction was allowed to warm to ambient temperature over a 30 min period. Saturated NH_4Cl (70 mL) was then added, and THF was removed via rotary evaporation. The resulting residue was diluted with water (500 mL), extracted with Et_2O (3 x 100 mL), dried with $MgSO_4$, filtered, and concentrated to dryness. The resulting material was purified via MPLC (Hex:EtOAc, 8:2) to provide ethyl 2-(6-chloropyridazin-3-yl)-2,2-difluoroacetate **45D** (20.8 g, 88 mmol, 52.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (t, *J*=7.07 Hz, 3 H) 4.38 (q, *J*=7.07 Hz, 2 H) 8.26 (d, *J*=9.09 Hz, 1 H) 8.33 (d, *J*=8.84 Hz, 1 H). ESI-MS:m/z 237.1 $(M+H)^+$.

[0479] N'-(5-Bromopyridin-2-yl)-2-(6-chloropyridazin-3-yl)-2,2-difluoroacetohydrazide: To a solution of ethyl 2-(6-chloropyridazin-3-yl)-2,2-difluoroacetate (10.8 g, 45.6 mmol) and 5-bromo-2-hydrazinylpyridine (8.58 g, 45.6 mmol) in anydrous MeOH (100 mL) was added DIEA (5.90 g, 45.6 mmol). The reaction was stirred at ambient temperature for 18 hrs. The solvent was removed via rotary evaporation and the resulting material was reconstituted in EtOAc. The organic phase was washed with water and concentrated to dryness. The resulting residue was purified by MPLC (EtOAc) to provide the title compound, N'-(5-bromopyridin-2-yl)-2-(6-chloropyridazin-3-yl)-2,2-difluoroacetohydrazide **45E** (13.3 g, 35.1 mmol, 77 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.62 (d, *J*=8.84 Hz, 1 H) 7.11 (d, *J*=9.35 Hz, 1 H) 7.47 - 7.60 (m, 2 H) 8.06 (d, *J*=2.53 Hz, 1 H). ESI-MS:m/z 377.9 $(M+H)^+$.

[0480] 6-Bromo-3-((6-chloropyridazin-3-yl)difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine: A mixture of N'-(5-bromopyridin-2-yl)-2-(6-chloropyridazin-3-yl)-2,2-difluoroacetohydrazide (1.0 g, 2.64 mmol) and PCl_5 (1.2 g, 8 mmol) in $POCl_3$ (40.5 g, 264 mmol) was heated at 140°C in a sealed tube for 18 hrs. Solvent was removed via rotary evaporation, and the resulting residue was reconstituted in EtOAc. The organic solution was washed with saturated $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated to dryness. The resulting material was purified via MPLC (Hex:EtOAc, 50-100% gradient) to provide the title compound, 6-bromo-3-((6-chloropyridazin-3-yl)difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine **45F** (0.8 g, 2.21 mmol, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.75 (dd,

J=9.85, 1.77 Hz, 1 H) 8.01 (dd, *J*=9.85, 1.01 Hz, 1 H) 8.31 (d, *J*=9.09 Hz, 1 H) 8.42 - 8.51 (m, 1 H) 8.93 (s, 1 H). ESI-MS:m/z 359.9 $(M+H)^+$.

[0481] 6-bromo-3-((6-chloropyridazin-3-yl)difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine **45F** was also prepared by mixing N'-(5-bromopyridin-2-yl)-2-(6-chloropyridazin-3-yl)-2,2-difluoroacetohydrazide (1.514 g, 4 mmol) and 4-methylbenzene-1-sulfonyl chloride (0.839 g, 4.40 mmol) in ethyl acetate (Volume: 25 ml) and cooling the mixture to 10 °C under protection of nitrogen. 4-methylmorpholine (1.142 ml, 10.40 mmol) was added over 2 minutes. The reaction mixture was warmed up to room temperature and stirred for 6 hours. Additional 4-methylmorpholine (0.44 ml, 4 mmol) was added. The reaction mixture was heated at 60 °C for 24 hours to reduce the imidoyl chloride intermediate level to less than 1% by HPLC. The reaction mixture was cooled to room temperature. EtOAc (30 ml) and water (13ml) was added, and the mixture was stirred for 30 minutes. The aqueous layer was separated. The organic layer was concentrated and the residue was purified by silica gel column to afford 1.28g of product (89% yield).

[0482] **6-((6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-N-(2,4-dimethoxybenzyl)pyridazin-3-amine**: A reaction mixture of 6-bromo-3-((6-chloropyridazin-3-yl)difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (0.5 g, 1.387 mmol), (2,4-dimethoxyphenyl)methanamine (0.696 g, 4.16 mmol) and $NaHCO_3$ (0.58 g , 7.0 mmol) in IPA (10 mL) was heated at 140°C in a microwave for 1 hr. The solvent was removed via rotary evaporation and the resulting residue was reconstituted in EtOAc. The organic solution was washed with water, separated and passed through a short silica plug to provide the title compound, 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-N-(2,4-dimethoxybenzyl)pyridazin-3-amine **45G** (0.6g, 1.22 mmol, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.71 - 3.76 (s, 3 H) 3.79 (s, 3 H) 3.85 - 3.89 (m, 2 H) 6.46 (dd, *J*=8.34, 2.53 Hz, 1 H) 6.57 (d, *J*=2.27 Hz, 1 H) 6.61 - 6.66 (m, 1 H) 7.08 (d, *J*=9.35 Hz, 1 H) 7.14 (d, *J*=8.34 Hz, 1 H) 7.81 (d, *J*=9.35 Hz, 1 H) 7.99 (dd, *J*=9.60, 1.01 Hz, 1 H) 8.70 (s, 1 H). ESI-MS:m/z 491.1 $(M+H)^+$.

[0483] **6-((6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)pyridazin-3-amine**: A solution of 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-N-(2,4-dimethoxybenzyl)pyridazin-3-amine (16.5 g, 33.6 mmol) and anisole (5.45 g, 50.4 mmol) in TFA (150 mL) was stirred at 70°C for 30 min. The reaction was concentrated to dryness via rotary evaporation and the resulting residue was sonicated in a solution of Et_2O /$NaHCO_3$

(pH=7). The resulting solid was collected by filtration, rinsed with water and then Et_2O, and dried in vacuum over P_2O_5 to provide the title compound, 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)pyridazin-3-amine **45H** (11.0g, 32.2 mmol, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 (d, *J*=9.35 Hz, 1 H) 7.71 (dd, *J*=9.85, 1.77 Hz, 1 H) 7.92 (d, *J*=9.35 Hz, 1 H) 7.92 (*d, J*=10.20 Hz, 1) 8.02 (*d, J*=10.20, 1 H) 8.74 (s, 1 H). ESI-MS:m/z 340.9 $(M+H)^+$.

[0484] Methyl 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazine-2-carboxylate: A reaction mixture of 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)pyridazin-3-amine (11.0 g, 32.2 mmol), methyl 3-bromo-2-oxopropanoate (11.67 g, 64.5 mmol), and $NaHCO_3$ (10.84 g) in dioxane (150 mL) was heated at 80°C for 4 hrs to provide a red reaction mixture. Solids were filtered off, rinsed with dioxane, and the combined filtrates were concentrated via rotary evaporation. The resulting residue was dissolved in EtOAc and washed with 0.1 N NaOH until the red color no longer persisted. The organic phase was then separated and concentrated to dryness. The resulting material was purified via MPLC (5:95, MeOH/EtOAc) to provide the title compound, **45I** (4.0 g, 9.45 mmol, 30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.88 (s, 3 H) 7.77 (dd, *J*=9.73, 1.64 Hz, 1 H) 7.85 (d, *J*=9.60 Hz, 1 H) 7.97 - 8.08 (m, 1 H) 8.53 (d, *J*=9.60 Hz, 1 H) 8.98 (d, *J*=1.01 Hz, 1 H) 9.02 (s, 1 H). ESI-MS:m/z 423.1 $(M+H)^+$.

[0485] 6-((6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazine-2-carboxylic acid: A solution of 3.methyl 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazine-2-carboxylate (4.0 g, 9.45 mmol) and LiOH (0.340 g, 14.18 mmol) in 10% H_2O/MeOH (150 mL) was stirred at ambient temperature for 4 hrs. Solvent was removed via rotary evaporation, and the resulting residue was diluted with H_2O (100 mL). The aqueous phase was adjusted to pH=5 with concentrated HCl. The resulting precipitate was collected, rinsed with water, rinsed with EtOAc, and dried under vacuum over P_2O_5 for 18 hrs to provide the title compound, 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazine-2-carboxylic acid **45J** (3.5g, 8.55 mmol, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.76 (dd, *J*=9.85, 1.77 Hz, 1 H) 7.82 (d, *J*=9.60 Hz, 1 H) 8.02 (d, J=9.60 Hz, 1H) 8.51 (d, *J*=9.85 Hz, 1 H) 8.90 (s, 1H) 8.97 (s,1H). ESI-MS:m/z 409.0 $(M+H)^+$.

[0486] 6-((6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazine-2-carbonyl azide: To a stirred solution of 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazine-2-carboxylic acid (3.5 g, 8.55 mmol), N-ethyl-N-isopropylpropan-2-amine (6.63 g, 51.3 mmol) and sodium azide (5.56 g, 86 mmol) in anhyydrous DMF (60 mL), PyBOP (5.34 g, 10.27 mmol) was added in portions at ambient temperature over 5 min. The reaction was stirred for an additional 30 min and diluted with EtOAc (200 mL). The reaction was then poured into a 10% aqueous citric acid (200 mL), and the organic phase was separated and washed with citric acid solution (2 x 100 mL), saturated $NaHCO_3$ (3 x 100 mL), and saturated NaCl solution. The aqueous phases were back extracted with EtOAc (200 mL) and the organic phases were combined, dried with $MgSO_4$, filtered, and concentrated to dryness via rotary evaporation. The resulting residue was triturated in 1:1 Et_2O/hexane, and the solid was collected by filtration and dried in vacuum over P_2O_5 to provide the title compound, 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazine-2-carbonyl azide **45K** (3.2 g, 7.37 mmol, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 (dd, J=9.85, 1.77 Hz, 1 H) 7.88 (d, J=9.60 Hz, 1 H) 8.00 - 8.05 (m, 1 H) 8.56 (d, J=9.60 Hz, 1 H) 8.98 (s, 1 H) 9.14 (s, 1 H). ESI-MS:m/z 434.0 $(M+H)^+$. ESI-MS:m/z 406.0 $(M+H)^+$.

[0487] tert-Butyl 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-ylcarbamate: 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazine-2-carbonyl azide (3.2 g, 7.37 mmol, divided into 4 portions) in t-butanol (10 mL) was heated in microwave oven at 100°C for 1 hr. The solvent was removed via rotary evaporation, and the resulting residue was reconstituted in EtOAc, washed with 5% citric acid, and the washed with saturated $NaHCO_3$. The organic phase was passed through a silica plug, rinsed with EtOAc:MeOH (95:5) and then concentrated to give the title compound, tert-Butyl 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-ylcarbamate **45L** (2.8g, 5.83 mmol, 79%), which was used in next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.47 (s, 9 H) 7.66 (d, J=9.35 Hz, 1 H) 7.72 - 7.78 (m, 1 H) 7.96 - 8.06 (m, 2 H) 8.22 (d, J=9.35 Hz, 1 H) 8.93 (s, 1 H) 10.40 (br, 1H). ESI-MS:m/z 480.1 $(M+H)^+$.

[0488] 6-((6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-amine: A solution of tert-butyl 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-

yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-ylcarbamate (2.8 g, 5.83 mmol) in 4N HCl/dioxane (25 mL) was stirred at ambient temperature for 1 hr. The solvent was removed via rotary evaporation and the residue was dried under vacuum to provide the title compound, 6-((6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-amine **45M** (2.2 g, 5.84 mmol, 92%), as HCl salt. This material was used without further purification. ESI-MS:m/z 380.1 $(M+H)^+$.

[0489] N-(6-((6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)-N-(cyclopropanecarbonyl)cyclopropanecarboxamide: To a solution of 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-amine (2.2 g, 5.84 mmol) and DIEA (4.53 g, 35.0 mmol) in CH_2Cl_2 (250 mL), cyclopropanecarbonyl chloride (1.831 g, 17.52 mmol) was added dropwise at 0°C. The reaction was stirred at ambient temperature for 18 hrs. The reaction was then washed with 5% citric acid (2 x 100 mL) and then washed with $NaHCO_3$ (2 x 100 mL). The organic phase was then dried with $MgSO_4$, filtered, and concentrated to dryness via rotary evaporation. The resulting material was purified via MPLC (95:5, DCM:MeOH) to provide the title compound, N-(6-((6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)-N-(cyclopropanecarbonyl)cyclopropanecarboxamide **45N** (2.2g, 4.27 mmol, 73%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 - 1.03 (m, 8 H) 2.05 - 2.12 (m, 2 H) 7.70 - 7.87 (m, 2 H) 7.97 - 8.06 (m, 1 H) 8.48 (d, J=9.60 Hz, 1 H) 8.65 (s, 1 H) 8.99 (s, 1 H). ESI-MS:m/z 516.1 $(M+H)^+$.

[0490] N-(6-(Difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: A mixture of N-(6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)-N-(cyclopropanecarbonyl)cyclopropanecarboxamide (0.6 g, 1.16 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.242 g, 1.162 mmol), and $PdCl_2$(dppf):CH_2Cl_2 (0.048 g, 0.058 mmol) in dioxane (10 mL)/2N Na_2CO_3 (5 mL) was heated in a microwave at 110°C for 30 min. This reaction was repeated 4 times and reaction mixtures were combined. The reaction was diluted with CH_2Cl_2 (500 mL) and washed with H_2O (3 x 200 mL). The organic phase was separated and concentrated to dryness via rotary evaporation. The resulting residue was suspended in EtOAc and sonicated. The resulting solid was collected by filtration and rinsed with EtOAc. The solid was the dissolved in MeOH/CH_2Cl_2 (5:95, 300 mL) and filtered through a silica plug and rinsed with

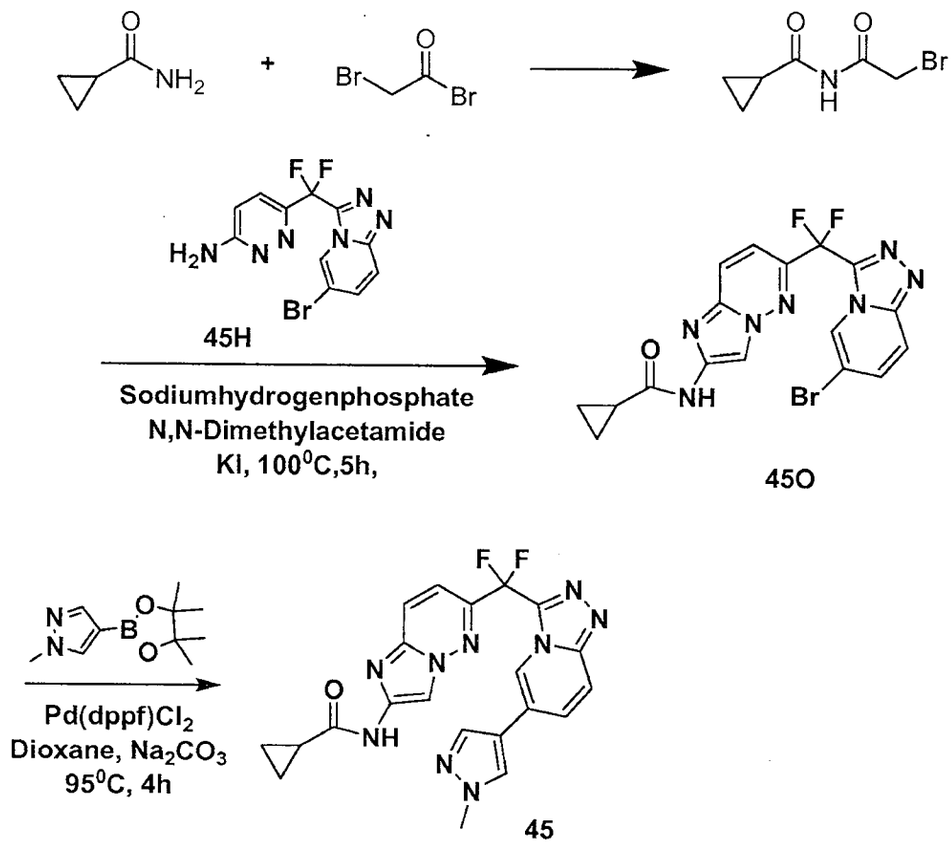
MeOH/CH_2Cl_2 (5:95). Concentrated HCl (0.5 mL) was added to the collected eluent followed by active charcoal. The solution was stirred at ambient temperature for 1 hour and filtered through celite. The solvent was evaporated and the resulting residue was then triturated in EtOAc. The solid was collected by filtration, rinsed with EtOAc and dried in vacuum to provide the title compound, N-(6-(Difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide hydrochloride (0.92 g, 1.78 mmol, 38%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 (d, *J*=6.32 Hz, 4 H) 1.91 - 2.01 (m, 1 H) 3.87 (s, 3 H) 7.70 (d, *J*=9.35 Hz, 1 H) 7.90 (dd, *J*=9.60, 1.52 Hz, 1 H) 7.98 - 8.11 (m, 2 H) 8.19 - 8.32 (m, 2 H) 8.40 (s, 1 H) 8.70 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 516.1 $(M+H)^+$. MP: 195°C dec.

[0491] N-(6-(Difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide hydrochloride was also prepared by dissolving 0.5g of crude N-(6-(difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide in AcOH (15ml) at 80°C to form a clear solution. The solution was cooled to room temperature, Sili-thiourea (commercially available from Silicycle; 0.25g) was added and the mixture was stirred overnight. The mixture was filtered through celite and 6.5ml of 1.7M HCl solution in MeOH was added to the AcOH solution. EtOAc (18ml) was then added slowly to induce crystallization. The mixture was then stirred at rt for 1 hour until a heavy precipitate formed. Additional EtOAc (30ml) was added and the mixture stirred for 60 min. The solid was then collected via filtration, wash with EtOAc (10ml) and dried in vacuum at 60°C over night.

[0492] Further, N-(6-(Difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide hydrochloride was prepared by suspending crude N-(6-(difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (2.2g; 4.9 mmol) in 333 ml of DCM. 50 ml of 0.2 M HCl in MeOH (10 mmol) was added. The mixture was stirred vigorously for 60 minutes and Sili-Thiourea (commercially available from Silicycle; 1.12g) was added. The mixture was stirred at room temperature for 14 hours, filtered through Celite and washed with 10% MeOH in DCM (40ml) to provide a total volume of filtrate of about 420ml. 15ml of a 2M HCl MeOH solution was added. The solution was concentrated by rotavap at 225mbar, 22°C bath

temperature to remove about 325ml of solvent. The solution was checked for clarity to ensure that solid formation was minimized. 10ml of a 2M HCl MeOH solution was added. The solution was seeded with 25mg of N-(6-(difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide hydrochloride salt. The solution was allowed to continue to concentrate at 130mbar to remove 65 ml solvent in the presence of seed crystal. After the solution turned cloudy, the solution was maintained at room temperature for 40 minutes. The mixture was cooled to 0°C, stirred for 2 hours, and the solids collected by filtration. The solids were dried in vacuum at 60°C overnight to afford 1.75 g of a pale-yellow solid.

Method B



[0493] ***N-(6-((6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (45O)***: Cyclopropanecarboxamide (58.7g, 690 mmol) in 1,4-Dioxane (1600 ml) was added 2-bromoacetyl bromide (59.9 ml, 690 mmol) at room temperature and stirred for 4h at 60°C. The reaction mixture was concentrated to dryness. The residue was dissolved in EtOAc and carefully washed with satd. $NaHCO_3$, water then with brine solution, dried over Na_2SO_4 and concentrated to get N-(2-

bromoacetyl) cyclopropanecarboxamide(138 g, 670 mmol, 97 % yield) as an off white solid. This material was used without purification. ESI-MS:m/z 208.0 $(M+2H)^+$.

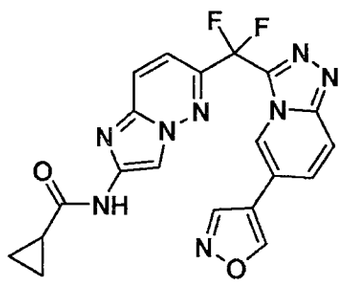
[0494] To a mixture of 6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)pyridazin-3-amine (21.8 g, 63.9 mmol) and sodium hydrogenphosphate (27.2 g, 192 mmol) in N,N-Dimethylacetamide (250 ml) were added N-(2-bromoacetyl) cyclopropanecarboxamide (19.75 g, 96 mmol) and potassium iodide (10.61 g, 63.9 mmol) at room temperature. The reaction mixture was stirred for 5h at 100°C. Reaction mixture cooled to room temperature, diluted with EtOAc(1000ml) and washed with brine solution (5X), dried over Na_2SO_4, volatiles evaporated and the residue was purified by combiflash (2 to 30%MeOH in dichloromethane over 120min). Product containing fractions were combined and concentrated to get N-(6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (13.9 g, 31.0 mmol, 48.5 % yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.92 (s, 1H), 8.18 - 8.35 (m, 2H), 7.92 - 8.06 (m, 1H), 7.61 - 7.80 (m, 2H), 1.91 - 2.02 (m, 1H), 0.78 - 0.89 (m, 4H). ESI-MS:m/z 450.0 $(M+2H)^+$.

[0495] N-(6-(Difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (45): A mixture of N-(6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (7.2 g, 16.06 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5.01 g, 24.10 mmol) and $PdCl_2$(dppf):CH_2Cl_2 (0.655 g, 0.803 mmol) in 1,4-Dioxane:1M Na_2CO_3 (Ratio: 2.1, Volume: 100 ml) was heated at 95°C for 4h. The reaction mixture cooled and concentrated to dryness via rotary evaporation, diluted with EtOAc and water. The resulting solid was collected by filtration, rinsed with H_2O followed by EtOAc. The grey color solid dissolved in 20%MeOH in chloroform and treated with activated charcoal for overnight, filtered through a pad of celite and the celite pad rinsed with 20%MeOH in chloroform until no compound detected by HPLC. This solution passed through a silica gel column. The solvent evaporated and the resulting solid rinsed with EtOAc, MeOH, followed by EtOAc and then Et_2O, dried under vacuum to provide N-(6-(difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (5.13 g, 11.41 mmol, 71.1 % yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.71 (s, 1H), 8.41 (s, 1H), 8.19 - 8.34 (m, 2H), 8.00 - 8.12 (m, 2H), 7.91 (dd, J = 1.64, 9.47 Hz, 1H), 7.71 (d, J =

9.35 Hz, 1H), 3.88 (s, 3H), 1.88 - 2.02 (m, 1H), 0.83 (d, J = 6.32 Hz, 4H). ESI-MS:m/z 450.1 $(M+H)^+$. MP: 274.9°C.

[0496] The bis HCl salt of Compound 45 was prepared as follows. N-(6-(Difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide bis hydrochloride: N-(6-(difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (2.100 g, 4.67 mmol) in a mixture of MeOH and DCM (Ratio: 1:2, Volume: 100 ml) was added hydrogen chloride (12N, 0.973 ml, 11.68 mmol) at room temperature and stirred for 2h. Volatiles evaporated to dryness and the solid was rinsed with EtOAc and ether then dried under vacuum to provide N-(6-(difluoro(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide,2HCl (2.4 g, 4.59 mmol, 98 % yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (br. s., 2H), 11.32 (s, 1H), 8.66 (s, 1H), 8.36 (s, 1H), 8.14 - 8.27 (m, 2H), 7.94 - 8.08 (m, 2H), 7.87 (dd, J = 1.52, 9.60 Hz, 1H), 7.65 (d, J = 9.35 Hz, 1H), 3.82 (s, 3H), 1.84 - 1.99 (m, 1H), 0.77 (d, J = 6.32 Hz, 4H). ESI-MS:m/z 450.1 $(M+H)^+$. MP: 208°C.

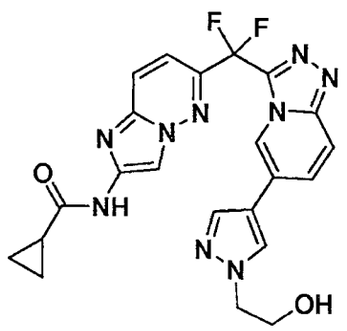
Compound 46: N-(6-(difluoro(6-(isoxazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0497] A mixture of N-(6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)-N (cyclopropanecarbonyl)cyclopropanecarboxamide (**45N**, 0.200 g, 0.38 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (0.1 g, 0.5 mmol) and $PdCl_2$(dppf):CH_2Cl_2 (5 mg, 0.006 mmol) in Na_2CO_3 (2N, 1 mL)/dioxane (2 mL) was heated at 110°C in a microwave for 30 min. The reaction mixture was filtered and the solids washed with EtOAc. The filtrate was then washed with saturated NaCl, dried with $MgSO_4$, filtered, and concentrated to dryness via rotary evaporation. The resulting residue was purified by preparative LCMS.

The collected fractions were combined and the resulting mixture was treated with two drops of concentrated HCl. The solution was lyophilized to provide the HCl salt of the title compound, N-(6-(difluoro(6-(isoxazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (20 mg, 0.04 mmol, 12%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 (d, J=6.32 Hz, 4 H) 1.91 - 2.01 (m, 1 H) 7.67 (dd, J=9.47, 5.43 Hz, 1 H) 7.75 (dd, J=9.73, 1.64 Hz, 1 H) 7.84 (dd, J=9.85, 1.77 Hz, 1 H) 7.98 - 8.07 (m, 1 H) 8.23 - 8.34 (m, 2 H) 8.46 (s, 1 H) 9.02 (s, 1 H) 11.36 (d, J=2.27 Hz, 1 H). ESI-MS:m/z 437.2 $(M+H)^+$.

Compound 47: N-(6-(difluoro(6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

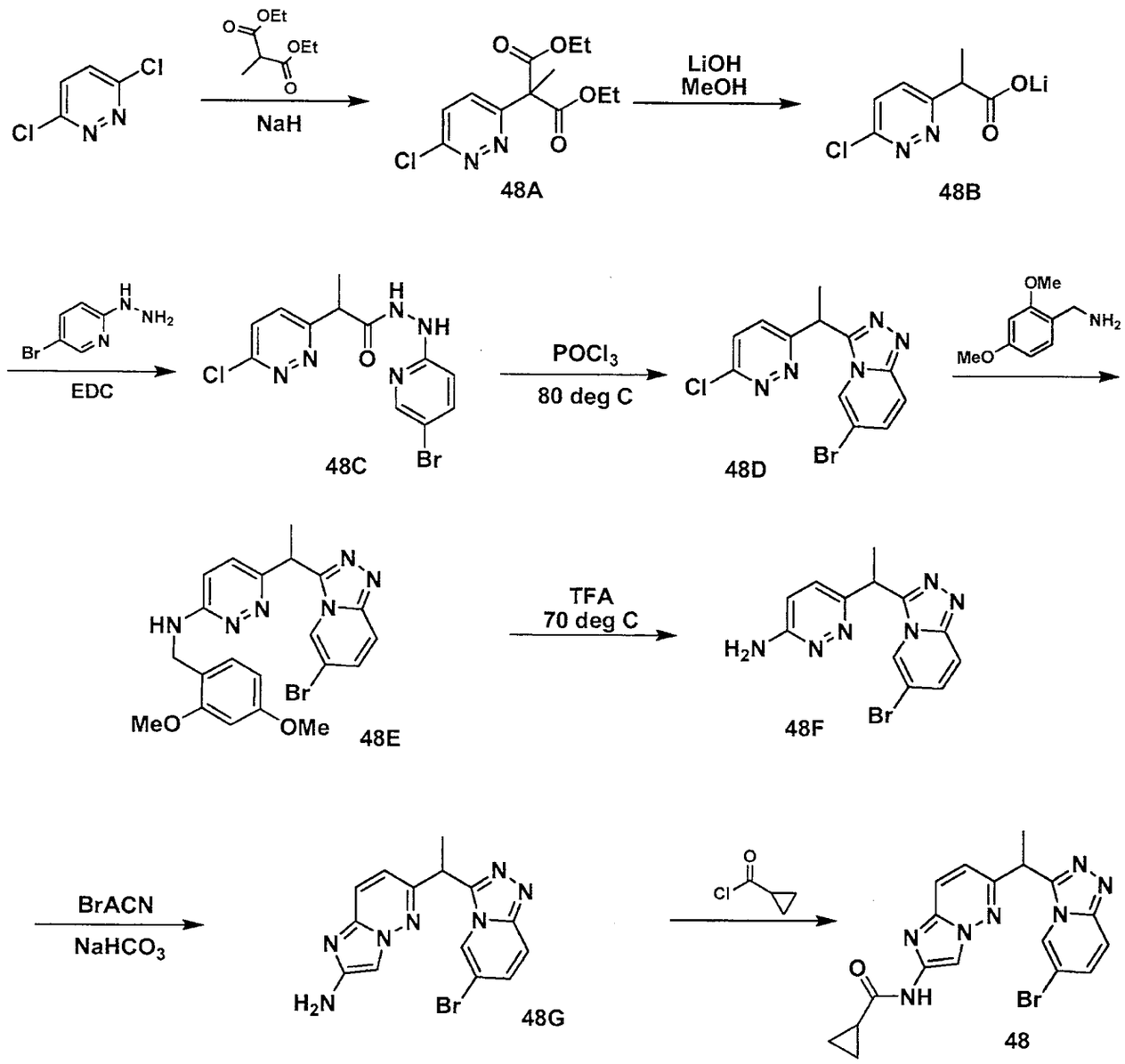


[0498] A mixture of N-(6-((6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)-N (cyclopropanecarbonyl) cyclopropanecarboxamide (**45N**, 0.067 g, 0.13 mmol), 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.042 g, 0.130 mmol) and $PdCl_2$(dppf) (5 mg, 0.006 mmol) in Na_2CO_3 (2N, 1 mL)/dioxane (2 mL) was heated at 110°C in a microwave for 30 min. Reaction mixture was filtered and washed with EtOAc. The organic phase was washed with saturated NaCl, dried with $MgSO_4$, filtered, and concentrated to dryness. The resulting residue was dissolved in 4 N HCl/dioxane and stirred at ambient temperature for 30 min and then concentrated to dryness. The resulting material was purified by preparative LCMS. The collected fractions were combined and the resulting mixture was treated with two drops of concentrated HCl. The solution was lyophilized to provide the HCl salt of the title compound, (18 mg, 0.037 mmol, 29%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, J=6.06 Hz, 4 H) 1.95 (d, J=5.81 Hz, 1 H) 3.77 (t, J=5.43 Hz, 2 H) 4.10 - 4.21 (m, 2 H) 7.71 (d, J=9.35 Hz, 1 H) 7.87 - 7.98 (m, 1 H) 8.00 - 8.07 (m, 1 H) 8.11

(s, 1 H) 8.20 - 8.33 (m, 2 H) 8.44 (s, 1 H) 8.73 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 480.2 $(M+H)^+$.

Compound 48: N-(6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

Method A



[0499] **Diethyl 2-(6-chloropyridazin-3-yl)-2-methylmalonate**: To a mixture of NaH (13.42 g, 336 mmol) in dioxane (800 mL) was added diethyl 2-methylmalonate (42.9 ml, 252 mmol) drop-wise at 0°C. The reaction was stirred at 0°C for 1 hr and allowed to warm to ambient temperature. 3,6-dichloropyridazine (25 g, 168 mmol) was then added portion-wise

at 25°C. The reaction was then stirred at reflux for 1 hr. Solvent was removed via rotary evaporation and the resulting residue was dissolved in EtOAc. The organic solution was washed with saturated $NaHCO_3$ (100 mL) followed by 5% citric acid. The organic layer was then dried with $MgSO_4$, filtered, and concentrated to dryness. The resulting residue was purified via MPLC (Hex:EtOAc, 3:1) to provide the title compound, diethyl 2-(6-chloropyridazin-3-yl)-2-methylmalonate **48A** (12 g, 25 % yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (s, 6 H) 1.81 (s, 3 H) 4.21 (dd, *J*=7.07, 2.27 Hz, 4 H) 8.00 (s, 2 H). ESI-MS:m/z 287.1 $(M+H)^+$.

[0500] **Lithium 2-(6-chloropyridazin-3-yl)propanoate**: A solution of diethyl 2-(6-chloropyridazin-3-yl)-2-methylmalonate (19.8 g, 69.1 mmol) and LiOH (3.31 g, 138 mmol) in MeOH:Water (3:1, 200 mL) was stirred at 25°C for 3 hrs. MeOH was removed from the reaction via rotary evaporation, and the resulting residue was reconstituted in H_2O (300 mL). The aqueous mixture was washed with Et_2O (3 x 100 mL) and then lyophilized to dryness to provide lithium 2-(6-chloropyridazin-3-yl)propanoate **48B** in quantitative yield. The material was used without further work-up. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 (3 H, d, *J*=7.33 Hz) 3.63 (1 H, q, *J*=7.24 Hz) 7.71 (2 H, s). ESI-MS:m/z 187.0 $(M+H)^+$.

[0501] **N'-(5-Bromopyridin-2-yl)-2-(6-chloropyridazin-3-yl)propanehydrazide**: A mixture of lithium 2-(6-chloropyridazin-3-yl)propanoate (7.2 g, 37.4 mmol), 5-bromo-2-hydrazinylpyridine (7.03 g, 37.4 mmol), 1*H*-benzo[d][1,2,3]triazol-1-ol (5.05 g, 37.4 mmol), and *N*1-((ethylimino)methylene)-*N*3,*N*3-dimethylpropane-1,3-diamine hydrochloride (7.89 g, 41.1 mmol) in DMF (Volume: 320 ml) was stirred for 4 hrs at 25°C. The reaction was poured into H_2O (2 L) and extracted with EtOAc (3 x 500 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. The resulting residue was purified by MPLC $CHCl_3$:MeOH (9:1) to provide the title compound, N'-(5-bromopyridin-2-yl)-2-(6-chloropyridazin-3-yl)propanehydrazide **48C** (5.5 g, 15.42 mmol, 41.2 % yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.52 (d, *J*=7.33 Hz, 3 H) 4.17 (d, *J*=7.07 Hz, 1 H) 6.52 (d, *J*=8.84 Hz, 1 H) 7.67 (dd, *J*=8.84, 2.53 Hz, 1 H) 7.87 (d, *J*=9.09 Hz, 1 H) 7.94 (d, *J*=8.84 Hz, 1 H) 8.11 (d, *J*=1.77 Hz, 1 H) 8.66 (d, *J*=1.52 Hz, 1 H) 10.20 (d, *J*=1.52 Hz, 1 H). ESI-MS:m/z 356.1 $(M+H)^+$.

[0502] **6-bromo-3-(1-(6-chloropyridazin-3-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine**: A solution of N'-(5-bromopyridin-2-yl)-2-(6-chloropyridazin-3-yl)propanehydrazide (5.0 g, 14.02 mmol) and phosphoryl trichloride (100 mL, 1073 mmol) was stirred at 90°C for 5 hrs.

The reaction was cooled, stripped to dryness, and the resulting material was reconstituted in a mixture of EtOAc and saturated $NaHCO_3$ (400 mL, 1:1)). The organic phase was isolated, washed with saturated $NaHCO_3$ (1 x 100 mL), and dried over $MgSO_4$. The organic phase was removed via rotary evaporation to provide the title compound, 6-bromo-3-(1-(6-chloropyridazin-3-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine **48D** (2.2 g, 6.50 mmol, 46.3 % yield). This material was used without further purification. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 1.86 (d, *J*=7.07 Hz, 3 H) 5.27 (d, *J*=7.33 Hz, 1 H) 7.49 (dd, *J*=9.60, 1.77 Hz, 1 H) 7.78 (dd, J=9.85, 1.01 Hz, 1 H) 7.94 (s, 2 H) 8.79 (s, 1 H). ESI-MS:m/z 339.1 $(M+H)^+$.

[0503] N-(2,4-dimethoxybenzyl)-6-(1-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)pyridazin-3-amine: A mixture of 6-bromo-3-(1-(6-chloropyridazin-3-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (650 mg, 1.920 mmol), (2,4-dimethoxyphenyl)methanamine (0.577 mL, 3.84 mmol), and $NaHCO_3$ (645 mg, 7.68 mmol) in IPA (10.0 mL) was heated in a microwave on high absorbance for 18 hrs at 140°C. The reaction was cooled to ambient temperature, stripped to dryness via rotary evaporation, and reconstitued in EtOAc (25 mL). The insolubles were filtered off and the filtrate was reduced to dryness. The resulting residue was purified via MPLC (DCM:MeOH, 98:2) to provide the title compound, 6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-N-(2,4-dimethoxybenzyl)pyridazin-3-amine **48E** (750 mg, 1.598 mmol, 83 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 1.77 (d, *J*=7.07 Hz, 3 H) 3.72 (s, 3 H) 4.37 (d, *J*=5.81 Hz, 2 H) 4.95 (d, *J*=7.07 Hz, 1 H) 6.44 (dd, *J*=8.34, 2.53 Hz, 1 H) 6.54 (d, *J*=2.27 Hz, 1 H) 6.85 (d, *J*=9.35 Hz, 1 H) 7.03 (s, 1 H) 7.12 (d, *J*=8.34 Hz, 1 H) 7.29 (d, *J*=9.35 Hz, 1 H) 7.45 (dd, *J*=9.73, 1.64 Hz, 1 H) 7.69 - 7.79 (m, 1 H) 8.59 (s, 1 H). ESI-MS:m/z 469.2 $(M+H)^+$.

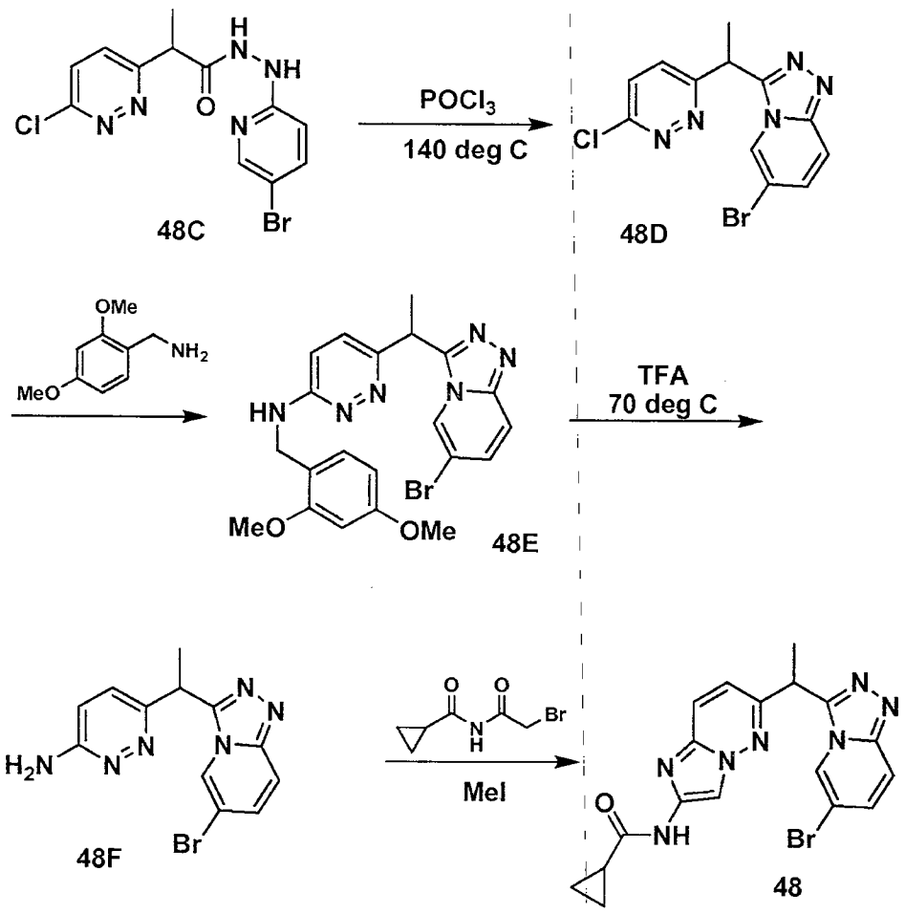
[0504] 6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)pyridazin-3-amine: A mixture of 6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-N-(2,4-dimethoxybenzyl)pyridazin-3-amine (750 mg, 1.598 mmol), anisole (0.349 mL, 3.20 mmol), and TFA (1.0 mL, 12.98 mmol) in DCM (5.0 mL) was heated in a microwave on high absorbance for 2 hrs at 75°C. The reaction was stripped to dryness via rotary evaporation, and the resulting oil was treated with Et_2O to produce a solid. The solid was filtered and dried under vacuum to provide the title compound, 6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)pyridazin-3-amine 2,2,2-trifluoroacetate (400 mg, 0.923 mmol, 57.8 % yield) as a yellow solid. ^{1}H NMR **48F** (400 MHz, DMSO-d6) δ ppm 1.77 (d, J=7.07 Hz, 3 H) 5.05 (d, J=7.07 Hz, 1 H) 7.44 (d, J=9.60 Hz, 1 H) 7.50 (dd, J=9.73, 1.64 Hz, 1 H) 7.73 -

7.84 (m, 1 H) 7.92 (d, J=9.60 Hz, 1 H) 8.56 (br. s., 2 H) 8.81 (s, 1 H). ESI-MS:m/z 319.1 $(M+H)^+$.

[0505] 6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-amine: A mixture of 6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)pyridazin-3-amine (1.0 g, 3.13 mmol), 2-bromoacetonitrile (0.251 ml, 3.76 mmol) and $NaHCO_3$ (0.053 g) in IPA (10 mL) was heated at 100°C in a sealed tube for 2 hrs. The solid was filtered off, rinsed with IPA, and stripped to dryness via rotary evaporation. The resulting residue was purified by LCMS and lyophilized as a TFA salt to provide the title compound, 6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-amine **48G** (0.62 mg, 1.73 mmol, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.85 (d, J=7.07 Hz, 3 H) 5.17 (d, J=7.07 Hz, 1 H) 7.38 - 7.57 (m, 3 H) 7.80 (d, J=9.60 Hz, 1 H) 7.99 (d, J=9.09 Hz, 1 H) 8.78 (s, 1 H). ESI-MS:m/z 358.1 $(M+H)^+$.

[0506] N-(6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: To a solution of 6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-amine TFA salt (250 mg, 0.52 mmol) in CH_2Cl_2 was added DIEA (0.65 g, 5.0 mmol) followed by cyclopropanecarbonyl chloride (0.16 g, 1.5 mmol). The reaction was stirred at ambient temperature for 30 min. Solvent was removed via rotary evaporation and the resulting residue was reconstituted in MeOH (10 mL). NH_4OH (0.5 mL) was added and the reaction was stirred at ambient temperature for 1 hr. The reaction was then concentrated to dryness and the resulting material was dissolved in EtOAc, washed with saturated $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated to dryness. The crude material was purified via MPLC (5%MeOH/0.1% NH_4OH/EA) to provide the title compound, N-(6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide **48** (0.22 g, 0.52 mmol, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm .73 - 0.87 (m, 4 H) 1.83 - 1.99 (m, 4 H) 5.17 (d, J=7.07 Hz, 1 H) 7.38 - 7.57 (m, 3 H) 7.80 (d, J=9.60 Hz, 1 H) 7.99 (d, J=9.09 Hz, 1 H) 8.78 (s, 1 H) 11.14 (s, 1 H). ESI-MS:m/z 426.2 $(M+H)^+$.

Method B



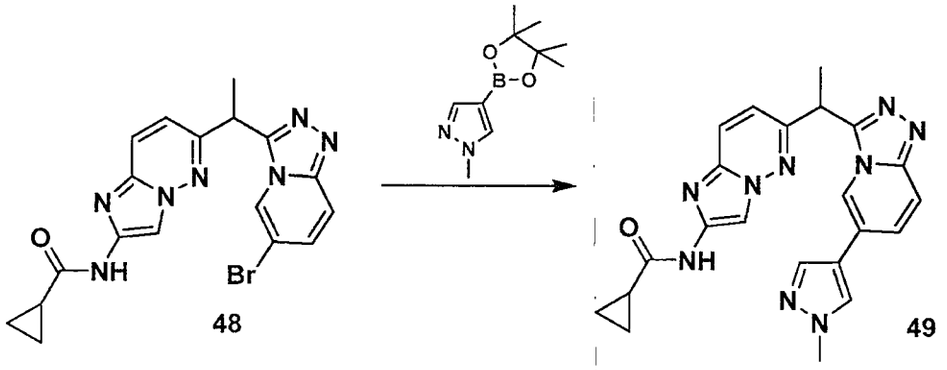
[0507] ***6-Bromo-3-(1-(6-chloropyridazin-3-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (48D)***: A solution of N'-(5-bromopyridin-2-yl)-2-(6-chloropyridazin-3-yl)propanehydrazide (13 g, 36.5 mmol) in phosphoryl trichloride (84 ml, 901 mmol) was heated in the microwave at 140°C for 15 min. The reaction was concentrated via rotary evaporation and the resulting mixture was added drop-wise to a mixture of EtOAc:Saturated Bicarbonate (aq) (4:6, 1L). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 75 mL). The EtOAc solutions were combined and evaporated to dryness. The resulting residue was purified by MPLC (DCM:MeOH, 97:3) to provide the title compound, 6-Bromo-3-(1-(6-chloropyridazin-3-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (48D, 3.3g, 26.7%). ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 1.86 (d, *J*=7.07 Hz, 3 H) 5.27 (d, *J*=7.33 Hz, 1 H) 7.49 (dd, *J*=9.60, 1.77 Hz, 1 H) 7.78 (dd, J=9.85, 1.01 Hz, 1 H) 7.94 (s, 2 H) 8.79 (s, 1 H). ESI-MS:m/z 339.1 $(M+H)^+$.

[0508] 6-(1-(6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-N-(2,4-dimethoxybenzyl)pyridazin-3-amine (48E): The title compound was synthesized using an analogous procedure to that described in the preparation of Compound 48E from Method A.

[0509] 6-(1-(6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)pyridazin-3-amine (48F): The title compound was synthesized using an analogous procedure to that described in the preparation of Compound 48E from Method A.

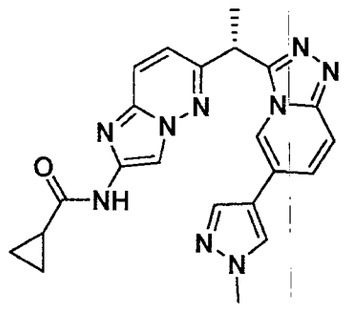
[0510] *N-(6-(1-(6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (48)*: The title compound was synthesized using an analogous procedure to that described in the preparation of Compound 45O.

Compound 49: N-(6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



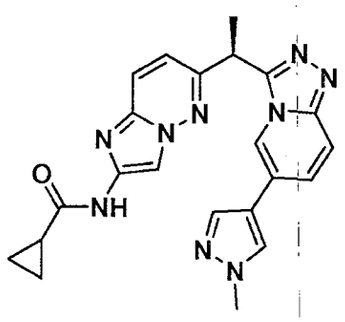
[0511] A mixture of N-(6-(1-(6-bromo-[1,2,4]triazolo[4,3-a]-pyridin-3-yl)imidazol[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide(0.23 g, 0.54 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.16 g, 0.8 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 (0.02 g, 0.02 mmol) in Na_2CO_3 (2N, 1 mL)/dioxane (2 mL) was heated in microwave at 110°C for 45 min. The reaction mixture was filtered, rinsed with EtOAc and concentrated to dryness via rotary evaporation. The resulting material was purified by preparative LCMS. The collected fractions were combined and the resulting mixture was treated with two drops of concentrated HCl. The solution was lyophilized to provide the HCl salt of the title compound, N-(6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide **49** (0.11 g, 0.25 mmol, 47%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (d, J=6.32 Hz, 4 H) 1.84 - 1.99 (m, 4 H) 3.87 (s, 3 H) 5.35 (d, J=7.07 Hz, 1 H) 7.43 (d, J=9.35 Hz, 1 H) 8.02 (d, J=9.35 Hz, 1 H) 8.05 - 8.13 (m, 3 H) 8.19 (dd, J=9.60, 1.52 Hz, 1 H) 8.38 (s, 1 H) 9.01 (s, 1 H) 11.18 (s, 1 H). MS:m/z 428.2 $(M+H)^+$.

Compound 50: (S)-N-(6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



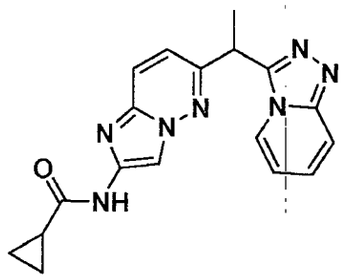
[0512] Compound **50** was obtained from chiral seperartion of Compound **49** under the following conditions: An SFC/UV system was used with mobile phases of 25 % EtOH (plus 10 mM NH_4OAc) in CO_2 on ChiralCel AS-H column (21 x 250 mm) at a flow rate of 50 mL/min with UV detection at 220 nm. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.88 (m, 3 H) 1.81 - 1.99 (m, 4 H) 3.87 (s, 3 H) 5.08 - 5.21 (m, 1 H) 7.27 (d, *J*=9.35 Hz, 1 H) 7.63 (dd, *J*=9.60, 1.52 Hz, 1 H) 7.80 (dd, *J*=9.60, 1.01 Hz, 1 H) 7.91 - 8.00 (m, 2 H) 8.12 (s, 1 H) 8.23 (s, 1 H) 8.62 (s, 1 H) 11.13 (s, 1 H). MS:m/z 428.2 $(M+H)^+$.

Compound 51: (R)-N-(6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



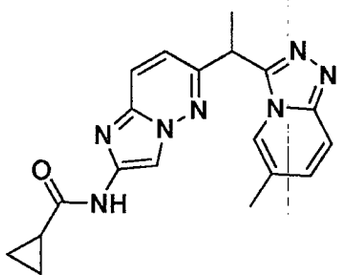
[0513] Compound **51** was obtained from chiral seperartion of Compound **49** under the following conditions: An SFC/UV system was used with mobile phases of 25 % EtOH (plus 10 mM NH_4OAc) in CO_2 on ChiralCel AS-H column (21 x 250 mm) at a flow rate of 50 mL/min with UV detection at 220 nm. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.88 (m, 3 H) 1.81 - 1.99 (m, 4 H) 3.87 (s, 3 H) 5.08 - 5.21 (m, 1 H) 7.27 (d, *J*=9.35 Hz, 1 H) 7.63 (dd, *J*=9.60, 1.52 Hz, 1 H) 7.80 (dd, *J*=9.60, 1.01 Hz, 1 H) 7.91 - 8.00 (m, 2 H) 8.12 (s, 1 H) 8.23 (s, 1 H) 8.62 (s, 1 H) 11.13 (s, 1 H). MS:m/z 428.2 $(M+H)^+$.

Compound 52: N-(6-(1-([1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



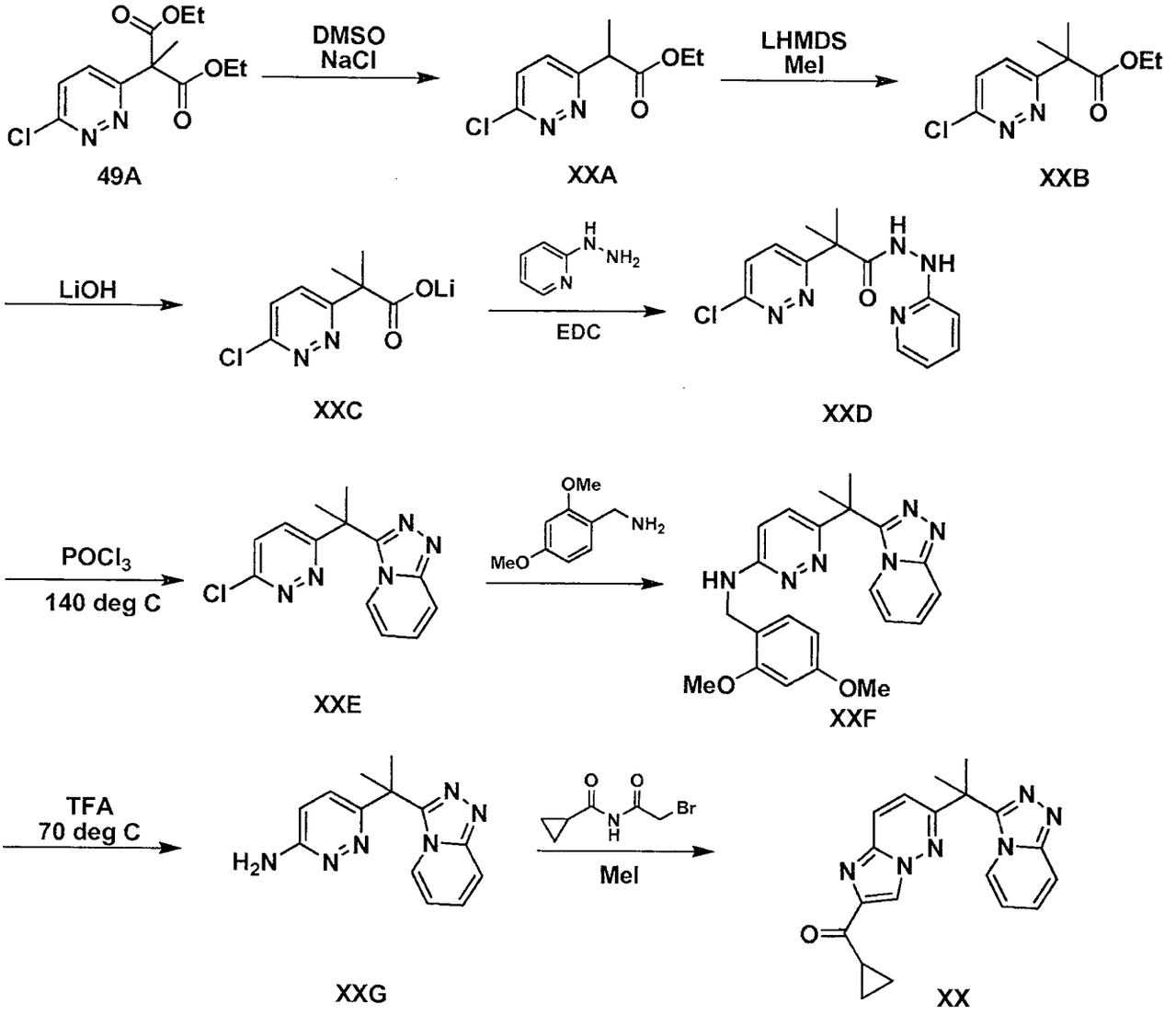
[0514] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **48** (Method A) using 2-hydrazinylpyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.87 (m, 4 H) 1.83 - 1.99 (m, 4 H) 5.04 - 5.15 (m, 1 H) 6.94 - 7.04 (m, 1 H) 7.19 (d, *J*=9.35 Hz, 1 H) 7.38 - 7.47 (m, 1 H) 7.80 (d, *J*=9.35 Hz, 1 H) 7.94 (d, *J*=9.85 Hz, 1 H) 8.10 (s, 1 H) 8.35 (d, *J*=7.07 Hz, 1 H) 11.14 (s, 1 H). MS:m/z 348.2 $(M+H)^+$.

Compound 53: N-(6-(1-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0515] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **48** (Method A) using 2-hydrazinyl-5-methylpyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.86 (m, 4 H) 1.85 (d, *J*=7.07 Hz, 3 H) 1.92 (m, 1 H) 3.56 (s, 3 H) 5.02 (d, *J*=7.07 Hz, 1 H) 7.18 (d, *J*=9.35 Hz, 1 H) 7.23 - 7.31 (m, 1 H) 7.70 (d, *J*=8.84 Hz, 1 H) 7.93 (d, *J*=9.85 Hz, 1 H) 8.10 (s, 1 H) 8.20 (s, 1 H) 11.13 (s, 1 H). MS:m/z 362.2 $(M+H)^+$.

Compound 54: (6-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)propan-2-yl)imidazo[1,2-b]pyridazin-2-yl)(cyclopropyl)methanone



[0516] *Ethyl 2-(6-chloropyridazin-3-yl)propanoate (*54A*)*: A solution of diethyl 2-(6-chloropyridazin-3-yl)-2-methylmalonate (11 g, 38.4 mmol) and NaCl (2.69 g, 46.0 mmol) in DMSO (91 mL) and H_2O (1.382 ml) was divided into eight separate microwave vials and each reaction was heated in a microwave at 175°C for 90 mins on high absorbance. The reactions were combined and then poured into H_2O (300 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL) and then the organic phase was washed with brine (2 x 100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness via rotary evaporation. The resulting oil was purified via MPLC (3:1, Hex:EtOAc) to provide the title compound, ethyl 2-(6-chloropyridazin-3-yl)propanoate (54A, 2.9g, 35%). ^{1}H NMR (400

MHz, DMSO-*d6*) δ ppm 1.13 (s, 3 H) 1.49 (d, *J*=7.33 Hz, 3 H) 4.09 (dd, *J*=7.07, 2.02 Hz, 2 H) 4.23 (d, *J*=7.33 Hz, 1 H) 7.83 (d, *J*=8.84 Hz, 1 H) 7.93 (d, *J*=8.84 Hz, 1 H). ESI-MS:m/z 215.0 $(M+H)^+$.

[0517] ***Ethyl 2-(6-chloropyridazin-3-yl)-2-methylpropanoate (54B)***: To a solution of ethyl 2-(6-chloropyridazin-3-yl)propanoate (2.8 g, 13.04 mmol) in THF (28 mL) was added lithium hexamethlydisilazide (1.0 molar in THF, 15.65 mL, 15.65 mmol) at -70°C in dropwise fashion. The reaction was stirred at -70 for 30 min and then iodomethane (0.816 mL, 13.04 mmol) was added. The reaction was stirred for 2 hrs as allowed to warm to room temperature. The reaction was concentrated to dryness via rotary evaporation and the resulting material was purified by MPLC (98:2, DCM:MeOH) to provide the title compound, ethyl 2-(6-chloropyridazin-3-yl)-2-methylpropanoate (54B, 2.82g, 95%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.11 (t, *J*=7.07 Hz, 3 H) 1.58 (s, 6 H) 4.08 (q, *J*=7.07 Hz, 2 H) 7.83 - 7.97 (m, 2 H).

[0518] ***Lithium 2-(6-chloropyridazin-3-yl)-2-methylpropanoate (54C)***: The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **48B**.

[0519] ***2-(6-Chloropyridazin-3-yl)-2-methyl-N'-(pyridin-2-yl)propanehydrazide (54D)***: The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **48C** using 2-hydrazinylpyridine.

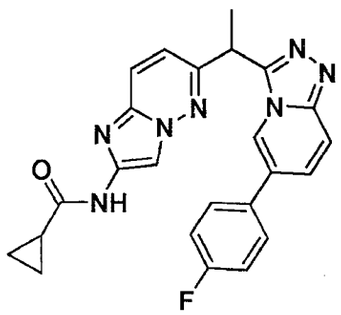
[0520] ***3-(2-(6-chloropyridazin-3-yl)propan-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (54E)***: A mixture of 2-(6-chloropyridazin-3-yl)-N'-(pyridin-2-yl)propanehydrazide (1.2 g, 4.32 mmol) and phosphoryl trichloride (10.0 mL, 107 mmol) was heated in a microwave on high absorbance for 15 min at 140°C. The resulting reaction was stripped to dryness via rotary evaporation. The resulting residue was reconstituted in EtOAc (50 mL) and washed with saturated bicarbonate (3 x 50 mL). The organic layer was seperated and dried over $MgSO_4$ and the EtOAc was removed via rotary evaporation to provide the title compound, 3-(2-(6-chloropyridazin-3-yl)propan-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (54E, 0.750 g, 2.74 mmol, 63.4 % yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.94 (6 H, s) 6.75 - 6.82 (1 H, m) 7.33 (1 H, ddd, *J*=9.35, 6.57, 1.01 Hz) 7.72 - 7.82 (2 H, m) 7.87 - 7.99 (2 H, m). ESI-MS:m/z 274.1 $(M+H)^+$.

[0521] ***6-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)propan-2-yl)-N-(2,4-dimethoxybenzyl)pyridazin-3-amine (54F)***: The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **48E**.

[0522] ***6-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)propan-2-yl)pyridazin-3-amine (54G)***: The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **48F**.

[0523] ***(6-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)propan-2-yl)imidazo[1,2-b]pyridazin-2-yl)(cyclopropyl)methanone (54)***: A mixture of 6-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)propan-2-yl)pyridazin-3-amine 2,2,2-trifluoroacetate (50 mg, 0.136 mmol), N-(2-bromoacetyl)cyclopropanecarboxamide (28.0 mg, 0.136 mmol), sodium hydrogenphosphate (57.8 mg, 0.407 mmol), and potassium iodide (22.54 mg, 0.136 mmol) in DMA (Volume: 1160 µl) was heated in a microwave on high absorbance for 1 hr at 100°C. The reaction was purified by preparative LCMS to provide the title compound, (6-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)propan-2-yl)imidazo[1,2-b]pyridazin-2-yl)(cyclopropyl)methanone (54, 13 mg, 26%) as a TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.81 (d, *J*=6.06 Hz, 4 H) 1.87 - 2.00 (m, 7 H) 6.92 - 6.97 (m, 1 H) 7.12 (d, *J*=9.60 Hz, 1 H) 7.55 (dd, *J*=8.97, 6.69 Hz, 1 H) 7.87 - 8.01 (m, 3 H) 8.04 (s, 1 H) 11.16 (s, 1 H). ESI-MS:m/z 362.1 $(M+H)^+$.

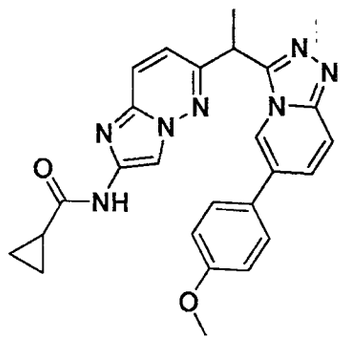
Compound 55: N-(6-(1-(6-(4-fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0524] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-fluorophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.72 - 0.88 (m, 4 H) 1.81 - 1.98 (m, 4 H) 5.30 (d, *J*=7.07 Hz, 1 H) 7.30 (d, *J*=9.35 Hz, 1 H) 7.32 - 7.40 (m, 2H) 7.76 - 7.82 (m, 2 H) 7.82 - 7.88

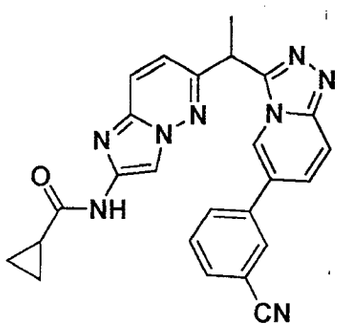
(m, 1 H) 7.95 (t, *J*=9.09 Hz, 2 H) 8.09 (s, 1 H) 8.78 (s, 1 H) 11.14 (s, 1 H). ESI-MS:m/z 442.2 $(M+H)^+$.

Compound56: N-(6-(1-(6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



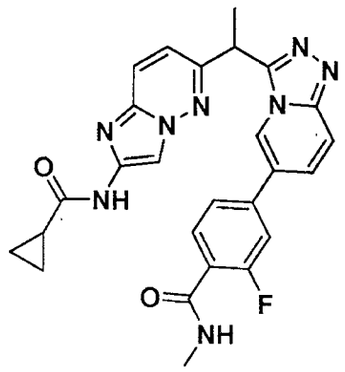
[0525] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-methoxyphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.73 - 0.87 (m, 5 H) 1.84 - 2.00 (m, 5 H) 5.30 (d, *J*=7.33 Hz, 1 H) 7.02 - 7.14 (m, 3 H) 7.29 (d, *J*=9.35 Hz, 1H) 7.61 - 7.72 (m, 3 H) 7.83 - 8.00 (m, 4 H) 8.10 (s, 1 H) 8.71 (s, 1 H) 11.15 (s, 1 H). ESI-MS:m/z 454.2 $(M+H)^+$.

Compound 57: N-(6-(1-(6-(3-cyanophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



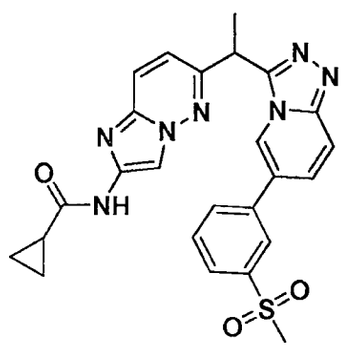
[0526] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 3-cyanophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.71 - 0.86 (m, 4 H) 1.82 - 1.97 (m, 4 H) 5.24 - 5.37 (m, 1 H) 7.31 (d, *J*=9.60 Hz, 1 H) 7.69 - 7.75 (m, 1 H) 7.87 - 7.99 (m, 4 H) 8.05 - 8.13 (m, 2 H) 8.31 (t, *J*=1.52 Hz, 1 H) 8.94 (s, 1 H) 11.12 (s, 1 H). ESI-MS:m/z 449.2 $(M+H)^+$.

Compound 58: 4-(3-(1-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-fluoro-N-methylbenzamide



[0527] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 3-fluoro-4-(methylcarbamoyl)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.72 - 0.86 (m, 4 H) 1.84 - 1.98 (m, 4 H) 2.80 (d, *J*=4.55 Hz, 3 H) 5.31 (d, *J*=7.07 Hz, 1 H) 7.30 (d, *J*=9.35 Hz, 1 H) 7.66 - 7.71 (m, 1 H) 7.71 - 7.81 (m, 2 H) 7.83 - 7.88 (m, 1 H) 7.89 - 7.98 (m, 2 H) 8.09 (s, 1 H) 8.30 (dd, *J*=4.55, 2.53 Hz, 1 H) 8.89 (s, 1 H) 11.13 (s, 1 H). ESI-MS:m/z 499.2 $(M+H)^+$.

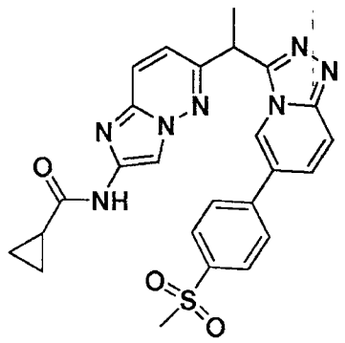
Compound 59: N-(6-(1-(6-(3-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0528] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 3-(methylsulfonyl)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.74 - 0.85 (m, 5 H) 1.83 - 1.98 (m, 5 H) 5.34 (d, *J*=7.07 Hz, 1 H) 7.32 (d, *J*=9.35 Hz, 1 H) 7.73 - 7.85 (m, 1 H) 7.89 - 8.03 (m, 5

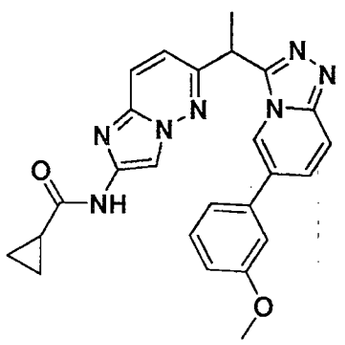
H) 8.05 - 8.14 (m, 2 H) 8.27 (t, *J*=1.64 Hz, 1 H) 8.93 (s, 1 H) 11.13 (s, 1 H). ESI-MS:m/z 502.2 $(M+H)^+$.

Compound 60: N-(6-(1-(6-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0529] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-(methylsulfonyl)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.73 - 0.87 (m, 5 H) 1.83 - 1.98 (m, 5 H) 5.31 (d, *J*=7.07 Hz, 1 H) 7.30 (d, *J*=9.35 Hz, 1 H) 7.85 - 7.90 (m, 1 H) 7.93 - 7.99 (m, 2 H) 7.99 - 8.07 (m, 5 H) 8.09 (s, 1 H) 8.90 (s, 1 H) 11.13 (s, 1 H). ESI-MS:m/z 502.2 $(M+H)^+$.

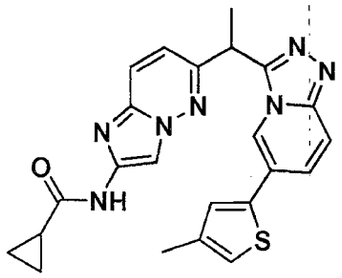
Compound 61: N-(6-(1-(6-(3-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0530] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 3-methoxyphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.74 - 0.85 (m, 4 H) 1.90 (d, *J*=7.33 Hz, 4 H) 3.61 (s, 3 H) 5.32 (d, *J*=7.07 Hz, 1 H) 7.02 (ddd, *J*=8.21, 2.40, 0.76 Hz, 1 H) 7.21 - 7.34

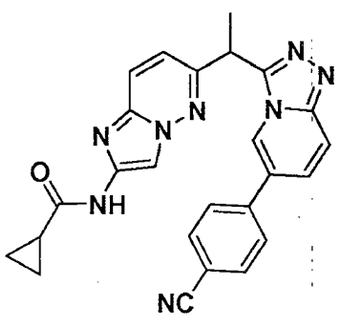
(m, 3 H) 7.37 - 7.49 (m, 1 H) 7.87 - 8.00 (m, 3 H) 8.09 (s, 1 H) 8.77 (s, 1 H) 11.14 (s, 1 H). ESI-MS:m/z 454.2 $(M+H)^+$.

Compound 62: N-(6-(1-(6-(4-methylthiophen-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



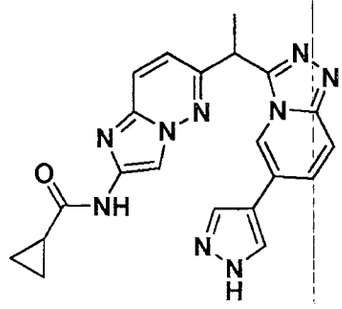
[0531] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-methylthiophen-2-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.75 - 0.87 (m, 4 H) 1.82 - 1.98 (m, 4 H) 2.24 (d, *J*=0.76 Hz, 3 H) 5.24 (d, *J*=7.33 Hz, 1 H) 7.17 - 7.30 (m, 2 H) 7.45 (d, *J*=1.26 Hz, 1 H) 7.71 (dd, *J*=9.60, 1.52 Hz, 1 H) 7.86 (dd, *J*=9.47, 0.88 Hz, 1 H) 7.95 (d, *J*=9.60 Hz, 1 H) 8.13 (s, 1 H) 8.64 (s, 1 H) 11.15 (s, 1 H). ESI-MS:m/z 444.2 $(M+H)^+$.

Compound 63: N-(6-(1-(6-(4-cyanophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



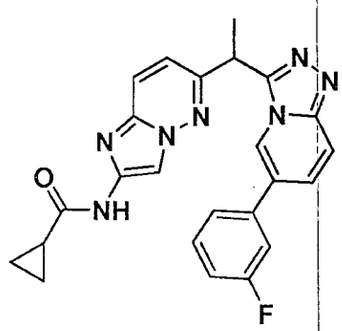
[0532] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-cyanophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.73 - 0.87 (m, 4 H) 1.83 - 2.00 (m, 4 H) 5.29 (d, *J*=7.07 Hz, 1 H) 7.29 (d, *J*=9.35 Hz, 1 H) 7.80 - 7.89 (m, 1 H) 7.90 - 8.04 (m, 6 H) 8.08 (s, 1 H) 8.90 (s, 1 H) 11.13 (s, 1 H). ESI-MS:m/z 449.2 $(M+H)^+$.

Compound 64: N-(6-(1-(6-(1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



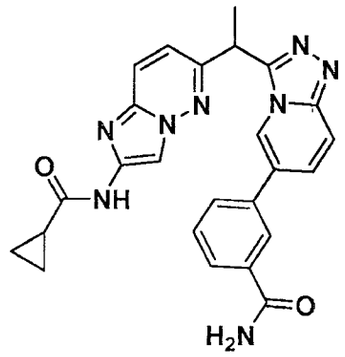
[0533] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 1H-pyrazol-4-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.73 - 0.86 (m, 4 H) 1.82 - 1.99 (m, 4 H) 5.21 (d, *J*=7.33 Hz, 1 H) 7.31 (d, *J*=9.60 Hz, 1 H) 7.88 (d, *J*=6.06 Hz, 2 H) 7.97 (d, *J*=9.35 Hz, 1 H) 8.11 (s, 1 H) 8.19 (s, 2 H) 8.75 (s, 1 H) 11.13 (s, 1 H). ESI-MS:m/z 414.2 $(M+H)^+$.

Compound 65: N-(6-(1-(6-(3-fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



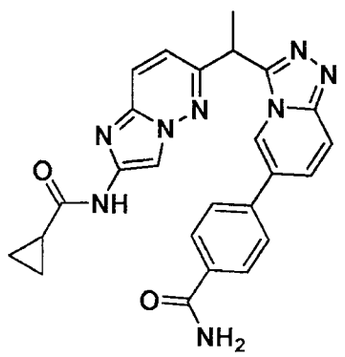
[0534] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-fluorophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.72 - 0.87 (m, 4 H) 1.83 - 1.97 (m, 4 H) 5.29 (d, *J*=7.33 Hz, 1 H) 7.51 - 7.61 (m, 2 H) 7.64 (dt, *J*=10.29, 2.05 Hz, 1 H) 7.81 (dd, *J*=9.73, 1.64 Hz, 1 H) 7.87 - 7.92 (m, 1 H) 7.94 (d, *J*=9.35 Hz, 1 H) 8.09 (s, 1 H) 8.80 (s, 1 H) 11.08 (s, 1 H). ESI-MS:m/z 442.2 $(M+H)^+$.

Compound 66: 3-(3-(1-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)benzamide



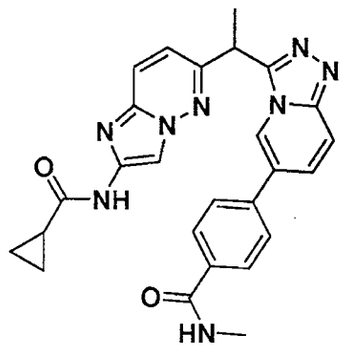
[0535] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 3-carbamoylphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) ppm 0.71 - 0.89 (m, 4 H) 1.83 - 2.00 (m, 4 H) 7.31 (d, *J*=9.35 Hz, 1 H) 7.46 (br. s., 1 H) 7.60 (t, *J*=7.71 Hz, 1 H) 7.82 - 8.03 (m, 5 H) 8.04 - 8.14 (m, 2 H) 8.22 (t, *J*=1.52 Hz, 1 H) 8.86 (s, 1 H) 11.09 (s, 1 H). ESI-MS:m/z 467.2 $(M+H)^+$.

Compound 67: 4-(3-(1-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)benzamide



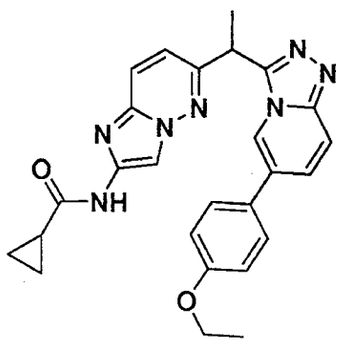
[0536] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-carbamoylphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.73 - 0.89 (m, 4 H) 1.83 - 1.99 (m, 4 H) 5.29 (d, *J*=7.33 Hz, 1 H) 7.28 (d, *J*=9.35 Hz, 1 H) 7.77 - 7.86 (m, 3 H) 7.87 - 7.92 (m, 1 H) 7.94 (d, *J*=9.35 Hz, 1 H) 7.97 - 8.06 (m, 3 H) 8.10 (s, 1 H) 8.79 (s, 1 H) 11.08 (s, 1 H). ESI-MS:m/z 467.2 $(M+H)^+$.

Compound 68: 4-(3-(1-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-N-methylbenzamide



[0537] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-(methylcarbamoyl)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.72 - 0.88 (m, 4 H) 1.83 - 1.99 (m, 4 H) 2.81 (d, *J*=4.55 Hz, 3 H) 5.30 (d, *J*=7.07 Hz, 1 H) 7.28 (d, *J*=9.35 Hz, 1 H) 7.78 - 7.87 (m, 3 H) 7.87 - 8.00 (m, 4 H) 8.10 (s, 1 H) 8.49 (d, *J*=4.55 Hz, 1 H) 8.81 (s, 1 H) 11.09 (s, 1 H). ESI-MS:m/z 481.2 $(M+H)^+$.

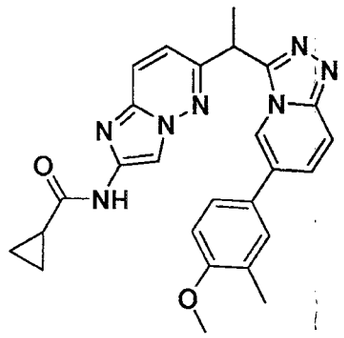
Compound 69: N-(6-(1-(6-(4-ethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0538] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-ethoxyphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.72 - 0.87 (m, 4 H) 1.34 (t, *J*=6.95 Hz, 3 H) 1.82 - 1.98 (m, 4 H) 5.27 (d, *J*=7.07 Hz, 1 H) 6.99 - 7.10 (m, 2 H) 7.26 (d, *J*=9.35 Hz, 1 H)

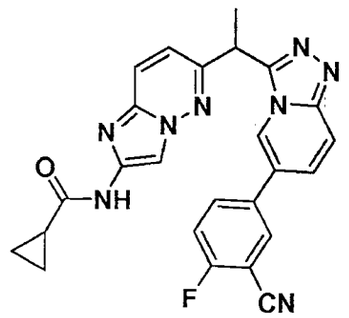
7.57 - 7.69 (m, 2 H) 7.74 - 7.83 (m, 1 H) 7.84 - 7.91 (m, 1 H) 7.94 (d, *J*=9.60 Hz, 1 H) 8.10 (s, 1 H) 8.64 (s, 1 H) 11.09 (s, 1 H). ESI-MS:m/z 468.2 $(M+H)^+$.

Compound 70: N-(6-(1-(6-(4-methoxy-3-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0539] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-methoxy-3-methylphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.74 - 0.86 (m, 5 H) 1.85 - 1.99 (m, 5 H) 2.21 (s, 4 H) 5.29 (d, *J*=7.33 Hz, 2 H) 7.06 (d, *J*=8.59 Hz, 1 H) 7.28 (d, *J*=9.35 Hz, 1 H) 7.42 - 7.57 (m, 2 H) 7.78 - 7.99 (m, 4 H) 8.12 (s, 1 H) 8.65 (s, 1 H) 11.10 (s, 1 H). ESI-MS:m/z 468.2 $(M+H)^+$.

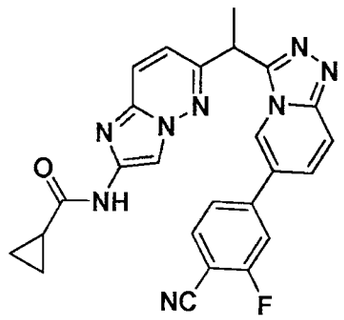
Compound 71: N-(6-(1-(6-(3-cyano-4-fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0540] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 3-cyano-4-fluorophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.73 - 0.86 (m, 4 H) 1.84 - 1.99 (m, 5 H) 5.26 (d, *J*=7.33 Hz, 1 H) 7.29 (d, *J*=9.60 Hz, 1 H) 7.68 (t, *J*=8.97 Hz, 1 H) 7.75 - 7.84 (m,

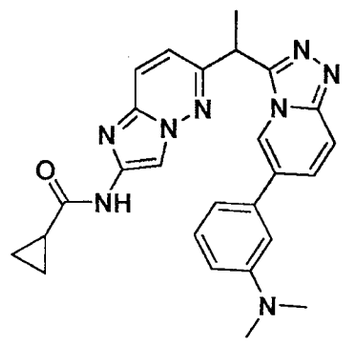
1 H) 7.87 - 7.98 (m, 2 H) 8.08 (s, 1 H) 8.12 - 8.22 (m, 1 H) 8.38 (dd, *J*=6.19, 2.40 Hz, 1 H) 8.86 (s, 1 H) 11.08 (s, 1 H). ESI-MS:m/z 467.2 $(M+H)^+$.

Compound 72: N-(6-(1-(6-(4-cyano-3-fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0541] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 4-cyano-3-fluorophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.73 - 0.86 (m, 4 H) 1.82 - 2.00 (m, 4 H) 5.29 (d, *J*=7.33 Hz, 1 H) 7.29 (d, *J*=9.60 Hz, 1 H) 7.82 - 7.88 (m, 2 H) 7.89 - 7.97 (m, 2 H) 8.02 (dd, *J*=10.99, 1.64 Hz, 1 H) 8.05 - 8.10 (m, 2 H) 8.95 (s, 1 H) 11.08 (s, 1 H). ESI-MS:m/z 467.2 $(M+H)^+$.

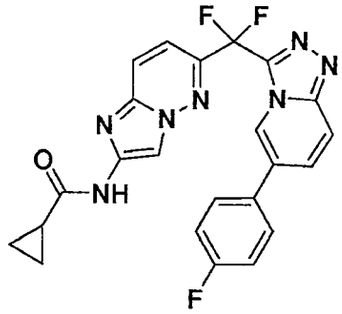
Compound 73: N-(6-(1-(6-(3-(dimethylamino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0542] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **49** using 3-(dimethylamino)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.74 - 0.86 (m, 4 H) 1.91 (d, *J*=7.07 Hz, 4 H) 2.94 (s, 6 H) 5.29 (d, *J*=7.33 Hz, 1 H) 6.82 (dd, *J*=8.21, 2.15 Hz, 1 H) 6.90 (s, 1 H)

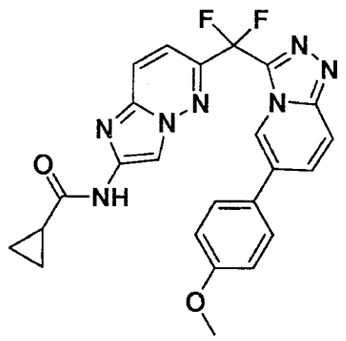
6.97 (d, *J*=7.83 Hz, 1 H) 7.25 - 7.34 (m, 2 H) 7.83 - 7.89 (m, 1 H) 7.89 - 7.98 (m, 2 H) 8.09 (s, 1 H) 8.62 (s, 1 H) 11.09 (s, 1 H). ESI-MS:m/z 467.2 $(M+H)^+$.

Compound 74: N-(6-(difluoro(6-(4-fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0543] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 4-fluorophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.19 Hz, 1 H) 7.37 (t, *J*=8.84 Hz, 2 H) 7.71 (d, *J*=9.35 Hz, 1 H) 7.79 - 7.85 (m, 2 H) 7.96 (dd, *J*=9.73, 1.39 Hz, 1 H) 8.12 (d, *J*=9.60 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.74 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 464.2 $(M+H)^+$.

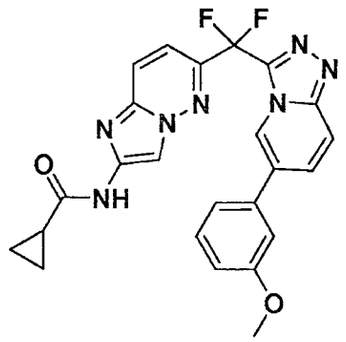
Compound 75: N-(6-(difluoro(6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0544] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** (*Method B*) using 4-methoxyphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.32 Hz, 4 H) 1.92 - 2.00 (m, 1 H) 3.82 (s, 3 H) 7.09 (d, *J*=8.84 Hz, 2 H) 7.70 (d, 2 H) 7.72 (s, 1 H) 7.95 (dd,

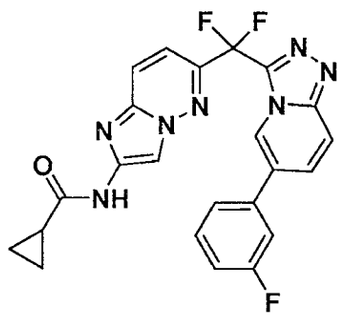
J=9.60, 1.52 Hz, 1 H) 8.08 (d, *J*=9.60 Hz, 1 H) 8.25 (s, 1 H) 8.27 (d, *J*=9.60 Hz, 1 H) 8.66 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 476.2 $(M+H)^+$.

Compound 76: N-(6-(difluoro(6-(3-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0545] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3-methoxyphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.91 - 2.01 (m, 1 H) 3.83 (s, 3 H) 7.05 (dd, *J*=8.21, 1.89 Hz, 1 H) 7.26 (d, *J*=2.02 Hz, 1 H) 7.30 (d, *J*=7.58 Hz, 1 H) 7.44 (t, 1 H) 7.71 (d, *J*=9.35 Hz, 1 H) 7.98 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.11 (d, *J*=8.84 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.73 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 476.2 $(M+H)^+$.

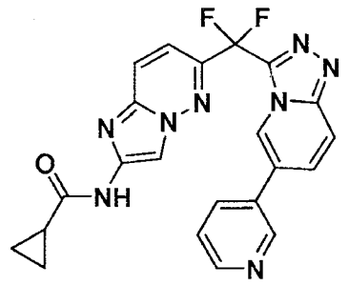
Compound 77: N-(6-(difluoro(6-(3-fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0546] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3-fluorophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.19 Hz, 1

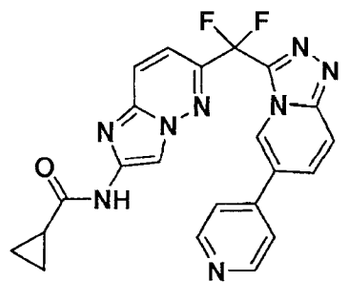
H) 7.32 (dt, 1 H) 7.54 - 7.59 (m, 1 H) 7.62 (t, *J*=7.58 Hz, 1 H) 7.68 (dt, 1 H) 7.71 (d, 1 H) 8.00 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.13 (d, *J*=9.60 Hz, 1 H) 8.23 (s, 1 H) 8.28 (d, *J*=9.60 Hz, 1 H) 8.81 (s, 1 H) 11.34 (s, 1 H). ESI-MS:m/z 464.2 $(M+H)^+$.

Compound 78: N-(6-(difluoro(6-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0547] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using pyridin-3-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.13 Hz, 1 H) 7.61 (dd, *J*=7.96, 4.93 Hz, 1 H) 7.73 (d, *J*=9.35 Hz, 1 H) 8.02 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.17 (d, *J*=9.09 Hz, 1 H) 8.22 (s, 1 H) 8.25 (s, 1 H) 8.26 - 8.32 (m, 1 H) 8.69 (d, *J*=4.29 Hz, 1 H) 8.90 (s, 1 H) 9.00 (br. s., 1 H) 11.34 (s, 1 H). ESI-MS:m/z 447.2 $(M+H)^+$.

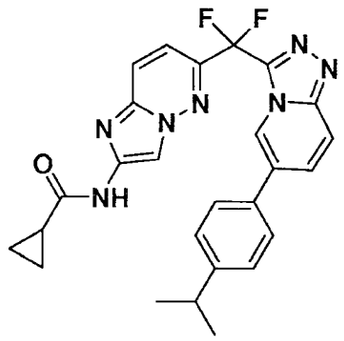
Compound 79: N-(6-(difluoro(6-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0548] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using pyridin-4-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=5.31 Hz, 4 H) 1.96 (quin, *J*=6.13 Hz, 1 H) 7.69 - 7.77 (m, 1 H) 7.93 (d, *J*=5.05 Hz, 2 H) 8.07 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.19 (d,

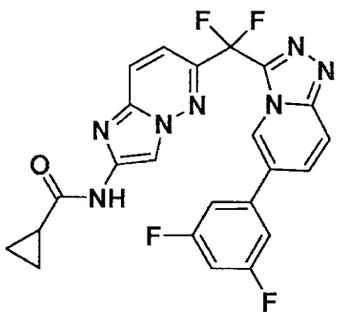
J=9.85 Hz, 1 H) 8.23 (s, 1 H) 8.29 (d, *J*=9.35 Hz, 1 H) 8.76 (br. s., 2 H) 8.98 (s, 1 H) 11.34 (s, 1 H). ESI-MS:m/z 447.2 $(M+H)^+$.

Compound 80: N-(6-(difluoro(6-(4-isopropylphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0549] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 4-isopropylphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.06 Hz, 4 H) 1.24 (d, *J*=6.82 Hz, 6 H) 1.95 (q, 1 H) 2.96 (spt, *J*=6.86 Hz, 1 H) 7.40 (d, *J*=8.34 Hz, 2 H) 7.67 (d, *J*=8.34 Hz, 2 H) 7.71 (d, *J*=9.35 Hz, 1 H) 7.96 (dd, *J*=9.60, 1.26 Hz, 1 H) 8.11 (d, *J*=9.60 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.70 (s, 1 H) 11.36 (s, 1 H). ESI-MS:m/z 488.2 $(M+H)^+$.

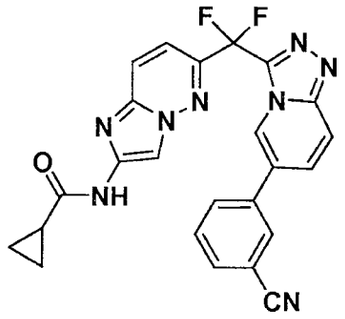
Compound 81: N-(6-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0550] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3,5-difluorophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=5.81 Hz, 4 H) 1.95 (quin, 1

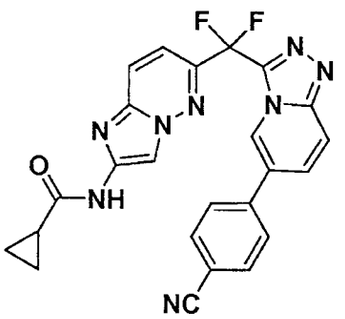
H) 7.32 - 7.42 (m, 1 H) 7.56 - 7.66 (m, 2 H) 7.73 (d, *J*=9.60 Hz, 1 H) 8.01 (dd, *J*=9.73, 1.39 Hz, 1 H) 8.14 (d, *J*=9.60 Hz, 1 H) 8.21 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.88 (s, 1 H) 11.34 (s, 1 H). ESI-MS:m/z 482.2 $(M+H)^+$.

Compound 82: N-(6-((6-(3-cyanophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0551] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3-cyanophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.13 Hz, 1 H) 7.68 - 7.77 (m, 2 H) 7.94 (d, *J*=7.83 Hz, 1 H) 8.03 (dd, *J*=9.73, 1.14 Hz, 1 H) 8.12 (d, *J*=8.34 Hz, 1 H) 8.16 (d, *J*=9.60 Hz, 1 H) 8.23 (s, 1 H) 8.29 (d, *J*=9.35 Hz, 1 H) 8.33 (s, 1 H) 8.93 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 471.2 $(M+H)^+$.

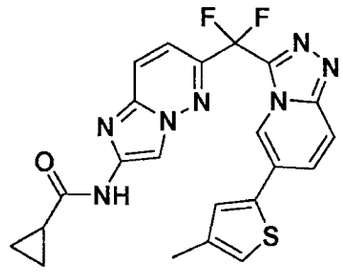
Compound 83: N-(6-((6-(4-cyanophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0552] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 4-cyanophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.19 Hz, 1

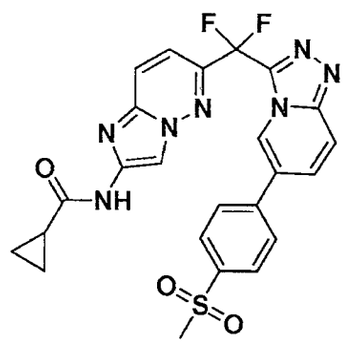
H) 7.72 (d, *J*=9.60 Hz, 1 H) 8.00 (s, 4 H) 8.03 (d, *J*=9.60 Hz, 1 H) 8.16 (d, *J*=9.60 Hz, 1 H) 8.20 - 8.24 (m, 1 H) 8.28 (d, *J*=9.60 Hz, 1 H) 8.89 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 471.2 $(M+H)^+$.

Compound 84: N-(6-(difluoro(6-(4-methylthiophen-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0553] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 4-methylthiophen-2-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.32 Hz, 4 H) 1.95 (q, 1 H) 2.26 (s, 3 H) 7.29 (s, 1 H) 7.59 (s, 1 H) 7.70 (d, *J*=9.35 Hz, 1 H) 7.91 (dd, *J*=9.73, 1.64 Hz, 1 H) 8.07 (d, *J*=9.60 Hz, 1 H) 8.26 (s, 1 H) 8.25 - 8.30 (m, 1 H) 8.69 (s, 1 H) 11.36 (s, 1 H). ESI-MS:m/z 466.2 $(M+H)^+$.

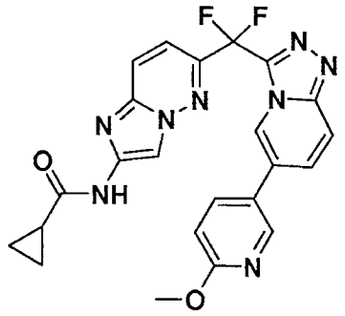
Compound 85: N-(6-(difluoro(6-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0554] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 4-(methylsulfonyl)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (q, 1 H) 3.28 (s, 3 H) 7.72 (d, *J*=9.35 Hz, 1 H) 8.02 (dd, 1 H) 8.05 (s, 4 H) 8.17 (d, *J*=9.60 Hz, 1 H)

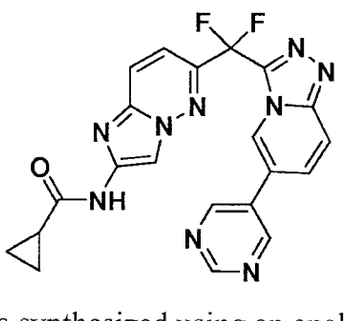
8.23 (s, 1 H) 8.28 (d, *J*=9.60 Hz, 1 H) 8.88 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 524.2 $(M+H)^+$.

Compound 86: N-(6-(difluoro(6-(6-methoxypyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0555] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 6-methoxypyridin-3-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.19 Hz, 1 H) 3.91 (s, 3 H) 6.97 (d, *J*=8.59 Hz, 1 H) 7.72 (d, *J*=9.35 Hz, 1 H) 7.97 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.09 - 8.15 (m, 2 H) 8.22 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.56 (d, *J*=2.53 Hz, 1 H) 8.78 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 477.2 $(M+H)^+$.

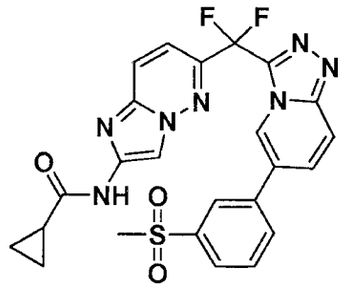
Compound 87: N-(6-(difluoro(6-(pyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0556] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using pyrimidin-5-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=5.56 Hz, 4 H) 1.90 - 2.00 (m, 1 H) 7.74 (d, *J*=9.60 Hz, 1 H) 8.06 (dd, *J*=9.60, 1.26 Hz, 1 H) 8.17 - 8.25 (m, 2 H) 8.29 (d, *J*=9.35

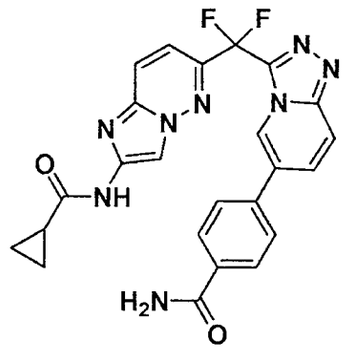
Hz, 1 H) 9.03 (s, 1 H) 9.21 (s, 2 H) 9.24 - 9.29 (m, 1 H) 11.34 (s, 1 H). ESI-MS:m/z 448.2 $(M+H)^+$.

Compound 88: N-(6-(difluoro(6-(3-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0557] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3-(methylsulfonyl)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, J=6.06 Hz, 4 H) 1.91 - 2.01 (m, 1 H) 3.32 (s, 3 H) 7.72 (d, J=9.35 Hz, 1 H) 7.81 (t, J=7.83 Hz, 1 H) 8.02 (d, J=7.83 Hz, 1 H) 8.06 (dd, J=9.60, 1.52 Hz, 1 H) 8.13 (d, J=7.83 Hz, 1 H) 8.18 (d, J=9.60 Hz, 1 H) 8.23 - 8.31 (m, 3 H) 8.92 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 524.2 $(M+H)^+$.

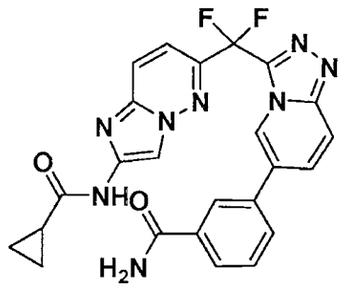
Compound 89: 4-(3-((2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)benzamide



[0558] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 4-carbamoylphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, J=6.32 Hz, 4 H) 1.90 - 2.01 (m, 1 H) 7.48 (br. s., 1 H) 7.72 (d, J=9.35 Hz, 1 H) 7.87 (d, J=8.34 Hz, 2 H) 7.98 - 8.06 (m, 3 H)

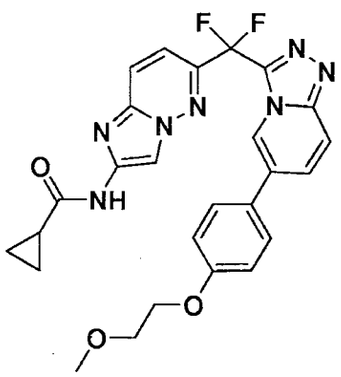
8.10 (br. s., 1 H) 8.11 - 8.17 (m, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.82 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 489.2 $(M+H)^+$.

Compound 90: 3-(3-((2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)benzamide



[0559] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3-carbamoylphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.13 Hz, 1 H) 7.53 (s, 1 H) 7.62 (t, *J*=7.70 Hz, 1 H) 7.72 (d, *J*=9.60 Hz, 1 H) 7.90 - 7.98 (m, 2 H) 8.04 (dd, *J*=9.73, 1.39 Hz, 1 H) 8.16 (d, *J*=9.60 Hz, 1 H) 8.19 (br. s., 1 H) 8.22 (s, 1 H) 8.25 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.85 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 489.2 $(M+H)^+$.

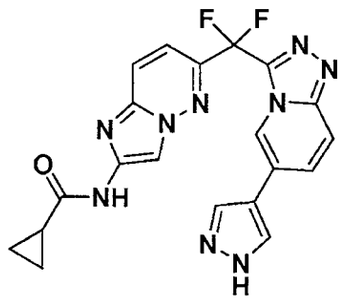
Compound 91: N-(6-(difluoro(6-(4-(2-methoxyethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0560] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 4-(2-methoxyethoxy)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.32 Hz, 4 H) 1.96 (quin,

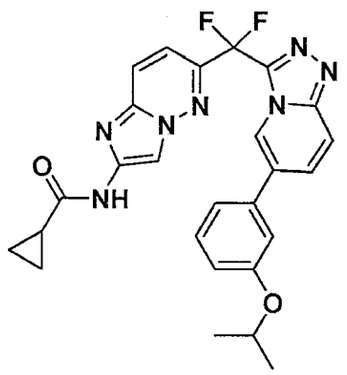
J=6.13 Hz, 1 H) 3.32 (s, 3 H) 3.66 - 3.71 (m, 2 H) 4.13 - 4.19 (m, 2 H) 7.09 (d, *J*=8.59 Hz, 2 H) 7.70 (dd, *J*=9.09, 2.78 Hz, 3 H) 7.95 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.08 (d, *J*=9.60 Hz, 1 H) 8.25 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.67 (s, 1 H) 11.36 (s, 1 H). ESI-MS:m/z 520.2 $(M+H)^+$.

Compound 92: N-(6-((6-(1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0561] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 1H-pyrazol-4-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.19 Hz, 1 H) 7.71 (d, *J*=9.35 Hz, 1 H) 7.97 (dd, 1 H) 8.03 - 8.08 (m, 1 H) 8.17 - 8.43 (m, 2 H) 8.25 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.75 (s, 1 H) 11.35 (s, 1 H).). ESI-MS:m/z 436.2 $(M+H)^+$.

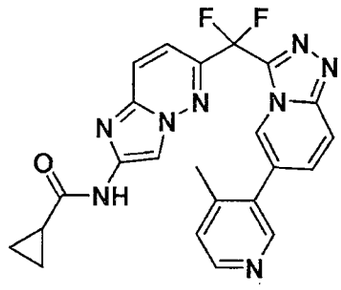
Compound 93: N-(6-(difluoro(6-(3-isopropoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0562] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3-isopropoxyphenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.28 (d, *J*=6.06

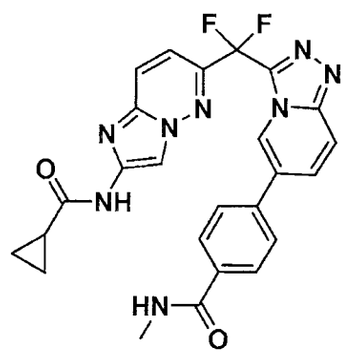
Hz, 6 H) 1.96 (quin, *J*=6.13 Hz, 1 H) 4.65 - 4.76 (m, 1 H) 7.02 (dd, *J*=8.21, 1.89 Hz, 1 H) 7.21 (s, 1 H) 7.26 (d, *J*=7.83 Hz, 1 H) 7.38 - 7.46 (m, 1 H) 7.71 (d, *J*=9.35 Hz, 1 H) 7.96 (dd, *J*=9.60, 1.26 Hz, 1 H) 8.10 (d, *J*=9.60 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.71 (s, 1 H) 11.36 (s, 1 H). ESI-MS:m/z 504.2 $(M+H)^+$.

Compound 94: N-(6-(difluoro(6-(4-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0563] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 4-methylpyridin-3-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 - 0.89 (m, 4 H) 1.19 - 1.29 (m, 3 H) 1.89 - 2.00 (m, 1 H) 6.87 (s, 1 H) 7.43 (br. s., 1 H) 7.68 - 7.76 (m, 2 H) 8.11 (d, *J*=8.84 Hz, 1 H) 8.22 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.51 (br. s., 1 H) 8.68 (s, 1 H) 11.35 (s, 1 H). ESI-MS:m/z 461.2 $(M+H)^+$.

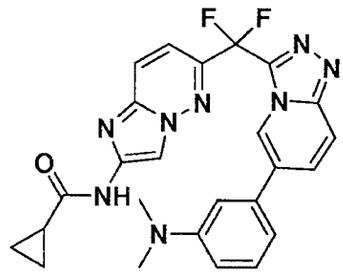
Compound 95: 4-(3-((2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-N-methylbenzamide



[0564] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 4-(methylcarbamoyl)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated

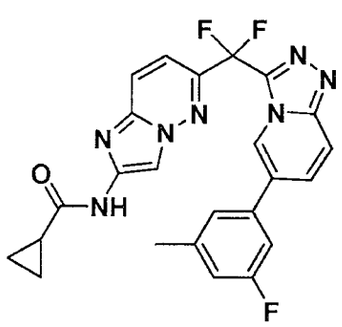
as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, J=6.06 Hz, 4 H) 1.96 (quin, J=6.13 Hz, 1 H) 2.76 - 2.86 (m, 3 H) 7.72 (d, J=9.60 Hz, 1 H) 7.88 (d, J=8.34 Hz, 2 H) 7.93 - 8.00 (m, 2 H) 8.03 (dd, J=9.73, 1.39 Hz, 1 H) 8.14 (d, J=9.35 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, J=9.35 Hz, 1 H) 8.57 (d, J=4.55 Hz, 1 H) 8.83 (s, 1 H) 11.35 (s, 1 H).). ESI-MS:m/z 503.2 $(M+H)^+$.

Compound 96: N-(6-((6-(3-(dimethylamino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0565] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3-(dimethylamino)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (d, J=6.06 Hz, 4 H) 1.96 (quin, J=6.13 Hz, 1 H) 2.96 (s, 6 H) 6.85 (d, J=8.34 Hz, 1 H) 6.94 (br. s., 1 H) 6.98 (d, J=7.33 Hz, 1 H) 7.33 (t, J=7.83 Hz, 1 H) 7.68 - 7.74 (m, 1 H) 7.93 - 7.99 (m, 1 H) 8.09 (d, J=9.60 Hz, 1 H) 8.25 (s, 1 H) 8.28 (d, J=9.60 Hz, 1 H) 8.65 (s, 1 H) 11.32 - 11.40 (m, 1 H). ESI-MS:m/z 489.2 $(M+H)^+$.

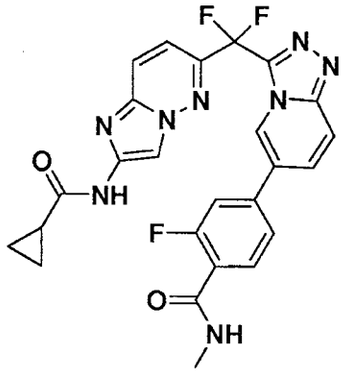
Compound 97: N-(6-(difluoro(6-(3-fluoro-5-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0566] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3-fluoro-5-methylphenylboronic acid.

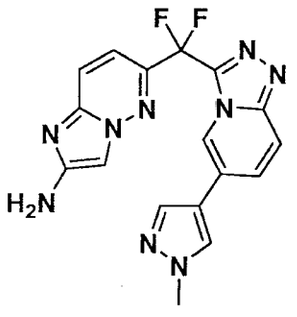
The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, J=6.06 Hz, 4 H) 1.95 (q, 1 H) 2.41 (s, 3 H) 7.15 (d, J=9.60 Hz, 1 H) 7.42 - 7.50 (m, 2 H) 7.72 (d, J=9.35 Hz, 1 H) 7.98 (dd, J=9.73, 1.39 Hz, 1 H) 8.12 (d, J=9.60 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, J=9.60 Hz, 1 H) 8.80 (s, 1 H) 11.36 (s, 1 H). ESI-MS:m/z 478.2 $(M+H)^+$.

Compound 98: 4-(3-((2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-fluoro-N-methylbenzamide



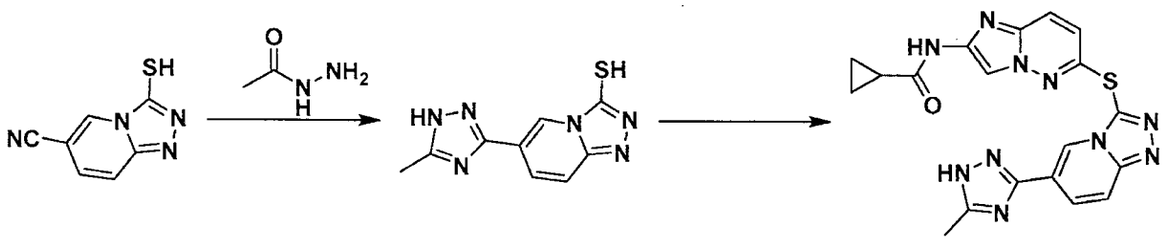
[0567] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **45** using 3-fluoro-4-(methylcarbamoyl)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 (d, J=5.81 Hz, 4 H) 1.90 - 2.00 (m, 1 H) 2.80 (d, J=4.55 Hz, 3 H) 7.68 - 7.78 (m, 2 H) 7.81 (d, J=11.87 Hz, 1 H) 8.00 - 8.07 (m, 1 H) 8.11 - 8.18 (m, 1 H) 8.22 (s, 1 H) 8.28 (d, J=9.35 Hz, 1 H) 8.33 (d, J=4.55 Hz, 1 H) 8.88 (s, 1 H) 11.35 (s, 1 H).). ESI-MS:m/z 521.2 $(M+H)^+$.

Compound 99: 6-(difluoro(6-(1-methyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)methyl)imidazo[1,2-*b*]pyridazin-2-amine



[0568] A solution of **45** (100 mg) in 3N HCl:50% MeOH:water was heated at 50°C for 3 hrs. The reaction was concentrated and purified by preparative LCMS to provide the title compound, 6-(difluoro(6-(1-methyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)methyl)imidazo[1,2-*b*]pyridazin-2-amine (30 mg) as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.89 (s, 3 H) 7.46 (br. s., 1 H) 7.51 - 7.58 (m, 1 H) 7.90 (dd, *J*=9.47, 1.39 Hz, 1 H) 7.93 - 7.99 (m, 1 H) 8.04 (d, *J*=9.60 Hz, 1 H) 8.08 (s, 1 H) 8.39 - 8.43 (m, 2 H) 8.67 (s, 1 H). ESI-MS:m/z 382.2 $(M+H)^+$.

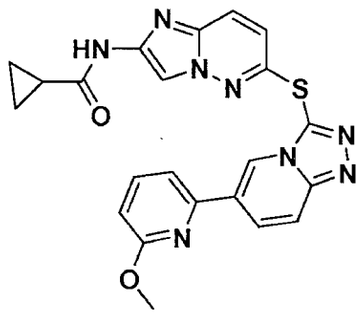
Compound 100: N-(6-(6-(5-methyl-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0569] ***6-(5-methyl-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-thiol***: A mixture of 3-mercapto-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile (**38A**, 450 mg, 2.56 mmol), acetohydrazide (400mg, 5.4 mmol), and sodium 2-methylpropan-2-olate (200mg, 2.08mmol) in propan-2-ol (2.5 ml) was heated at 180°C under microwave condition for 2 hrs. The product was purified by preparative LCMS to provide the title compound, 6-(5-methyl-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-thiol.

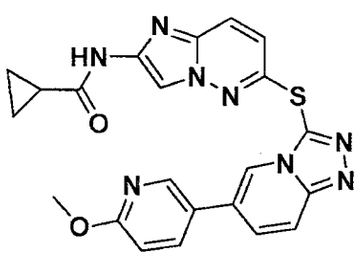
[0570] N-(6-(6-(5-methyl-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: The title compound was synthesized using an analogous procedure to that described in the preparation of Compound 4 using 6-(5-methyl-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-thiol. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (DMSO-d_6 ,400MHz): δ = 11.26 (s, 1 H), 9.25 (s, 1 H), 8.19 - 8.29 (m, 2 H), 8.00 (d, J=9.6 Hz, 1 H), 7.85 - 7.93 (m, 1 H), 7.40 (d, J=9.3 Hz, 1 H), 2.43 (s, 3 H), 1.96 (br. s., 1 H), 0.75 - 0.93 ppm (m, 5 H). ESI-MS:m/z 433.1 $(M+H)^+$.

Compound 101: N-(6-(6-(6-methoxypyridin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



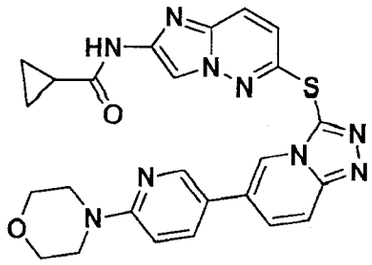
[0571] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **5** using 6-methoxypyridin-2-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (METHANOL-d_4 ,400MHz): δ = 9.09 (s, 1 H), 8.35 (d, *J*=9.9 Hz, 1 H), 7.95 - 8.04 (m, 2 H), 7.84 (d, *J*=9.3 Hz, 1 H), 7.71 - 7.78 (m, 1 H), 7.55 (d, *J*=7.3 Hz, 1 H), 7.23 (d, *J*=9.1 Hz, 1 H), 6.79 (d, *J*=8.3 Hz, 1 H), 3.85 (s, 3 H), 1.84 (m, 1 H), 0.82 - 0.96 ppm (m,4 H). ESI-MS:m/z 459.2 $(M+H)^+$.

Compound 102: N-(6-(6-(6-methoxypyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



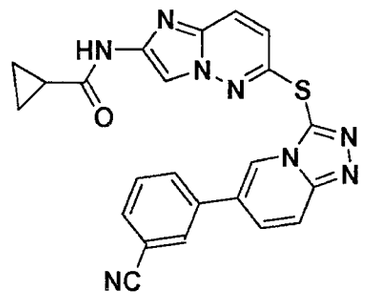
[0572] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **5** using 6-methoxypyridin-3-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (METHANOL-d_4 ,400MHz): δ = 8.71 (br. s., 1 H), 8.40 (br. s., 1 H), 7.86 - 8.16 (m, 4 H), 7.80 (br. s., 1 H), 7.20 (br. s., 1 H), 6.87 (d, *J*=8.8 Hz, 1 H), 3.92 (s, 3 H), 1.85 (br. s., 1 H), 0.73 - 1.02 ppm (m, 4 H). ESI-MS:m/z 459.2 $(M+H)^+$.

Compound 103: N-(6-(6-(6-morpholinopyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



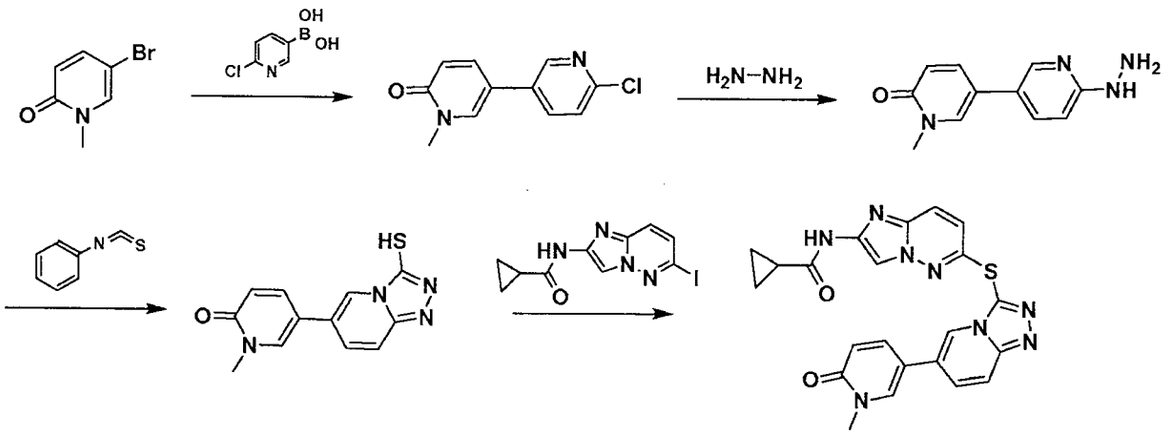
[0573] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **5** using 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt.

Compound 104: N-(6-(6-(3-cyanophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0574] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **5** using 3-cyanophenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (METHANOL-d_4 ,400MHz): δ = 8.72 (s, 1 H), 8.34 (d, *J*=2.3 Hz, 1 H), 8.12 (dd, *J*=9.2, 2.4 Hz, 1 H), 8.04 (d, *J*=9.6 Hz, 1 H), 7.92 (d, *J*=8.8 Hz, 1 H), 7.82 (s, 2 H), 7.16 - 7.27 (m, 2 H), 3.80 - 3.89 (m, 4 H), 3.61 - 3.69 (m, 4 H), 1.85 (br. s., 1 H), 0.95 (m, 2 H), 0.80 - 0.92 ppm (m, 2 H). ESI-MS:m/z 514.2 $(M+H)^+$.

Compound 105: N-(6-(6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0575] ***5-(6-Chloropyridin-3-yl)-1-methylpyridin-2(1H)-one***: A mixture of 5-bromo-1-methylpyridin-2(1H)-one (2.2g, 11.7mmol), 6-chloropyridin-3-ylboronic acid (1.57g, 9.98mmol), Na_2CO_3 (2.2g, 20.76mmol), and tetrakis(triphenylphosphine)palladium (0) (500mg, 0.05mmol) in dioxane:water (15:1, 20ml) was degassed and heated at 110°C in a microwave for 1 hr. The reaction was diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The resulting residue was purified by silica gel chromatography (AcOEt-Hexanes) to provide title compound, 5-(6-Chloropyridin-3-yl)-1-methylpyridin-2(1H)-one (1.6g, 73% yield).

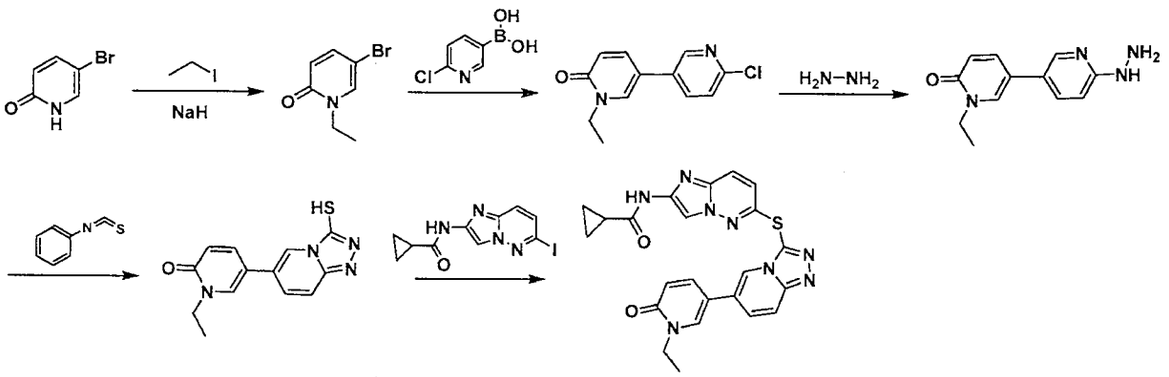
[0576] ***5-(6-hydrazinylpyridin-3-yl)-1-methylpyridin-2(1H)-one***: A mixture of 5-(6-chloropyridin-3-yl)-1-methylpyridin-2(1H)-one (1.2g, 5.44 mmol) and hydrazine (870mg, 2.2 mmol) in 2-propanol (5ml) was heated in a microwave at 140°C for 5 hrs. The reaction mixture was co-evaporated with MeOH (3x) and then suspended in water (50ml). Solid product was collected by filtration and dried under high vacuum for 24 hrs to provide the title compound, 5-(6-hydrazinylpyridin-3-yl)-1-methylpyridin-2(1H)-one (600 mg, 51% yield).

[0577] ***5-(3-mercapto-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-1-methylpyridin-2(1H)-one***: A mixture of 5-(6-hydrazinylpyridin-3-yl)-1-methylpyridin-2(1H)-one (600mg, 2.78mmol) and isothiocyanatobenzene (450mg, 3.33mmol) in NMP-1,3-dichlorobenzene (1:1, 10mL) was heated in a microwave at 160°C for 1 hr and then purified by preparative LCMS to provide the title compound, 5-(3-mercapto-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-1-methylpyridin-2(1H)-one (310 mg, 43% yield).

[0578] N-(6-(6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: The title compound was prepare from N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide and 5-(3-

mercapto-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-1-methylpyridin-2(1H)-one following the procedure for the synthesis of compound 4. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. The product was then dissolved in MeOH, treated 4M HCl in dioxane, and concentrated to dryness to provide the HCl salt of the title compound. ^{1}H NMR (METHANOL-d_4 ,400MHz): δ = 8.83 (s, 1 H), 8.18 (d, J=9.9 Hz, 2 H), 8.11 (d, J=9.6 Hz, 1 H), 7.98 (d, J=9.3 Hz, 1 H), 7.77 - 7.92 (m, 2 H), 7.55 (d, J=9.1 Hz, 1 H), 6.58 (d, J=9.3 Hz, 1 H), 3.52 - 3.59 (m, 3 H), 1.73 (br. s., 1 H), 0.80 - 0.90 ppm (m, 4 H). ESI-MS:m/z 459.2 $(M+H)^+$.

Compound 106: N-(6-(6-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0579] ***5-bromo-1-ethylpyridin-2(1H)-one***: A solution of 5-bromopyridin-2-ol (1.74 g, 10.00 mmol) in DMF (20ml) was treated with NaH at room temperature and then stirred for 30 min. Iodoethane (0.823 ml, 12.00 mmol) was added to the mixture and the reaction was stirred overnight at room temperature. The reaction was diluted with DCM, washed with water, dried over Na_2SO_4,and concentrated to dryness via rotary evaporation to provide the title compound as a crude product which was used without further purification.

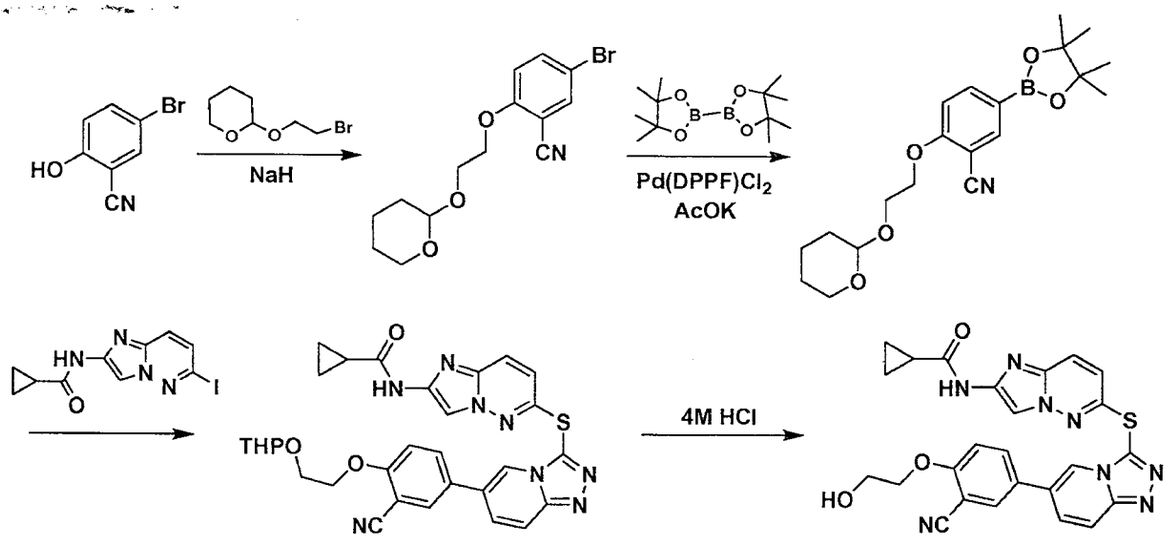
[0580] **5-(6-chloropyridin-3-yl)-1-ethylpyridin-2(1H)-one:** A mixture of 5-bromo-1-ethylpyridin-2(1H)-one (1.9g, 9.45mmol), 6-chloropyridin-3-ylboronic acid (1.8g, 11.46mmol), Cs_2CO_3 (9.9g, 30.37mmol) and tetrakis(triphenylphosphine)palladium (0) (543mg, 0.55mmol) were suspended in dioxane:water (15:1, 20ml). After degassing, the mixture was heated in a microwave at 140°C for 30min. The reaction was then diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness via rotary evaporation. The resulting residue was purified by LCMS to provide the title compound, 5-(6-chloropyridin-3-yl)-1-ethylpyridin-2(1H)-one (1.2 g, 51% yield).

[0581] **5-(6-hydrazinylpyridin-3-yl)-1-ethylpyridin-2(1H)-one:** A mixture of 5-(6-chloropyridin-3-yl)-1-ethylpyridin-2(1H)-one (1.2g, 5.44 mmol) and hydrazine (820mg, 25.62mmol) in 2-propanol (5ml) was heated in a microwave at 140°C for 4 hrs. The mixture was co-evaporated with MeOH (3x) and then suspended in water (50ml). The resulting solid was collected by filtration and dried under high vacuum for one day to give crude title compound, 5-(6-hydrazinylpyridin-3-yl)-1-ethylpyridin-2(1H)-one (1.2 g, 95.9% yield).

[0582] **5-(3-mercapto-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-1-ethylpyridin-2(1H)-one:** A mixture of 5-(6-hydrazinylpyridin-3-yl)-1-ethylpyridin-2(1H)-one (1.2g, 5.22mmol) and isothiocyanatobenzene (775mg, 5.74mmol) in NMP(3ml) and DCM (10ml) was stirred at room temperature for 30min. The DCM was removed via rotary evaporation and the reaction was diluted with 1,3-dichlorobenzene (7mL). The mixture was then heated in a microwave at 160°C for 1 hr. Ether (10ml) was added to the reaction and the resulting solid was collected by filtration and washed with ether to provide the title compound, **5-(**3-mercapto-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-1-ethylpyridin-2(1H)-one (600mg, 42.3% yield).

[0583] N-(6-(6-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: The title compound was prepare from N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide and 5-(3-mercapto-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-1-ethylpyridin-2(1H)-one followed the procedure of the synthesis of compound 4. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. The product was then dissolved in MeOH, treated 4M HCl in dioxane, and concentrated to dryness to provide the HCl salt of the title compound. ^{1}H NMR (DMSO-d_6 ,400MHz): δ = 11.15 (s, 1 H), 8.66 - 8.72 (m, 1 H), 8.24 (d, J=2.5 Hz, 1 H), 8.08 (dd, J=9.6, 1.0 Hz, 1 H), 7.93 (s, 2 H), 7.90 - 7.92 (m, 1 H), 7.87 (dd, J=9.5, 2.9 Hz, 1 H), 7.06 (d, J=9.3 Hz, 2 H), 6.47 (d, J=9.3 Hz, 1 H), 3.96 (q, J=7.1 Hz, 2 H), 1.92 (t, J=6.1 Hz, 1 H), 1.24 (t, J=7.2 Hz, 3 H), 0.75 - 0.82 ppm (m, 4 H). ESI-MS:m/z 473.2 $(M+H)^+$.

Compound 107: N-(6-(6-(3-cyano-4-(2-hydroxyethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0584] ***5-bromo-2-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)benzonitrile***: A solution of 5-bromo-2-hydroxybenzonitrile (1g, 5.05 mmol) in DMF was treated with 95% NaH (242mg, 9.6mmol) for 20 min at room temperature. 2-(2-Bromoethoxy)tetrahydro-2H-pyran (0.839 ml, 5.56 mmol) was then added to the reaction and the mixture was stirred at room temperature for 5 hrs. T he reaction was then diluted with DCM and washed with water. The organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness to provide the crude title compound, 5-bromo-2-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)benzonitrile (1.6 g, 9.75% yield) which was used without further purification.

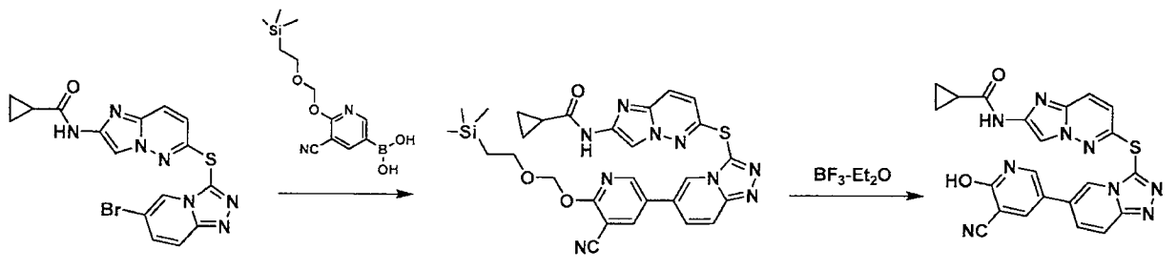
[0585] ***2-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile*:** A mixture of 5-bromo-2-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)benzonitrile (1.6g, 4.92mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.9g, 7.48mmol), AcOK (1.47g, 15mmol) and $Pd(DPPF)Cl_2$ (366mg, 0.5mmol) in dioxane (50 ml) was heated at 110 °C for 60 min. The reaction was evaporated to dryness via rotary evaporation and the resulting residue was purified by silica gel chromatography (DCM-Hexane) to provide the title compound, 2-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.7 g, 92.6% yield).

[0586] N-(6-(6-(3-cyano-4-(3-(tetrahydro-2H-pyran-2-yloxy)propyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: The title compound was prepared from compound 4 and 2-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)benzonitrile following the procedure for the synthesis of compound 5. The reaction mixture was used without further purification.

[0587] N-(6-(6-(3-cyano-4-(2-hydroxyethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: As a crude reaction mixture, N-(6-(6-(3-cyano-4-(3-(tetrahydro-2H-pyran-2-yloxy)propyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide was treated with [HCl]:dioxane (1:5) at 70 ^{0}C for 30 min. The reaction was concentrated and purified by LCMS to provide the title compound as a TFA salt. The product was then dissolved in MeOH, treated 4M HCl in dioxane, and concentrated to dryness to provide the HCl salt of the title compound. ^{1}H NMR (METHANOL-d_4 ,400MHz): δ = 9.00 (br. s., 1 H), 8.36 (br. s., 1 H), 8.24 (br. s., 1 H), 8.08 (br. s., 2 H), 8.01 (br. s., 1 H), 7.94 (br. s., 1 H), 7.66 - 7.74 (m, 1 H), 7.36 (br. s., 1 H), 4.27 (br. s., 2 H), 3.95 (br. s., 2 H), 1.83 (br. s., 1 H), 0.84 - 1.04 ppm (m, 4 H). ESI-MS:m/z 513.4 $(M+H)^+$.

Compound 108: N-(6-(6-(5-cyano-6-hydroxypyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

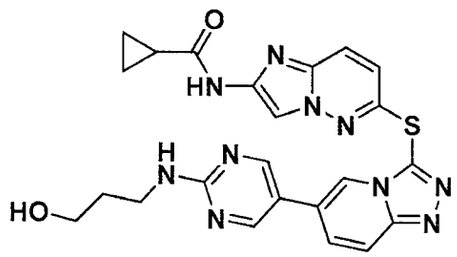


[0588] N-(6-(6-(5-cyano-6-((2-(trimethylsilyl)ethoxy)methoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: The title compound was synthesized using an analogous procedure to that described in the preparation of Compound 5 using 5-cyano-6-((2-(trimethylsilyl)ethoxy)methoxy)pyridin-3-ylboronic acid. The crude reaction was used for the next step without further purification.

[0589] N-(6-(6-(5-cyano-6-hydroxypyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: As a crude reaction mixture, N-(6-(6-(5-cyano-6-((2-(trimethylsilyl)ethoxy)methoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide was refluxed in TFA:DCM (1:1, 5mL) for 30min. The reaction was then concentrated and purified by preparative LCMS to provide the title compound, N-(6-(6-(5-cyano-6-hydroxypyridin-3-yl)-

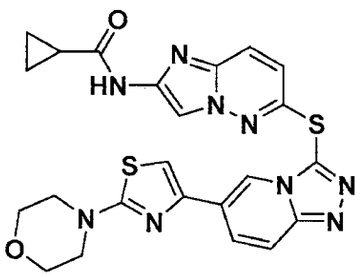
[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide as a TFA salt. The product was then dissolved in MeOH, treated 4M HCl in dioxane, and concentrated to dryness to provide the HCl salt of the title compound. ^{1}H NMR (METHANOL-d_4 ,400MHz): δ = 8.80 (br. s., 1 H), 8.51 (d, J=2.5 Hz, 1 H), 8.13 (d, J=2.8 Hz, 1 H), 8.04 (d, J=9.6 Hz, 1 H), 7.79 - 7.96 (m, 3 H), 7.27 (d, J=7.8 Hz, 1 H), 1.83 (br. s., 1 H), 0.91 ppm (d, J=16.7 Hz, 4 H). ESI-MS:m/z 513.4 $(M+H)^+$.

Compound 109: N-(6-(6-(2-(3-hydroxypropylamino)pyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0590] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **5** using 2-(3-hydroxypropylamino)pyrimidin-5-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (ACETONITRILE-d_3 ,400MHz): δ = 8.50 (s, 2 H), 8.44 (s, 1 H), 7.89 - 8.00 (m, 2 H), 7.67 - 7.78 (m, 2 H), 7.62 (s, 3 H), 7.01 (d, *J*=9.3 Hz, 1 H), 3.55 (t, *J*=6.1 Hz, 2 H), 3.45 (t, *J*=6.6 Hz, 2 H), 1.70 - 1.79 (m, 3 H), 0.85 ppm (d, *J*=16.2 Hz, 4 H). ESI-MS:m/z 503.3 $(M+H)^+$.

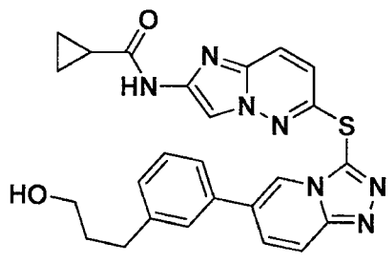
Compound 110: N-(6-(6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0591] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **5** using 2-morpholinothiazol-4-ylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated

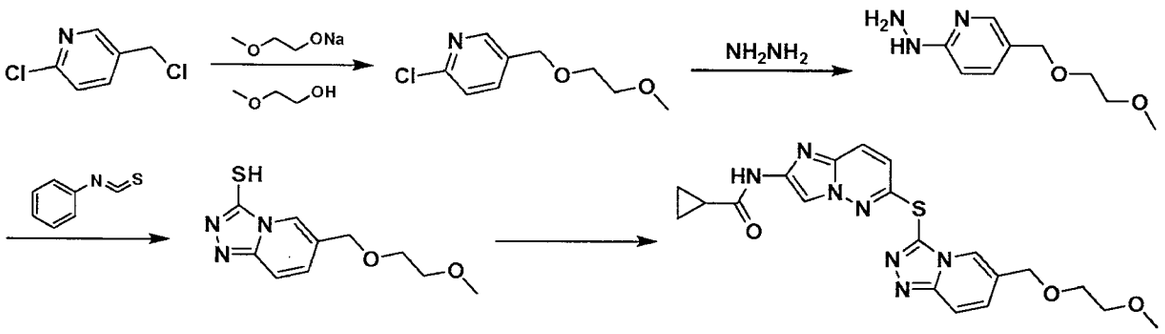
as the TFA salt. ^{1}H NMR (ACETONITRILE-d_3 ,400MHz): δ = 8.74 (s, 1 H), 8.03 (br. s., 1 H), 7.91 - 7.97 (m, 1 H), 7.83 - 7.90 (m, 1 H), 7.71 (br. s., 1 H), 7.15 (s, 1 H), 7.03 (br. s., 1 H), 3.75 (s, 4 H), 3.39 - 3.45 (m, 4 H), 1.78 (dt, *J*=5.0, 2.4 Hz, 1 H), 0.81 - 0.92 ppm (m, 4 H). ESI-MS:m/z 520.2 $(M+H)^+$.

Compound 111: N-(6-(6-(3-(3-hydroxypropyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



[0592] The title compound was synthesized using an analogous procedure to that described in the preparation of Compound **5** using 3-(3-hydroxypropyl)phenylboronic acid. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. ^{1}H NMR (METHANOL-d_4 ,400MHz): δ = 8.54 (s, 1 H), 7.84 - 7.94 (m, 3 H), 7.72 (d, *J*=9.3 Hz, 1 H), 7.33 - 7.39 (m, 2 H), 7.25 - 7.32 (m, 1 H), 7.18 (d, *J*=7.6 Hz, 1 H), 7.10 (d, *J*=9.3 Hz, 1 H), 3.46 (t, *J*=6.3 Hz, 2 H), 2.58 - 2.67 (dd, *J*=8.0 and 7.6, 2 H), 1.67 - 1.79 (m, 3 H), 0.72 - 0.87 ppm (m, 4 H). ESI-MS:m/z 486.3 $(M+H)^+$.

Compound 112: N-(6-(6-((2-methoxyethoxy)methyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



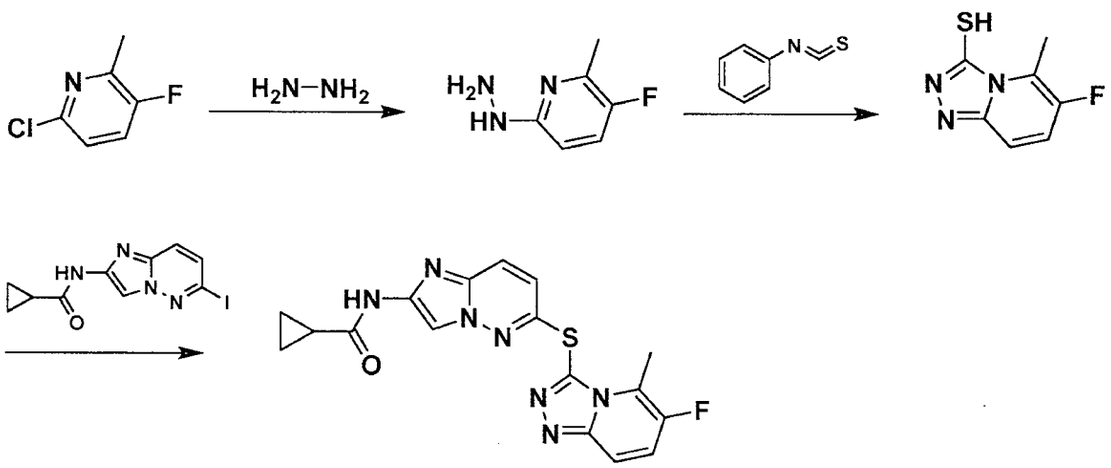
[0593] ***2-hydrazinyl-5-((2-methoxyethoxy)methyl)pyridine***: To a solution of 2-chloro-5-(chloromethyl)pyridine (1620 mg, 10 mmol) in 2-methoxyethanol (10mL) was added sodium 2-methoxyethanolate (5.9g, 12.00 mmol). The mixture was stirred at room temperature for 10 min and then at 50°C for 2 hrs. Hydrazine (1.6 g, 50.0 mmol) was then added to the

mixture and the reaction was heated at 120°C for 1 hr. The mixture was purified by preparative LCMS to provide the title compound, 2-hydrazinyl-5-((2-methoxyethoxy)methyl)pyridine (540mg, 27.4% yield).

[0594] **6-((2-methoxyethoxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-3-thiol:** The title compound was prepared from 2-hydrazinyl-5-((2-methoxyethoxy)methyl)pyridine and isothiocyanatobenzene following the procedure described in the synthesis of compound **4A**.

[0595] N-(6-(6-((2-methoxyethoxy)methyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide: The title compound was prepared from N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide and 6-((2-methoxyethoxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-3-thiol following the procedure described for the synthesis of Compound 4. ^{1}H NMR (METHANOL-d_4 ,400MHz): δ = 8.75 - 8.78 (m, 1 H), 8.15 (dd, *J*=9.3, 1.0 Hz, 1 H), 8.04 - 8.11 (m, 1 H), 8.02 (d, *J*=9.3 Hz, 1 H), 7.94 (s, 1 H), 7.56 (d, *J*=9.3 Hz, 1 H), 4.71 (d, *J*=1.0 Hz, 2 H), 3.61 - 3.67 (m, 2 H), 3.47 - 3.53 (m, 2 H), 3.29 (s, 3 H), 1.80 - 1.87 (m, 1 H), 0.88 - 1.01 ppm (m, 4 H). ESI-MS:m/z 440.2 $(M+H)^+$.

Compound 113: N-(6-(6-fluoro-5-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

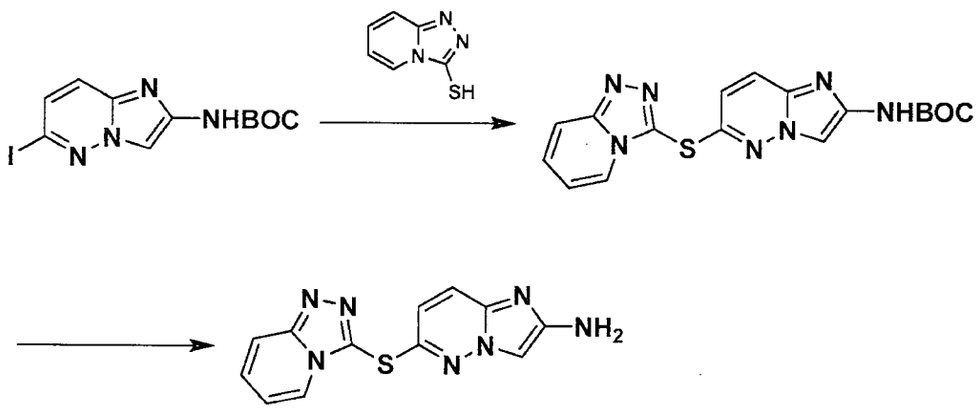


[0596] ***3-fluoro-6-hydrazinyl-2-methylpyridine***: To a mixture of 6-chloro-3-fluoro-2-methylpyridine (4.7g, 32.3 mmol) in isopropanol (100 mL) was added hydrazine hydrate (5 g, 100 mmol). After the mixture was refluxed for 5 hrs, additional hydrazine hydrate (5 g, 100 mmol) was added, and the reaction was refluxed for 3 days. The mixture was then concentrated to dryness and stored under high vacuum overnight. This material was used without further purification.

[0597] ***6-fluoro-5-methyl-[1,2,4]triazolo[4,3-a]pyridine-3-thiol***: The title compound was prepared from 3-fluoro-6-hydrazinyl-2-methylpyridine and isothiocyanatobenzene following the procedure described for the synthesis of compound **4A**.

[0598] ***N-(6-(6-fluoro-5-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide***: The title compound was prepared from N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide and 6-fluoro-5-methyl-[1,2,4]triazolo[4,3-a]pyridine-3-thiol following the procedure described for the synthesis of compound **4**. The crude reaction mixture was purified by preparative LCMS, and the product was isolated as the TFA salt. The product was then dissolved in MeOH, treated 4M HCl in dioxane, and concentrated to dryness to provide the HCl salt of the title compound. ^{1}H NMR (METHANOL-d_4 ,400MHz): δ = 8.00 (s, 1 H), 7.83 - 7.89 (m, 3 H), 7.63 (dd, *J*=9.9, 8.3 Hz, 1 H), 7.22 (d, *J*=9.6 Hz, 1 H), 2.96 (d, *J*=3.5 Hz, 4 H), 1.81 - 1.91 (m, 1 H), 0.96 (dt, *J*=4.5, 3.0 Hz, 2 H), 0.86 - 0.92 (m, 2 H). ESI-MS:m/z 384.3 $(M+H)^+$.

Compound 114: 6-([1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-amine



[0599] ***tert-Butyl 6-([1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-ylcarbamate***: The title compound was prepared from tert-butyl 6-iodoimidazo[1,2-b]pyridazin-2-ylcarbamate and [1,2,4]triazolo[4,3-a]pyridine-3-thiol following the procedure for the synthesis of compound **4.**

[0600] **6-([1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-amine:** A solution of tert-butyl 6-([1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-ylcarbamate (300mg, 0.78mmol) in dioxane (5ml) was treated with 4M HCl in dioxane (5ml) at 80°C for 1hr. The mixture was concentrated and purified by LCMS to give the title compound, 6-([1,2,4]triazolo[4,3-*a*]pyridin-3-ylthio)imidazo[1,2-*b*]pyridazin-2-amine (201 mg, 68% yield) as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.00 (d, *J*=9.35 Hz,

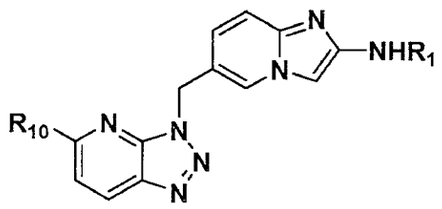
1 H) 7.16 (t, *J*=6.44 Hz, 1 H) 7.22 (s, 1 H) 7.54 - 7.65 (m, 1 H) 7.73 (d, *J*=9.35 Hz, 1 H) 8.00 (d, *J*=9.09 Hz, 1 H) 8.47 (d, *J*=6.82 Hz, 1 H). ESI-MS:m/z 284.2 $(M+H)^+$.

General Procedure for Free Base and HCl Salt Formation

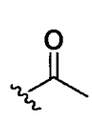
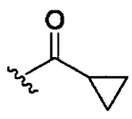
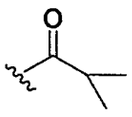
[0601] The free base forms of the above exemplary compounds can be prepared by purifying the crude material by MPLC using Hex:EtOAc (9:1 → 4:6) or DCM:MeOH (99:1 → 9:1) as eluent. Specifically, the free base forms of compounds 3, 13, 45 and 49 were prepared.

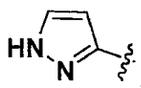
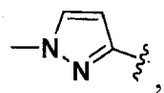
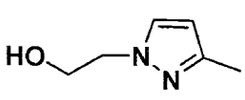
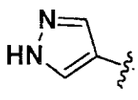
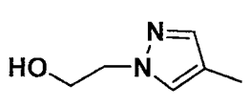
[0602] The HCl salts of the above exemplary compounds can be prepared by dissolving the TFA salt in water, treating the solution with concentrated HCl, and lyophilizing to dryness. Specifically, the HCl salts of compounds 3, 13, 45, 49 and 112 were prepared.

[0603] In addition to the foregoing, the above reaction schemes and variations thereof can be used to prepare compounds having the formula:

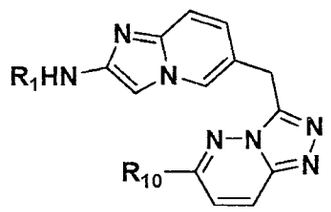


wherein

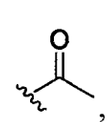
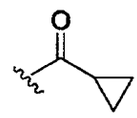
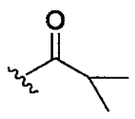
R_1 is selected from the group consisting of hydrogen,  ,  and  ; and

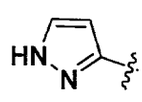
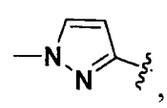
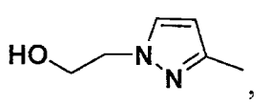
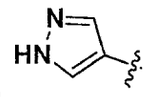
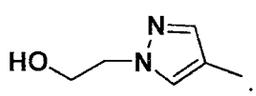
R_{10} is selected from the group consisting of  ,  ,  ,  and  .

[0604] Further, the above reaction schemes and variations thereof can be used to prepare compounds having the formula:

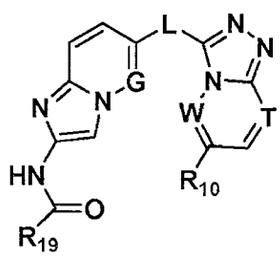


wherein

R_1 is selected from the group consisting of hydrogen,  ,  and  ; and

R_{10} is selected from the group consisting of  ,  ,  ,  and  .

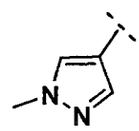
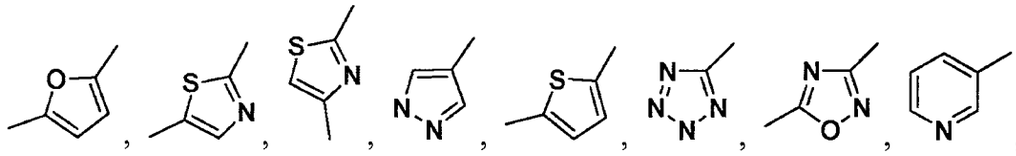
[0605] Further, the above reaction schemes and variations thereof can be used to prepare compounds having the formula:

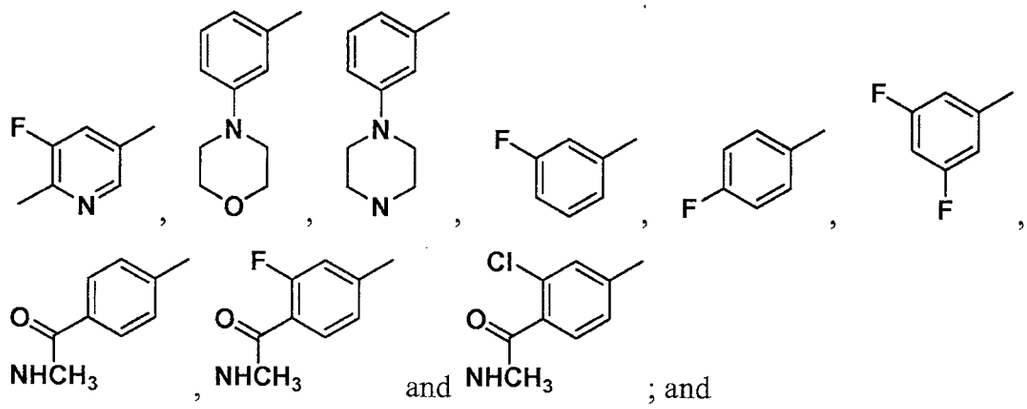


wherein

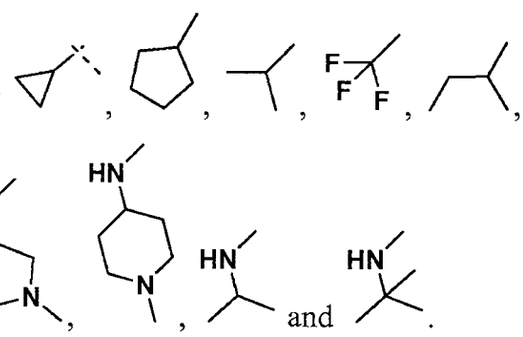
L is selected from the group consisting of S, CH_2, $CH(CH_3)$, $C(CH_3)_2$ AND CF_2;

G, T and W are each independently selected from the group consisting of CH and N;

R_1 is selected from the group consisting of Cl, Br, I, CH_3, CF_3, CN,  , 

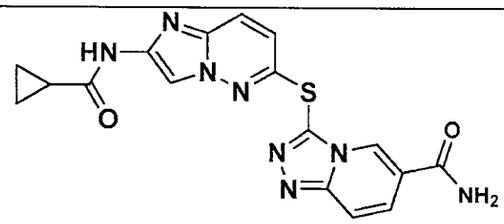
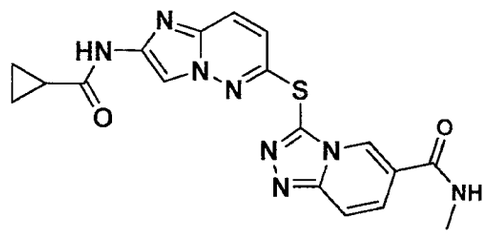
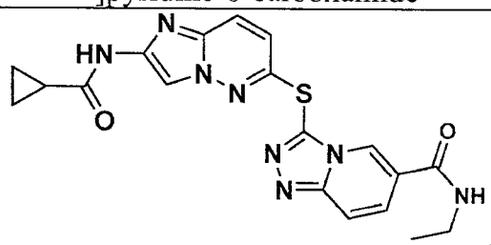
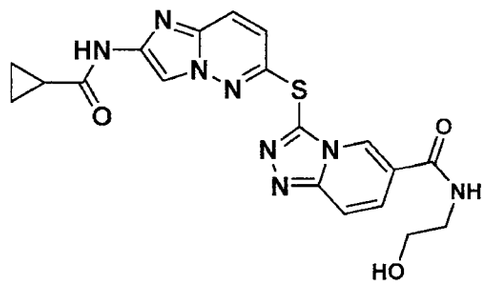


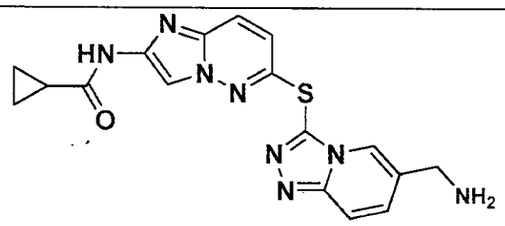
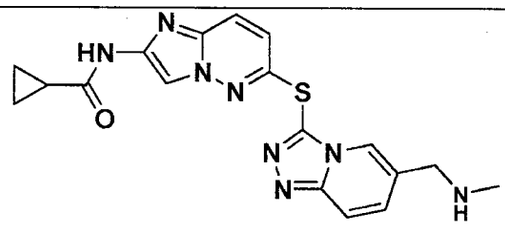
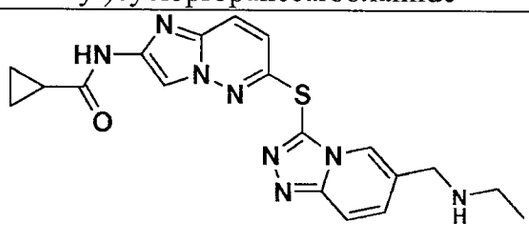
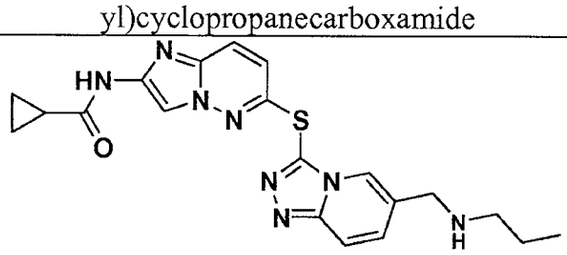
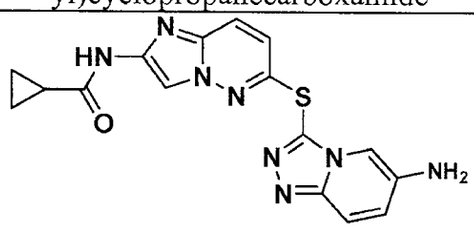
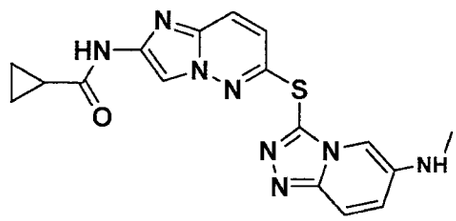
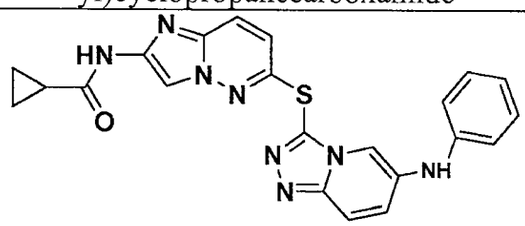
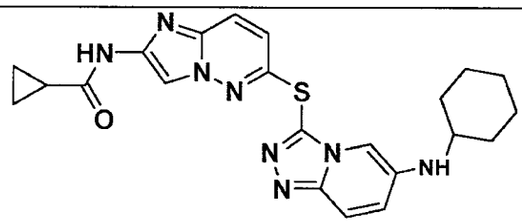
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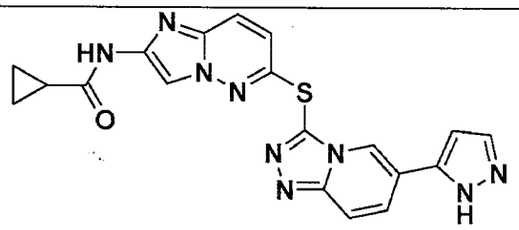
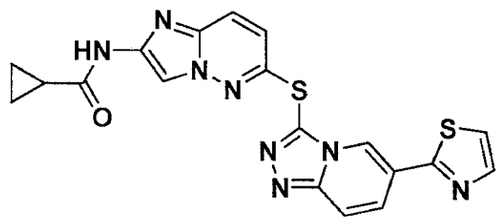
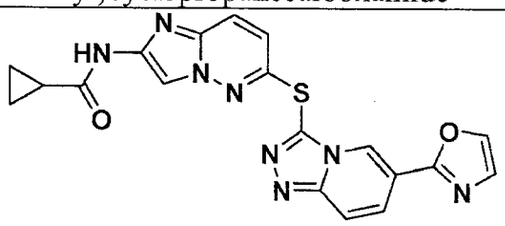
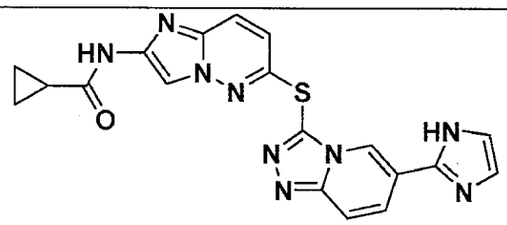
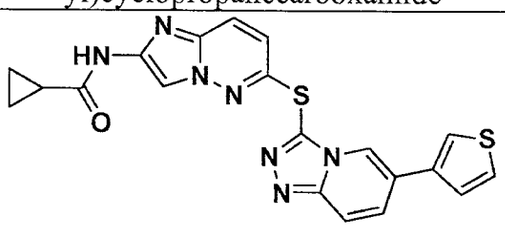
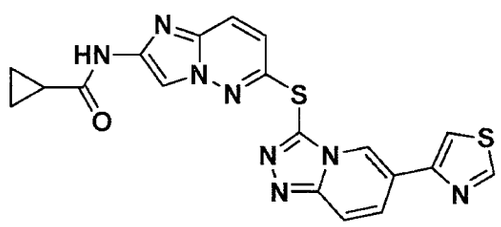
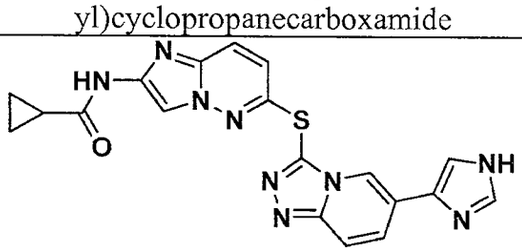
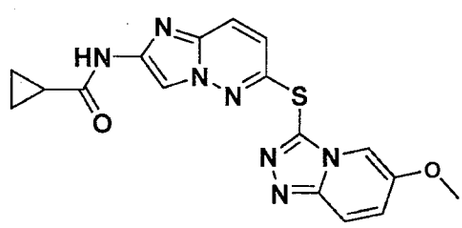
R_{19} is selected from the group consisting of 

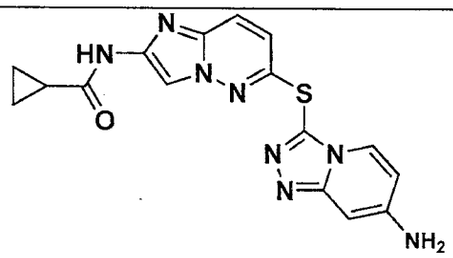
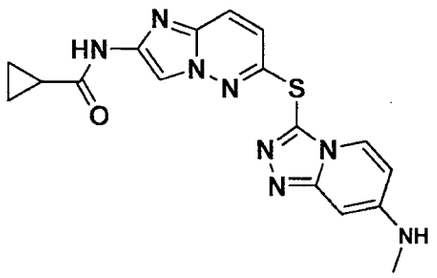
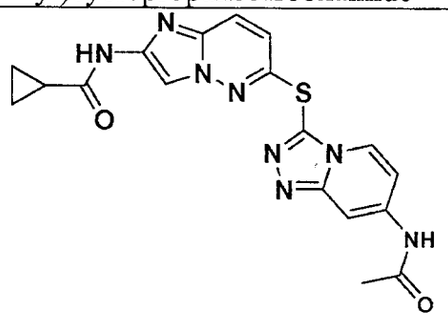
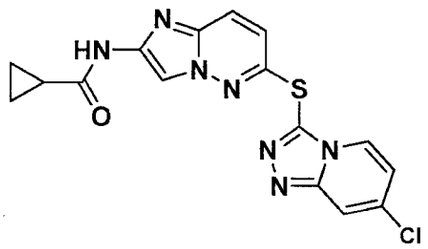
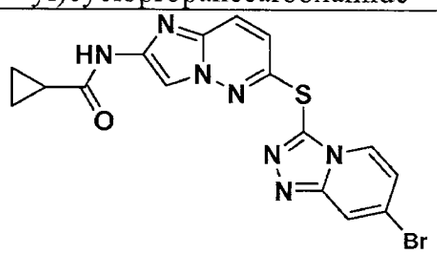
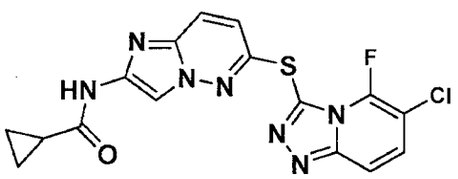
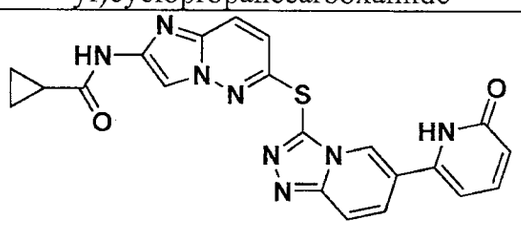
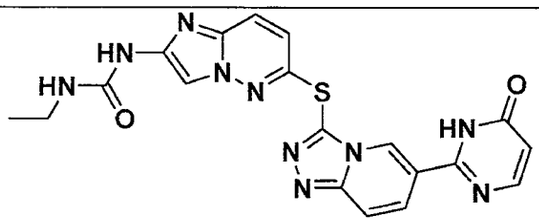
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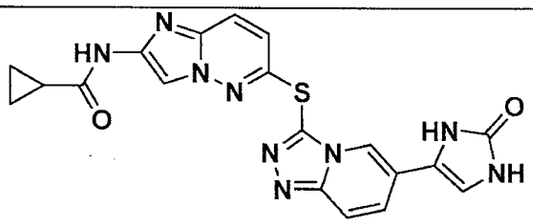
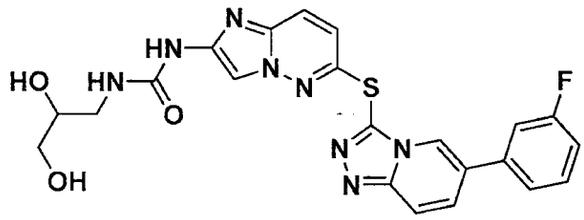
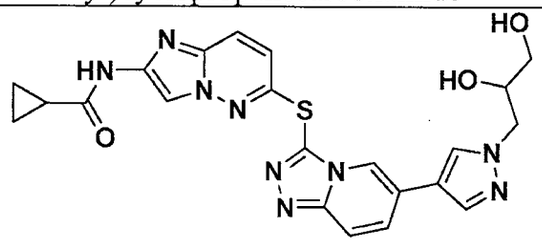
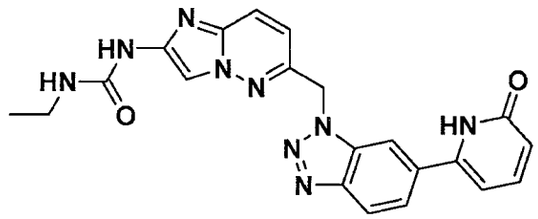
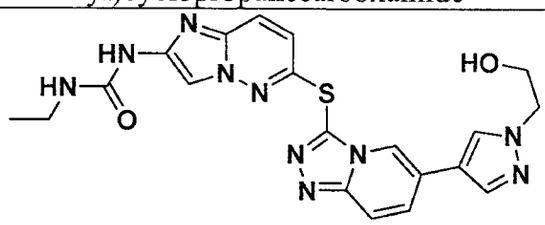
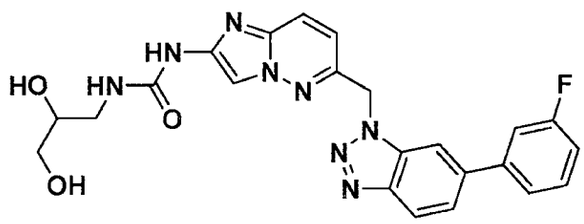
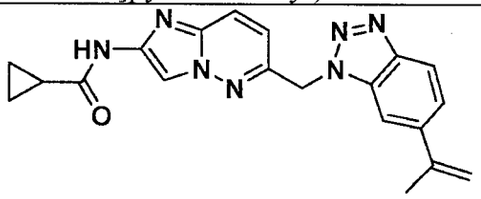
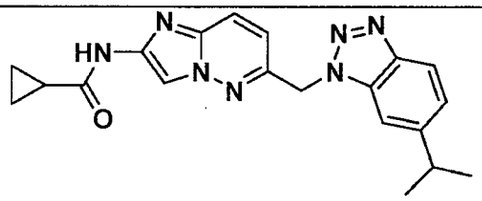
[0606] In addition to the foregoing, the above reaction schemes and variations thereof can be used to prepare the following:

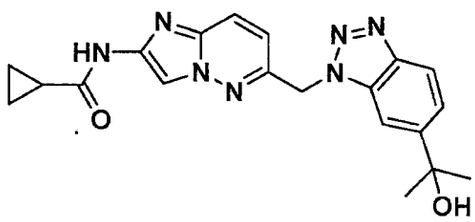
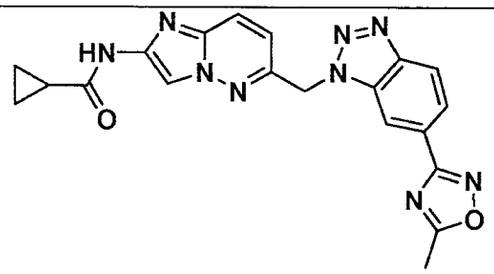
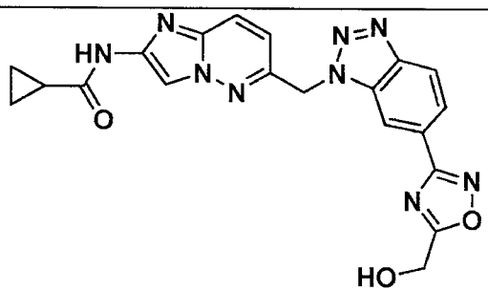
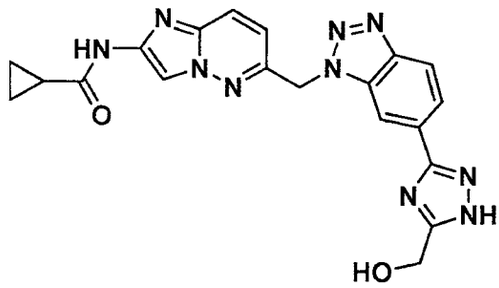
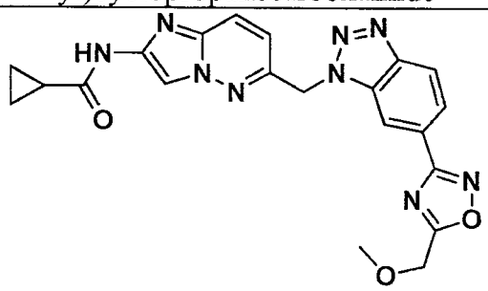
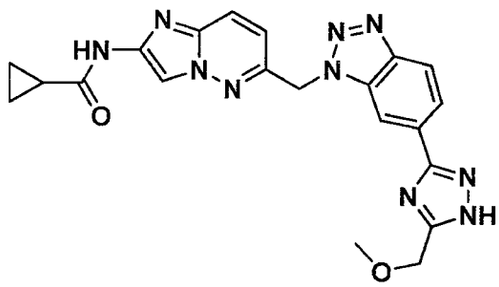
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 3-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-ylthio)-N-ethyl-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide	 3-(2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-ylthio)-N-(2-hydroxyethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide

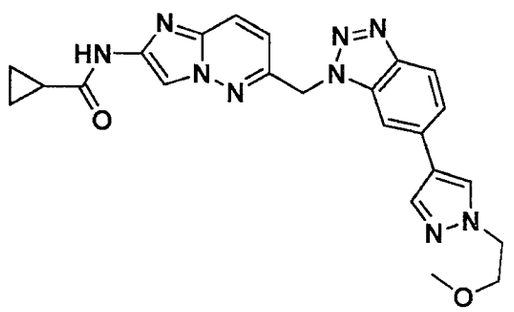
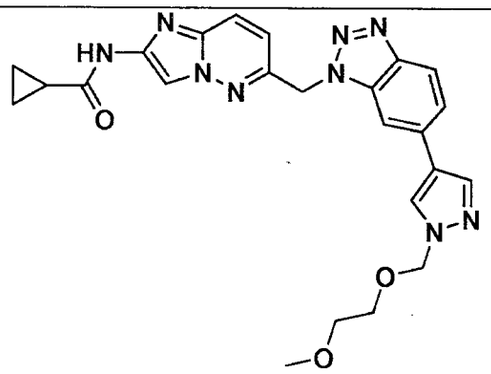
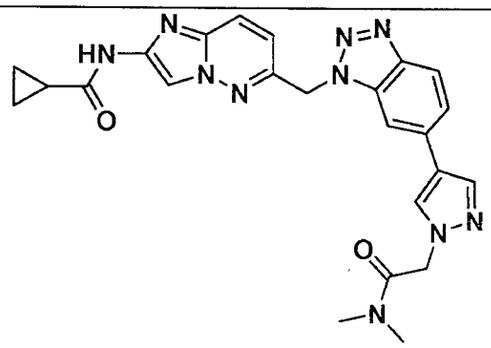
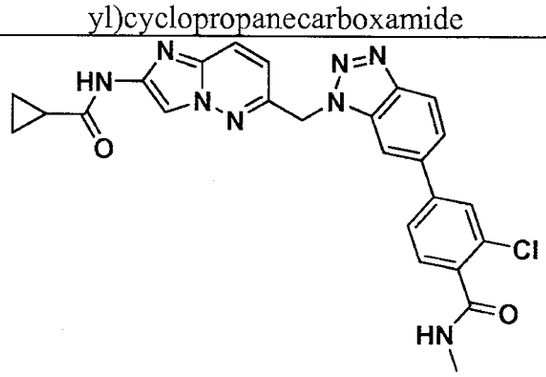
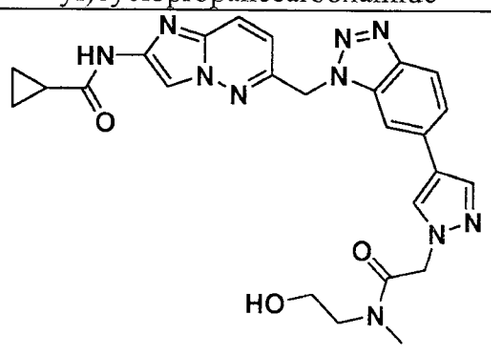
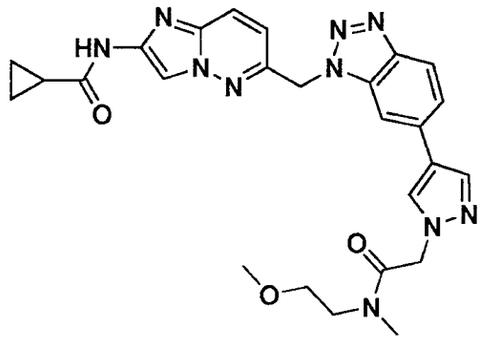
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 N-(6-(6-((ethylamino)methyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-((propylamino)methyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-amino-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(methylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(phenylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(cyclohexylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

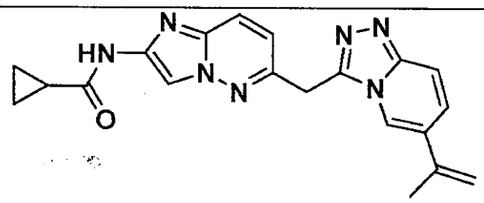
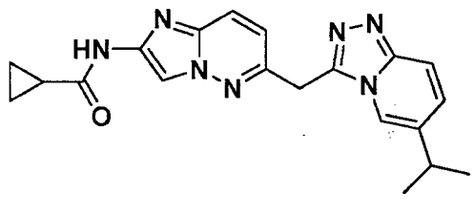
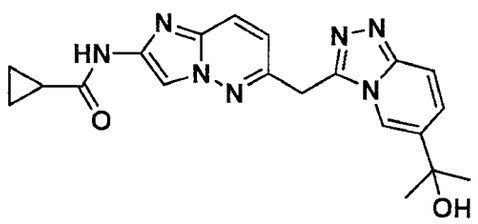
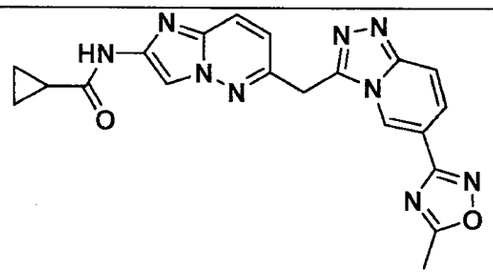
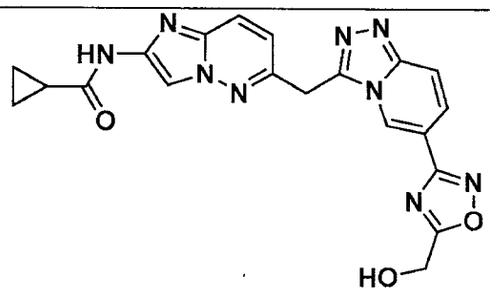
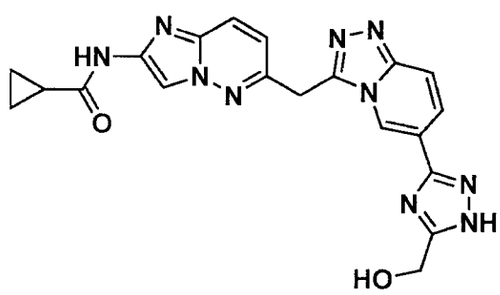
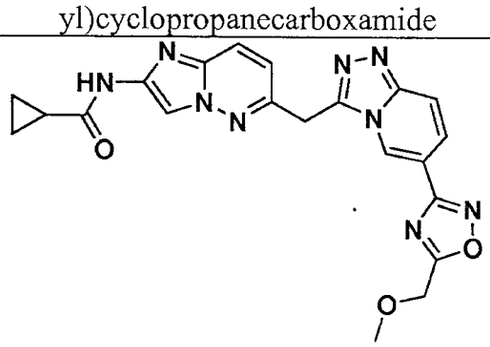
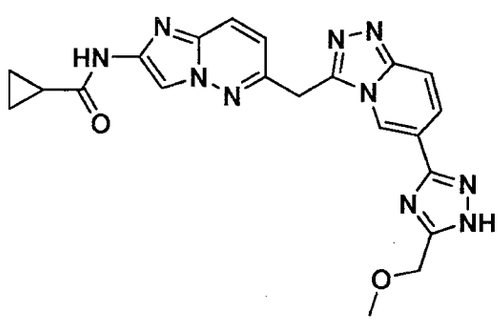
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 N-(6-(6-(oxazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(1H-imidazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(thiophen-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(thiazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(1H-imidazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

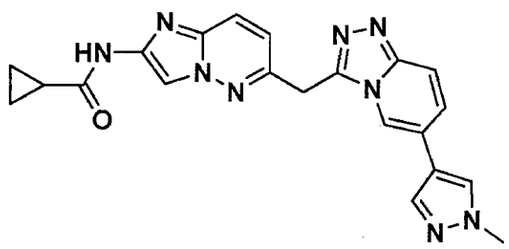
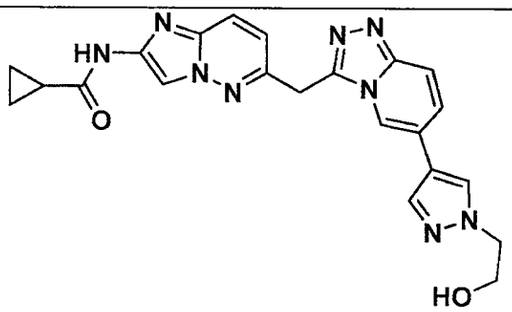
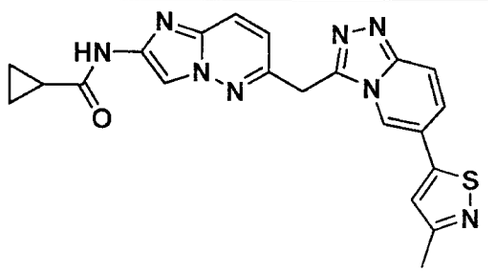
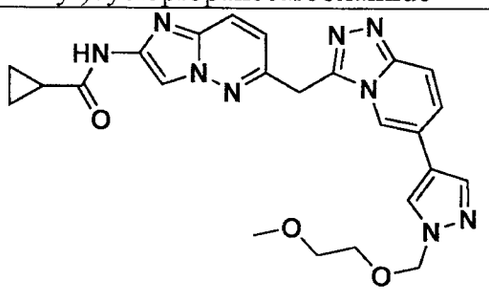
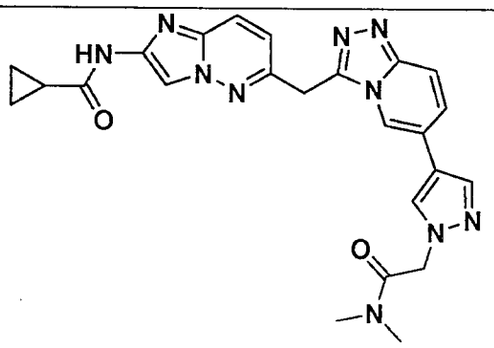
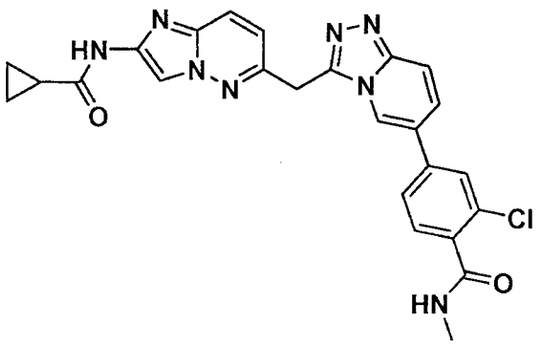
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 N-(6-(7-acetamido-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(7-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-chloro-5-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 3-(2N-(6-(6-(6-oxo-1,6-dihydropyridin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 3-(21-ethyl-3-(6-(6-(6-oxo-1,6-dihydropyrimidin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)urea

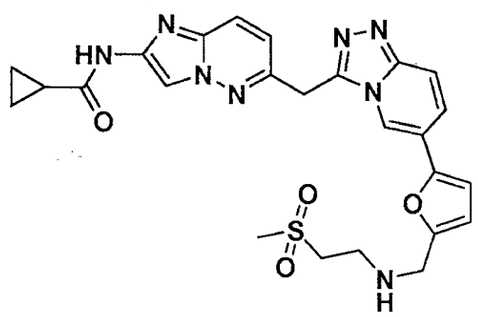
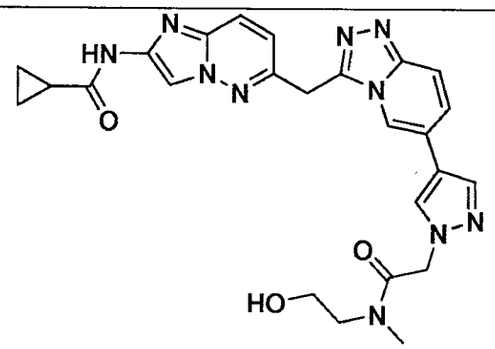
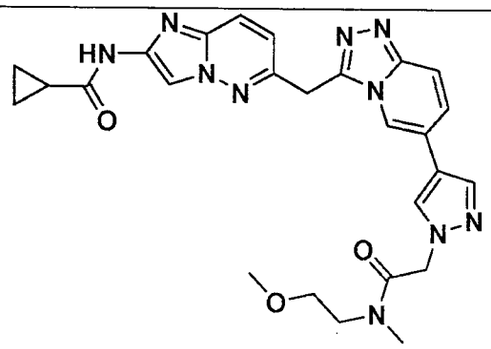
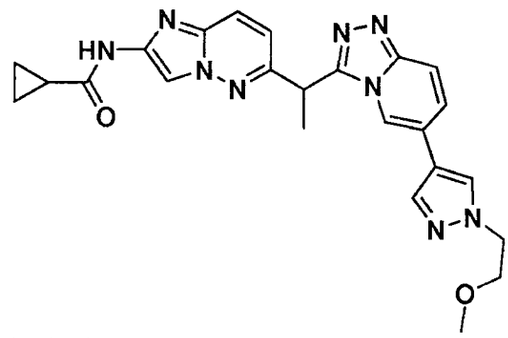
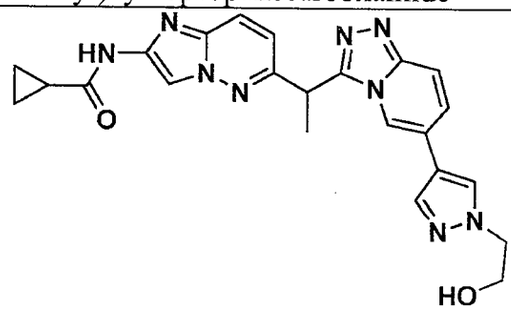
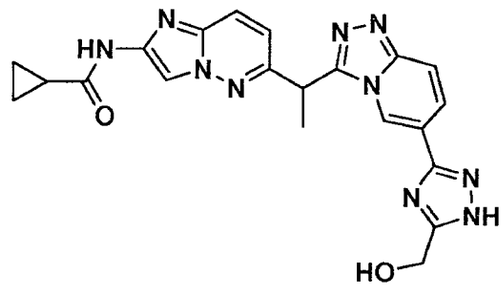
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 N-(6-(6-(1-(2,3-dihydroxypropyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 1-ethyl-3-(6-((6-(6-oxo-1,6-dihydropyridin-2-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)urea
 1-ethyl-3-(6-(6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)urea	 1-(2,3-dihydroxypropyl)-3-(6-((6-(3-fluorophenyl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)urea
 N-(6-((6-(prop-1-en-2-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-isopropyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

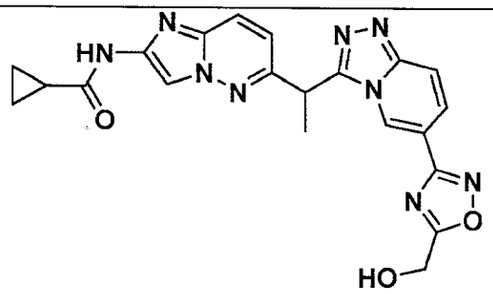
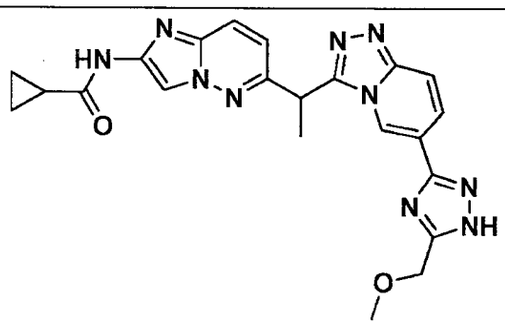
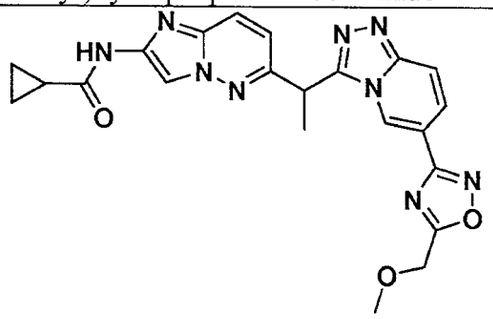
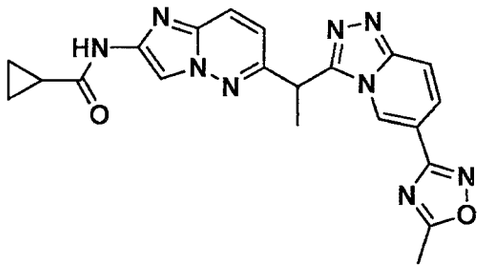
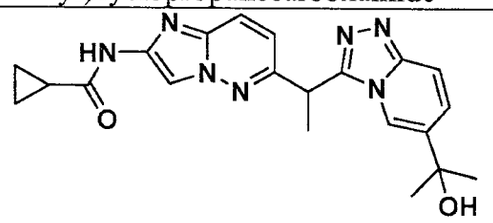
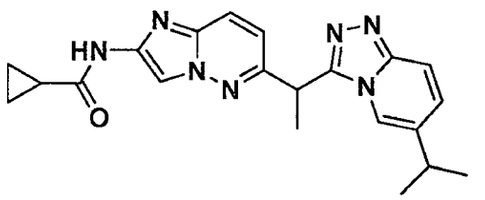
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 N-(6-((6-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(5-(hydroxymethyl)-1H-1,2,4-triazol-3-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-((6-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(5-(methoxymethyl)-1H-1,2,4-triazol-3-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

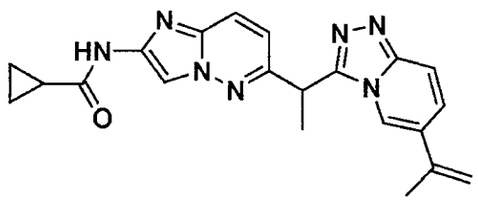
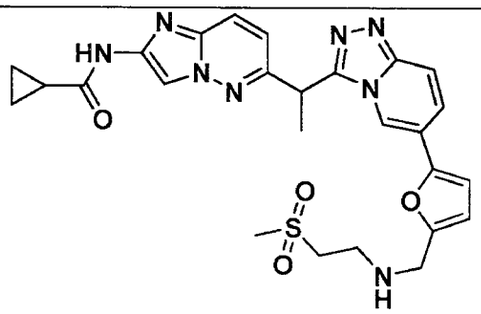
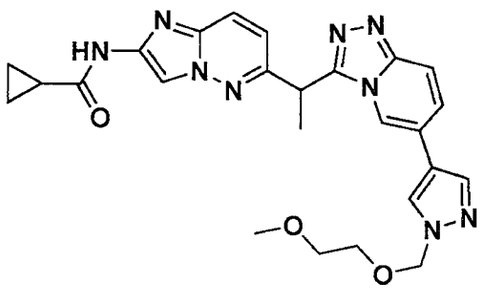
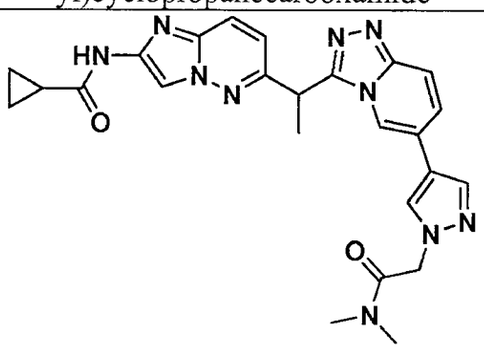
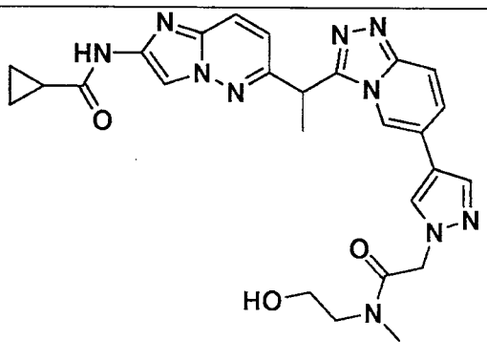
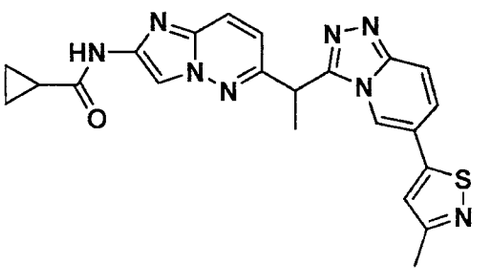
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 N-(6-((6-(1-(2-(dimethylamino)-2-oxoethyl)-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 2-chloro-4-(1-((2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)methyl)-1H-benzo[d][1,2,3]triazol-6-yl)-N-methylbenzamide
 N-(6-((6-(1-(2-((2-hydroxyethyl)(methyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(1-(2-((2-methoxyethyl)(methyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

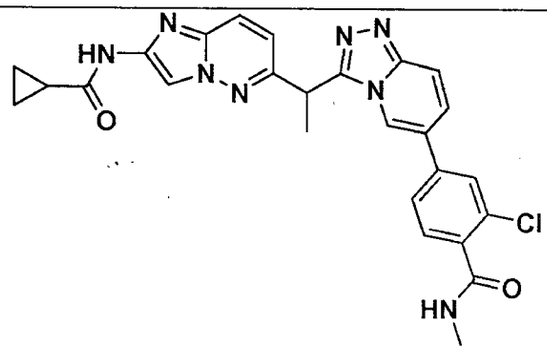
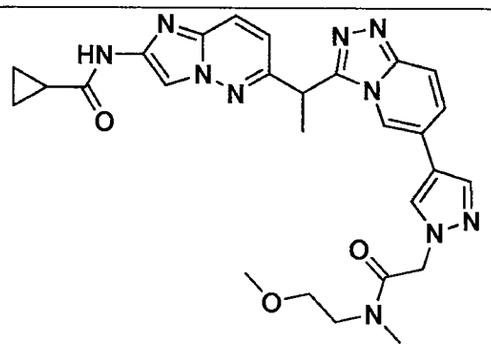
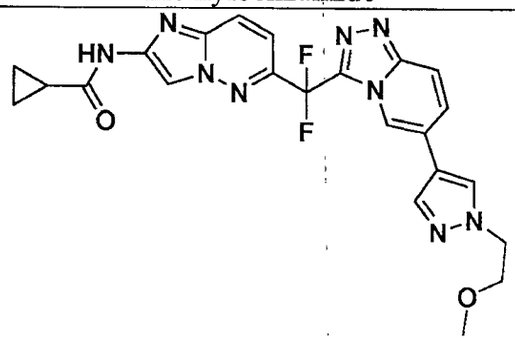
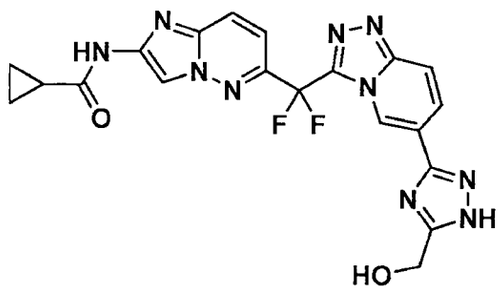
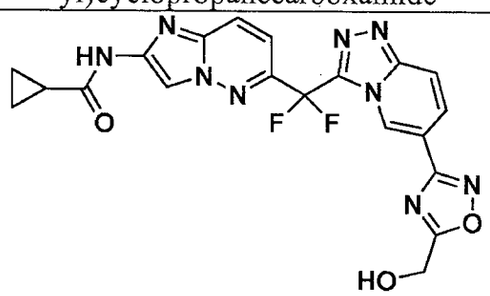
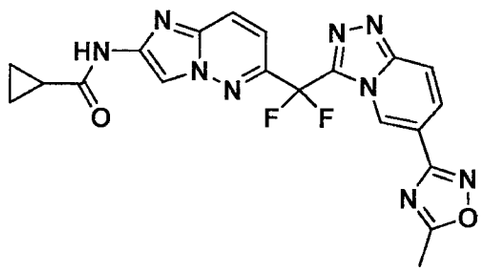
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 N-(6-((6-(2-hydroxypropan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-((6-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(5-(hydroxymethyl)-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-((6-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(5-(methoxymethyl)-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

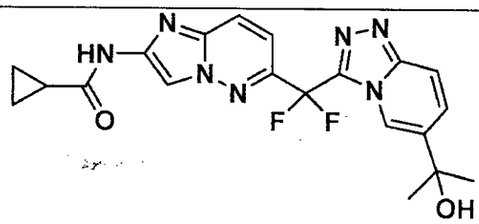
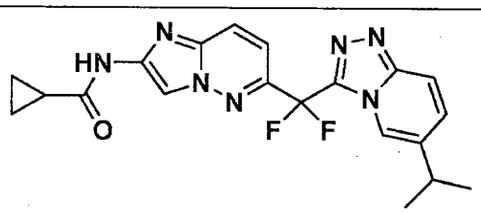
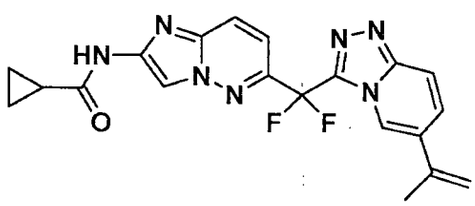
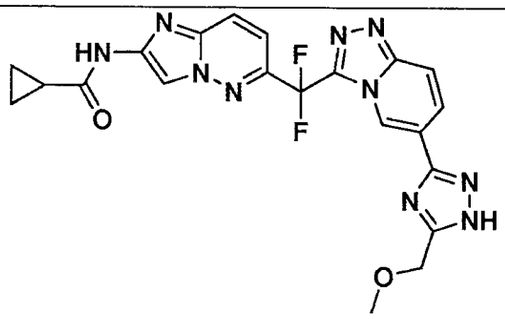
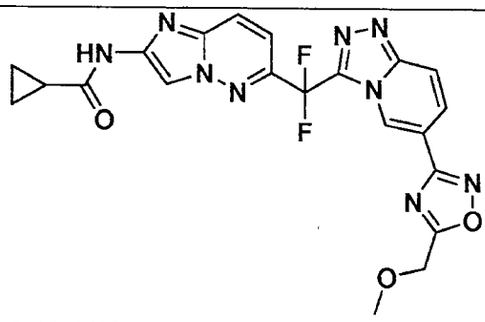
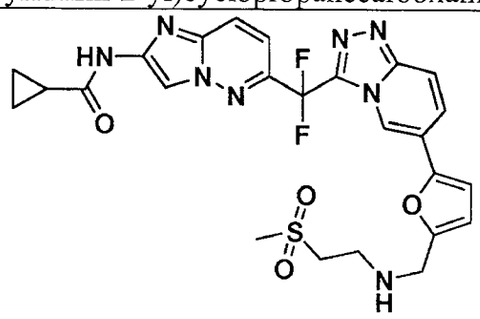
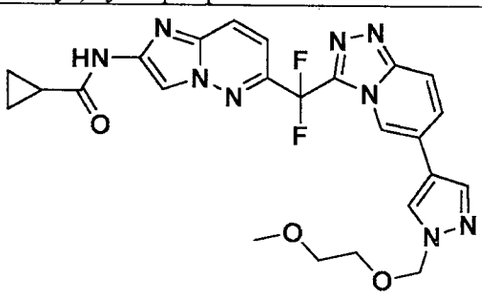
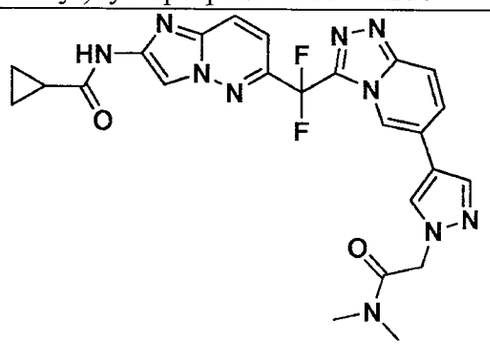
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 N-(6-((6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(1-((2-methoxyethoxy)methyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-((6-(1-(2-(dimethylamino)-2-oxoethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 2-chloro-4-(3-((2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)methyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-N-methylbenzamide

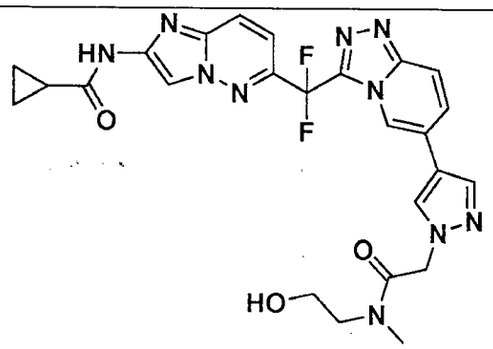
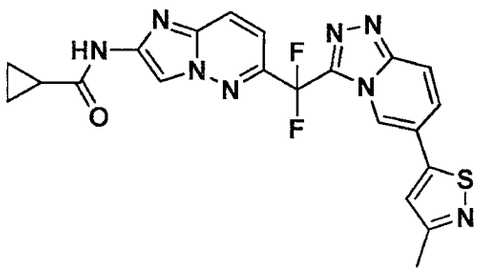
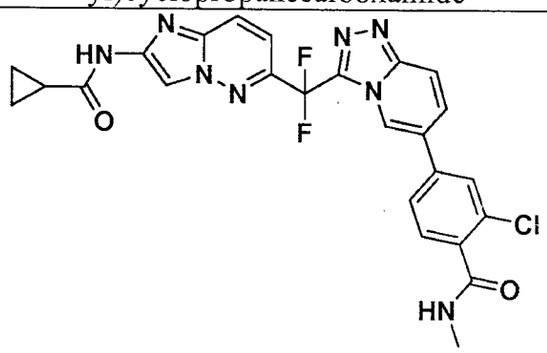
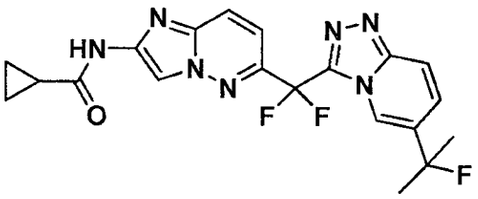
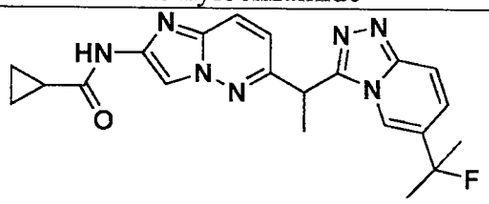
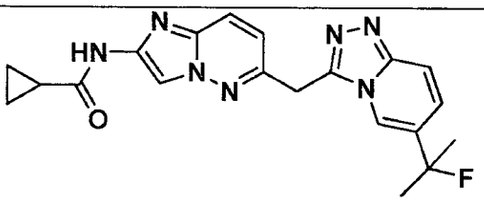
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 N-(6-((6-(1-(2-((2-methoxyethyl)(methyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(1-(6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(1-(6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(1-(6-(5-(hydroxymethyl)-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

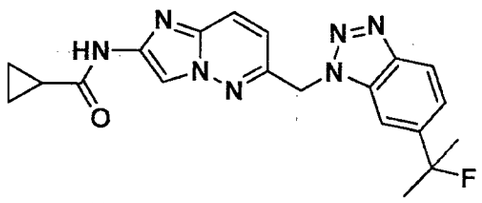
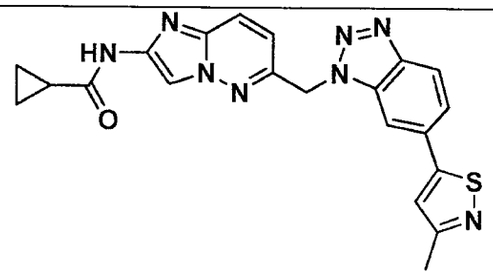
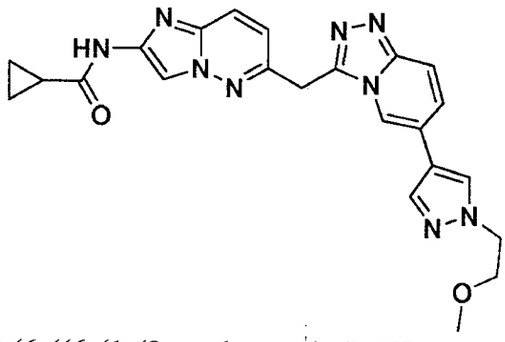
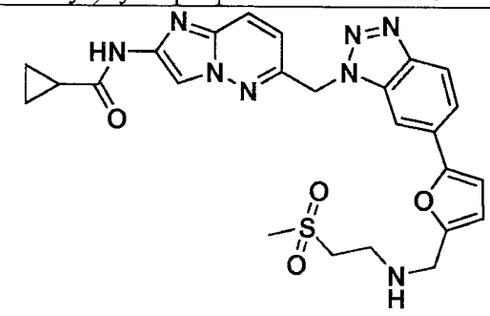
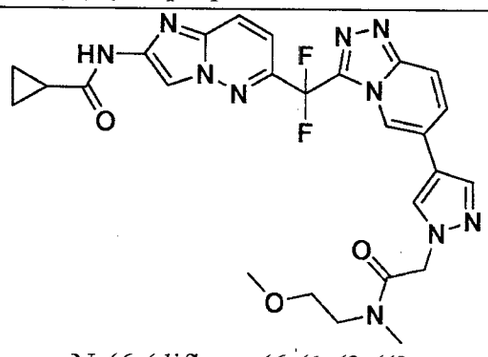
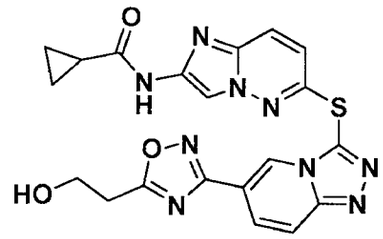
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 N-(6-(1-(6-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(1-(6-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(1-(6-(2-hydroxypropan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(1-(6-isopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

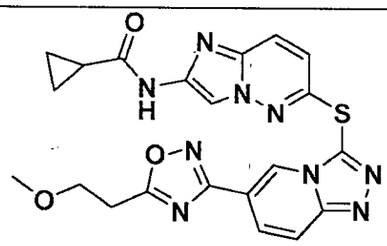
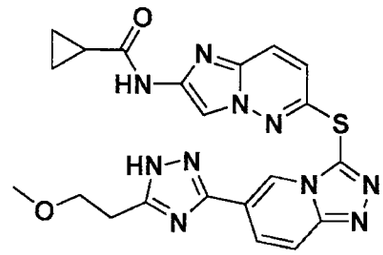
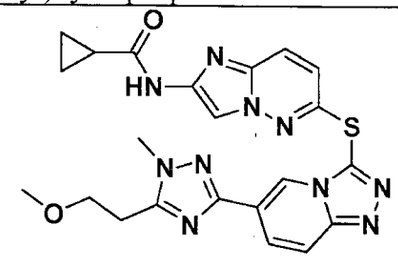
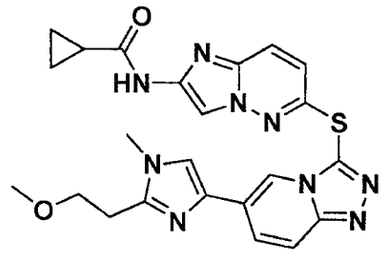
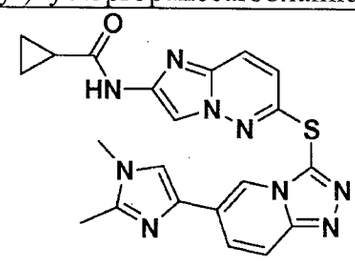
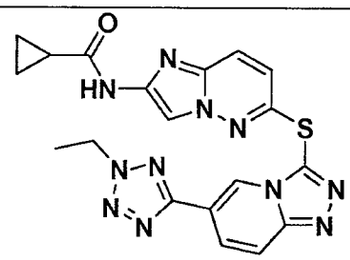
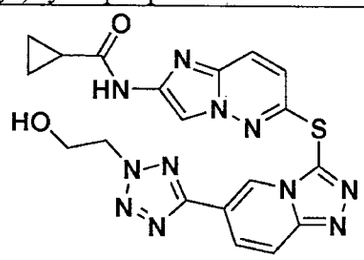
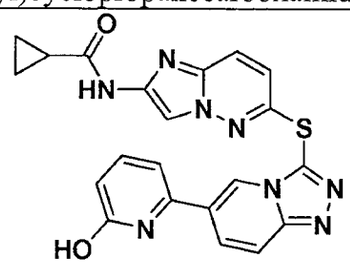
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 N-(6-(1-(6-(1-((2-methoxyethoxy)methyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(1-(6-(1-(2-(dimethylamino)-2-oxoethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(1-(6-(1-(2-((2-hydroxyethyl)(methyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(1-(6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

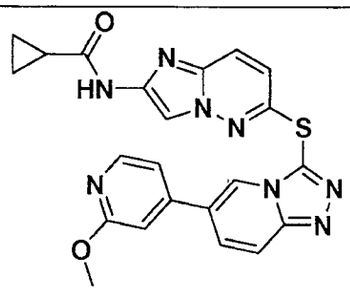
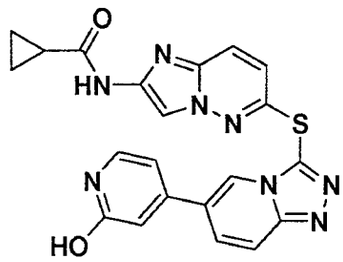
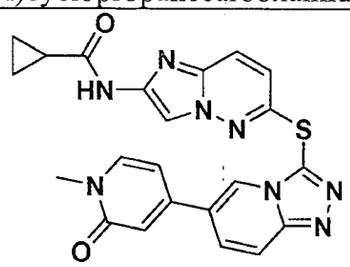
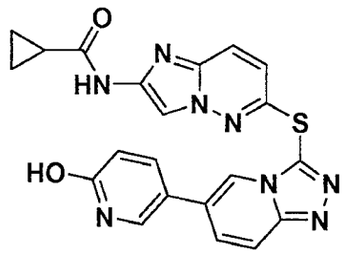
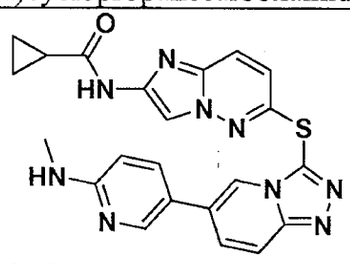
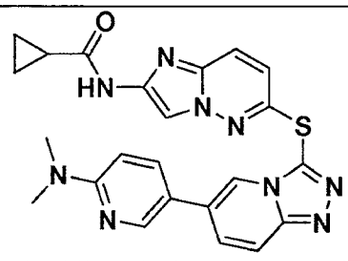
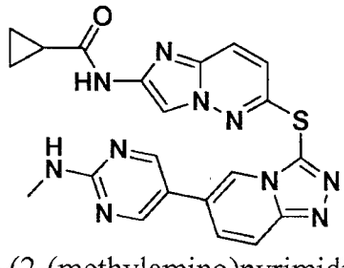
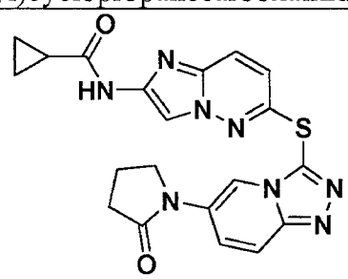
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 N-(6-(difluoro(6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(difluoro(6-(5-(hydroxymethyl)-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(difluoro(6-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(difluoro(6-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

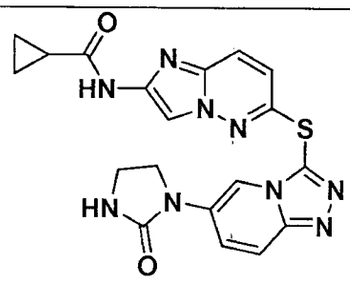
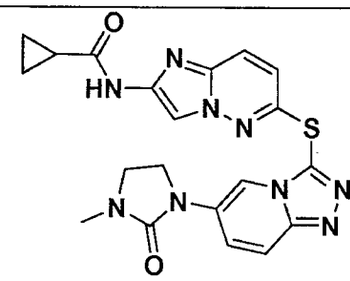
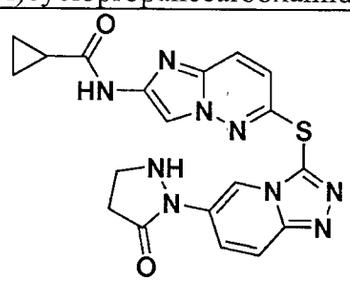
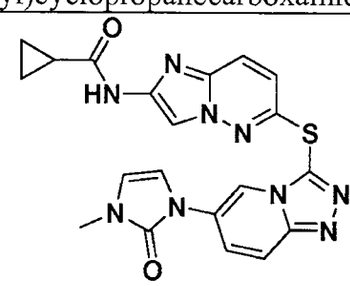
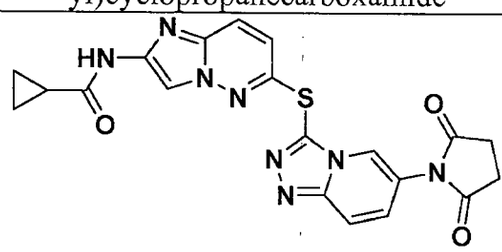
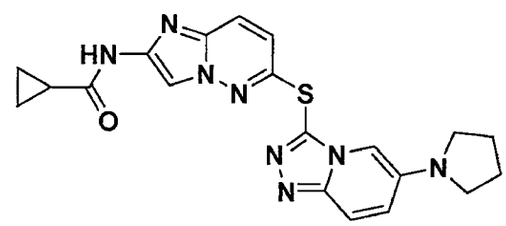
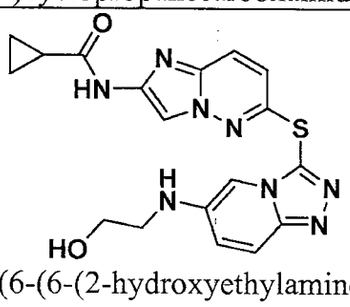
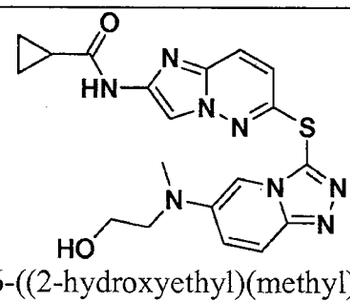
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 N-(6-(difluoro(6-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(difluoro(6-(5-(methoxymethyl)-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(difluoro(6-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(difluoro(6-(5-((2-(methylsulfonyl)ethylamino)methyl)furan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(difluoro(6-(1-((2-methoxyethoxy)methyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(1-(2-(dimethylamino)-2-oxoethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

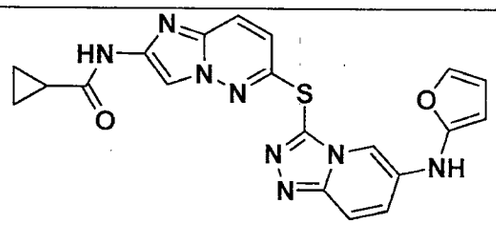
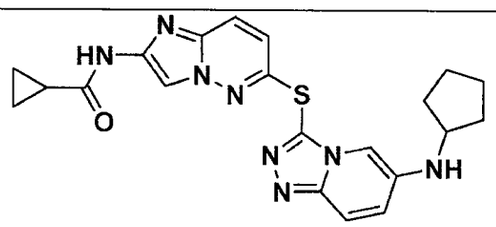
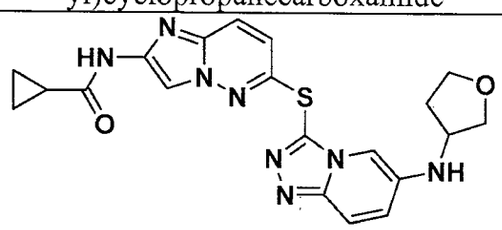
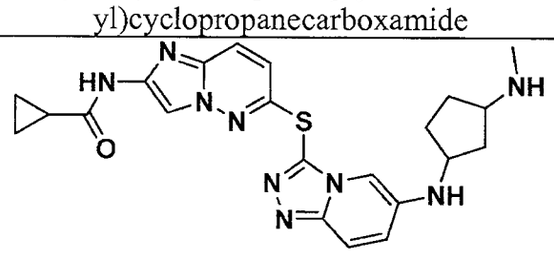
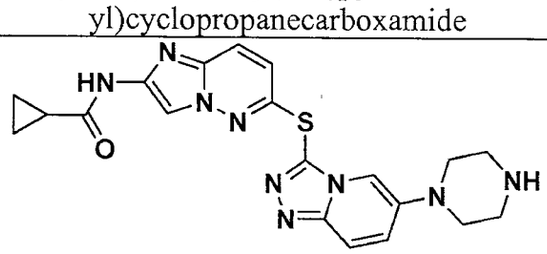
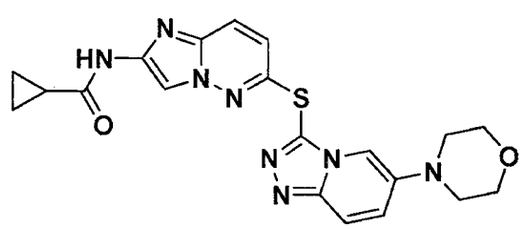
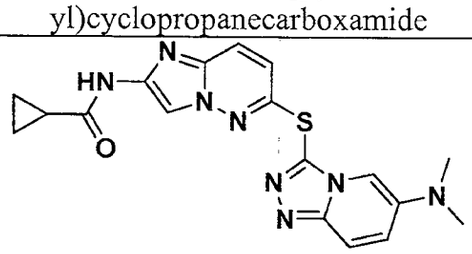
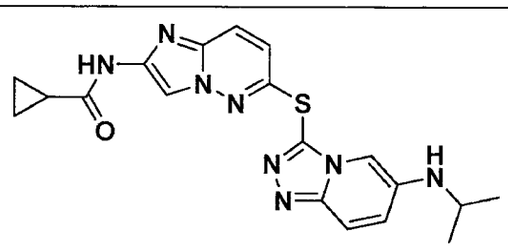
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 2-chloro-4-(3-((2-(cyclopropanecarboxamido)imidazo[1,2-b]pyridazin-6-yl)difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-N-methylbenzamide	 N-(6-(difluoro(6-(2-fluoropropan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(1-(6-(2-fluoropropan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(2-fluoropropan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

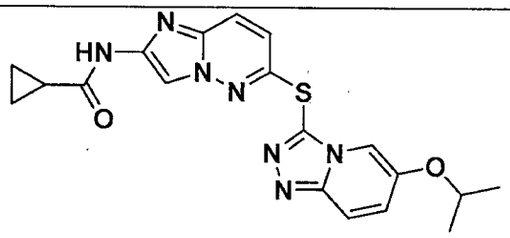
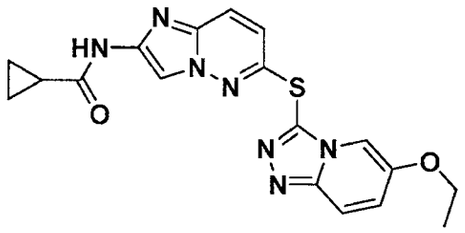
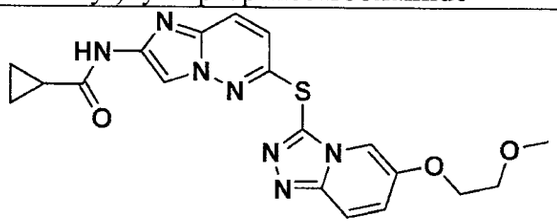
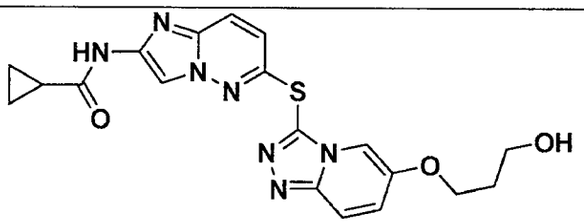
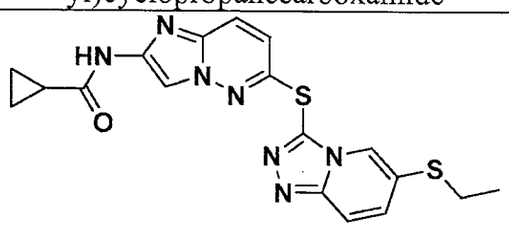
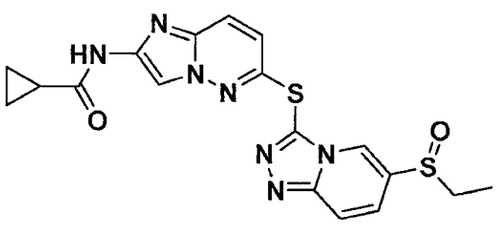
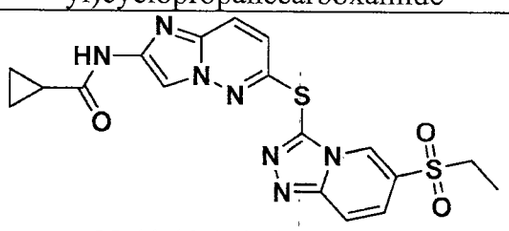
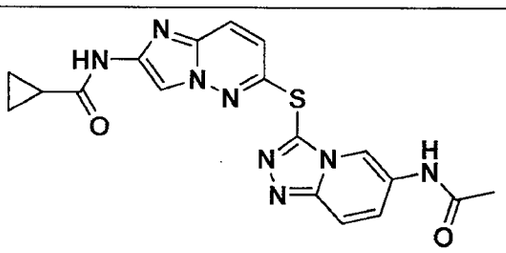
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 N-(6-((6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-((6-(5-((2-(methylsulfonyl)ethylamino)methyl)furan-2-yl)-1H-benzo[d][1,2,3]triazol-1-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(difluoro(6-(1-(2-((2-methoxyethyl)(methyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(5-(2-hydroxyethyl)-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

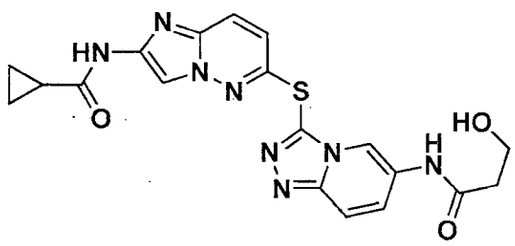
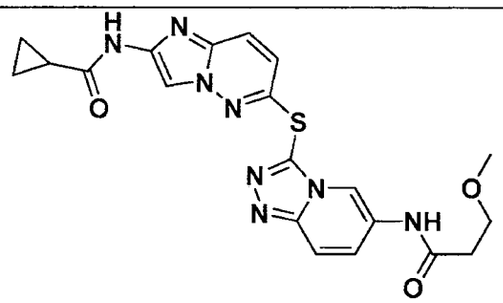
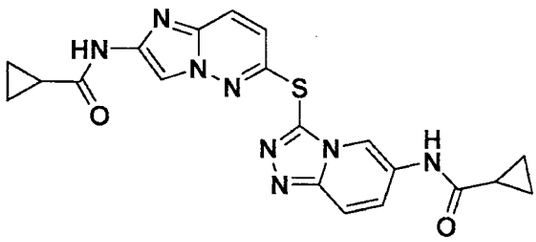
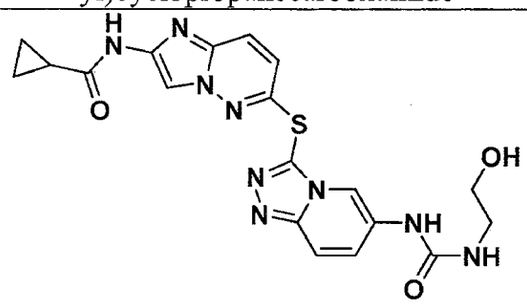
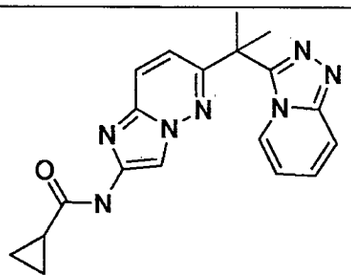
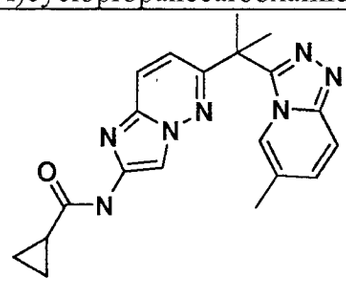
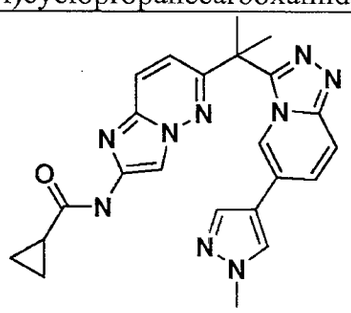
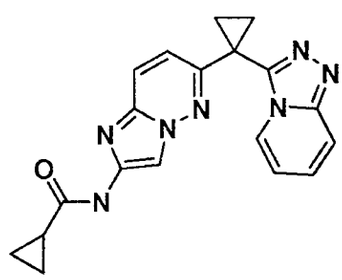
 N-(6-(6-(5-(2-methoxyethyl)-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(5-(2-methoxyethyl)-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(5-(2-methoxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(2-(2-methoxyethyl)-1-methyl-1H-imidazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(1,2-dimethyl-1H-imidazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(2-ethyl-2H-tetrazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(2-(2-hydroxyethyl)-2H-tetrazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(6-hydroxypyridin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

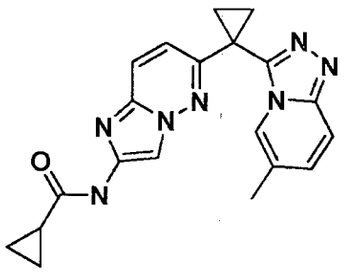
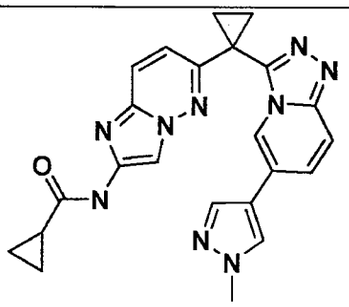
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 N-(6-(6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(6-hydroxypyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(6-(methylamino)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(6-(dimethylamino)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(2-(methylamino)pyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(2-oxopyrrolidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

 N-(6-(6-(2-oxoimidazolidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(3-methyl-2-oxoimidazolidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(5-oxopyrazolidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(3-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(2,5-dioxopyrrolidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(2-hydroxyethylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-((2-hydroxyethyl)(methyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

 N-(6-(6-(furan-2-ylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(cyclopentylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(tetrahydrofuran-3-ylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(3-(methylamino)cyclopentylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-morpholino-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(dimethylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(isopropylamino)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

 N-(6-(6-isopropoxy-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-ethoxy-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(3-hydroxypropoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(ethylthio)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(ethylsulfinyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(ethylsulfonyl)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-acetamido-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

 N-(6-(6-(3-hydroxypropanamido)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(3-methoxypropanamido)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(6-(cyclopropanecarboxamido)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(6-(3-(2-hydroxyethyl)ureido)-[1,2,4]triazolo[4,3-a]pyridin-3-ylthio)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)propan-2-yl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(2-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)propan-2-yl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide
 N-(6-(2-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)propan-2-yl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(1-([1,2,4]triazolo[4,3-a]pyridin-3-yl)cyclopropyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

 N-(6-(1-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)cyclopropyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide	 N-(6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)cyclopropyl)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

Biological Testing

[0607] The activity of compounds as protein kinase inhibitors may be assayed *in vitro*, *in vivo* or in a cell line. In vitro assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of the activated protein kinase. Alternate in vitro assays quantitate the ability of the inhibitor to bind to the protein kinase. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/protein kinase complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with the protein kinase bound to known radioligands.

A. Determination of inhibition of cMET

[0608] The inhibitory property of a compound relative to cMET catalysis was determined by use of capillary electrophoresis with fluorescence quantification of a phosphorylated peptide product for cMET. The cMET enzyme (amino acids 1023-1360) nominally at 24 μM was held at -80°C until use, in a buffer containing 25 mM Tris-HCl pH 8.5, 150 mM NaCl, 3 mM DTT and 10% glycerol. Enzyme was prepared from Sf9 cells using nickel affinity chromatography of N-terminal histidine tagged cMET kinase domain. Following purification, the tag was removed and enzyme concentrated. The final enzyme was partially phosphorylated and partially catalytically active. To activate the enzyme fully, frozen cMET was thawed quickly and activated with the addition of assay buffer (50 mM HEPES pH 7.5, 10 mM NaCl, 10 mM $MgCl_2$, 0.01% Brij®35), 1.25 mM ATP, 5 mM $MgCl_2$ and 5 mM DTT at a cMET concentration of 2.4 μM followed by a 30 minute incubation at room temperature. Solutions of test compounds in varying concentrations were prepared in DMSO and diluted

to a final DMSO concentration of 2% into assay cocktail containing assay buffer, 0.5 mM EDTA, and 2 μM of the peptide substrate FL-2 (5-FAM-EAIYAAPFAKKK-CONH2 where 5-FAM = 5-carboxyfluorescein). Next, cMET enzyme (1.2 nM final) was added and the system incubated at room temperature for 20 minutes. Catalysis was initiated by the addition of ATP (50 μM final). Assays were incubated at room temperature for 2 hours then quenched by the addition of EDTA. Phosphorylated peptide product was quantified by monitoring fluorescence during capillary electrophoresis with Caliper LifeSciences LabChip 3000 under the following settings: base pressure = -0.1 psi, screen pressure = -1.2 psi, downstream voltage = -500 V, upstream voltage = -2300 V, chip type = TC372. The elution buffer was identical to the assay buffer except for the absence of DTT, FL-2 and ATP and the addition of 0.1% coating reagent (Caliper). Under these conditions, phosphorylated product eluted at 37 seconds and the unphosphorylated substrate eluted at 45 seconds. Peak height was quantified and used to determine enzyme velocities.

[0609] IC_{50} values were calculated by non-linear least squares curve fitting of the standard IC_{50} equation to background-corrected cMET velocity versus compound concentration. As a reference point for this assay, staurosporin displayed an IC_{50} of ~150 nM. IC_{50} values for select compounds of the invention against cMET are given in Table 1.

B. Determination of inhibition of cell viability

[0610] Cells were maintained at 37°C in a humidified atmosphere containing 5%-8% CO_2 following the instructions of the supplier (American Type Culture Collection (Rockville, MD)). Inhibition of cell viability was determined for a panel of tumor cell lines (MKN45, EBC1 and A549), using the soluble tetrazolium salt, MTS (Promega, Madison, WI). Cells were seeded at 2,000-7,500 cells/well in 96-well tissue culture plates and were allowed to attach for approximately 24 hours prior to addition of compounds or DMSO vehicle. After 96 hours of incubation with test compounds, MTS conversion by metabolically active cells was determined by measuring the OD490 nm with a Spectamax microplate reader (Molecular Devices, San Diego, CA). Cells were treated in duplicate with test compounds. Compounds were serially diluted (1:2.5) from column 1 to 11 and column 12 contained DMSO vehicle. Compounds were diluted into cell growth medium then compound solution was added to cells. Equal amounts of DMSO were added to cells (final concentration is 0.5%). After background correction and normalization against DMSO-treated cells, EC_{50} values were

calculated using non-linear curve-fitting of the cell viability as a function of compound concentration. The MKN45 and EBC1 cell lines contain high levels of phospho-Met and are dependent on cMET for proliferation, whereas the A549 line is used as negative control.

[0611] EC_{50} values may be calculated by non-linear curve fitting of the compound concentrations and fluorescence intensities to the standard EC_{50} equation. EC_{50} values for select compounds of the invention against MKN45, EBC1 and A549 are given in Table 1.

TABLE 1

Compound	cMet IC_{50}, nm	MKN45 EC_{50}, nm	EBC1 EC_{50}, nm	A549 EC_{50}, nm
1	> 100	---	---	---
2	> 100	---	---	---
3 (HCl Salt)	> 100	250 - 630	100 - 199	8000 - 25000
3 (TFA Salt)	> 100	250 - 630	100 - 199	8000 - 25000
3 (free base)	> 100	100 - 199	60 - 100	8000 - 25000
4	30 - 59	100 - 249	< 35	> 50000
5	< 30	< 100	< 35	> 50000
6	> 100	> 630	> 200	> 50000
9	60 - 100	250 - 630	100 - 199	8000 - 25000
12	> 100	> 630	> 200	> 50000
13 (HCl Salt)	30 - 59	100 - 249	< 35	8000 - 25000
13 (TFA Salt)	30 - 59	60 - 100	< 30	5000 - 8000
13 (free base)	30 - 59	< 30	< 30	> 50000
14	30 - 59	250 - 630	100 - 199	600 - 1600
15	60 - 100	250 - 630	100 - 199	8000 - 25000
16	> 100	> 630	> 200	> 50000
17	60 - 100	< 100	< 35	> 19500
18	30 - 59	100 - 249	100 - 199	> 19500
19	60 - 100	250 - 630	100 - 199	> 19500
20	60 - 100	250 - 630	> 200	> 50000
21	> 100	> 630	> 200	> 50000
22	60 - 100	> 630	> 200	> 50000
23	30 - 59	250 - 630	100 - 199	> 50000
24	60 - 100	100 - 249	35 - 99	> 50000
25	< 30	< 100	< 35	8000 - 25000
26	< 30	< 100	< 35	> 19500
27	< 30	< 100	35 - 99	> 50000
28	< 30	< 100	< 35	> 50000
29	60 - 100	< 100	35 - 99	> 50000
30	30 - 59	> 630	> 200	> 19500
31	30 - 59	< 100	< 35	> 50000
32	< 30	100 - 249	35 - 99	> 50000

Compound	cMet IC_{50}, nm	MKN45 EC_{50}, nm	EBC1 EC_{50}, nm	A549 EC_{50}, nm
33	> 100	> 630	> 200	> 50000
34	60 - 100	> 630	> 200	> 50000
35	> 100	> 630	100 - 199	> 19500
36	< 30	250 - 630	35 - 99	> 50000
37	30 - 59	250 - 630	100 - 199	> 50000
38	> 100	> 630	> 200	> 50000
39	60 - 100	100 - 249	35 - 99	600 - 1600
40	> 100	> 630	> 200	> 50000
41	60 - 100	100 - 249	35 - 99	8000 - 25000
42	60 - 100	100 - 249	35 - 99	> 50000
43	> 100	---	---	---
44	< 30	< 100	< 35	600 - 1600
45 (HCl Salt)	< 30	< 30	< 30	> 50000
45 (TFA Salt)	30 - 59	---	---	---
46	30 - 59	60 - 100	60 - 100	> 50000
47	< 30	< 30	< 30	> 50000
49 (HCl Salt)	< 30	30 - 59	< 30	8000 - 25000
49 (TFA Salt)	30 - 59	60 - 100	60 - 100	> 50000
49 (free base)	< 30	60 - 100	< 30	> 50000
50	< 30	30 - 59	< 30	> 50000
51	> 100	> 100	> 100	> 50000
52	> 100	> 100	> 100	> 50000
53	250 - 630	250 - 630	250 - 630	> 50000
55	< 30	< 30	< 30	> 50000
56	< 30	< 30	< 30	> 50000
57	< 30	< 30	< 30	> 50000
58	< 30	< 30	< 30	> 50000
59	< 30	100 - 249	60 - 100	> 50000
60	< 30	60 - 100	60 - 100	> 50000
61	< 30	< 30	< 30	> 50000
62	< 30	< 30	< 30	5000 - 8000
63	< 30	< 30	< 30	> 50000
64	< 30	100 - 249	100 - 249	> 50000
65	< 30	< 30	< 30	> 50000
66	< 30	100 - 249	100 - 249	> 50000
67	< 30	100 - 249	60 - 100	> 50000
68	< 30	30 - 59	30 - 59	> 50000
69	< 30	< 30	< 30	> 50000
70	< 30	< 30	< 30	> 50000
71	< 30	< 30	< 30	> 50000
72	< 30	< 30	< 30	> 50000
73	< 30	< 30	< 30	8000 - 25000
74	< 30	< 30	< 30	8000 - 25000
75	< 30	< 30	< 30	8000 - 25000

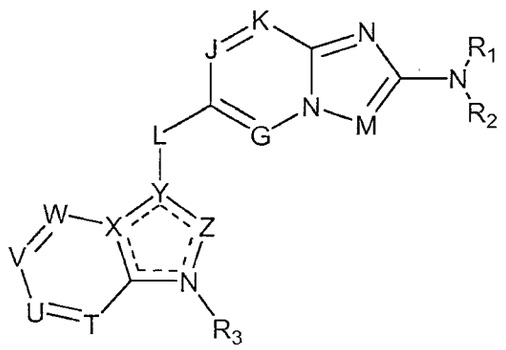
Compound	cMet IC_{50}, nm	MKN45 EC_{50}, nm	EBC1 EC_{50}, nm	A549 EC_{50}, nm
76	< 30	< 30	< 30	> 50000
77	< 30	< 30	< 30	> 50000
78	30 - 59	< 30	< 30	> 50000
79	60 - 100	< 30	< 30	> 50000
80	30 - 59	< 30	30 - 59	> 50000
81	< 30	< 30	< 30	> 50000
82	< 30	< 30	< 30	> 50000
83	< 30	< 30	< 30	> 50000
84	< 30	< 30	< 30	> 50000
85	< 30	< 30	< 30	> 50000
86	30 - 59	< 30	< 30	> 50000
87	100 - 249	30 - 59	30 - 59	> 50000
88	< 30	< 30	< 30	> 50000
89	< 30	-	-	-
90	< 30	< 30	< 30	> 50000
91	< 30	< 30	< 30	> 50000
92	< 30	< 30	< 30	> 50000
93	60 - 100	30 - 59	30 - 59	8000 - 25000
94	250 - 630	-	-	-
95	< 30	-	-	-
96	< 30	< 30	< 30	8000 - 25000
97	< 30	< 30	< 30	> 50000
98	< 30	< 30	< 30	> 50000
99	250 - 630	100 - 249	100 - 249	> 50000
101	< 30	100 - 249	30 - 59	> 50000
102	30 - 59	60 - 100	30 - 59	> 50000
103	< 30	30 - 59	< 30	> 50000
104	< 30	< 30	< 30	> 50000
105	< 30	250 - 630	100 - 249	> 50000
106	< 30	60 - 100	30 - 59	> 50000
107	< 30	100 - 249	60 - 100	> 50000
108	30 - 59	8000 - 25000	8000 - 25000	> 50000
109	250 - 630	8000 - 25000	8000 - 25000	8000 - 25000
110	30 - 59	100 - 249	30 - 59	> 50000
111	< 30	100 - 249	30 - 59	8000 - 25000
112	100 - 249	-	-	-
113	250 - 630	-	-	-
114	> 630	> 630	> 630	> 50000

[0612] 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 pharmaceutically acceptable salt thereof, wherein

G is selected from the group consisting of CR_4 and N;

J is selected from the group consisting of CR_5 and N;

K is selected from the group consisting of CR_6 and N;

M is selected from the group consisting of CR_7 and N;

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

T is selected from the group consisting of CR_8 and N;

U is selected from the group consisting of CR_9 and N;

V is selected from the group consisting of CR_{10} and N;

W is selected from the group consisting of CR_{11} and N;

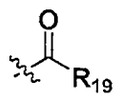
X is selected from the group consisting of CR_{12} and N;

Y is selected from the group consisting of CR_{13} and N;

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

R_1 is selected from the group consisting of hydrogen, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, (C_{1-10})alkylcarbonyl, (C_{3-12})cycloalkyl(C_{1-5})carbonyl, hetero(C_{3-12})cycloalkyl(C_{1-10})carbonyl, aryl(C_{1-10})carbonyl, hetero(C_{1-10})aryl(C_{1-5})carbonyl, (C_{9-12})bicycloaryl(C_{1-5})carbonyl, hetero(C_{8-12})bicycloaryl(C_{1-5})carbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_1 has the formula



R_2 is hydrogen or a substituent convertible *in vivo* to hydrogen;

R_3 is selected from the group consisting of hydrogen, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_3 is absent when the nitrogen to which it is bound forms part of a double bond;

R_4 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

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

R_8 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

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, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, amido, 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, amino(C_{1-10})alkyl, amido(C_{1-10})alkylamino(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, carbonyl(C_{4-12})aryl, hetero(C_{4-10})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, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, amido, 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, amino(C_{1-10})alkyl, amido(C_{1-10})alkylamino(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, carbonyl(C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})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, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{12} is absent when the carbon to which it is bound forms part of a double bond;

R_{13} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{13} is absent when the carbon to which it is bound forms part of a double bond;

R_{14} and R_{15} 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, aminocarbonyl,

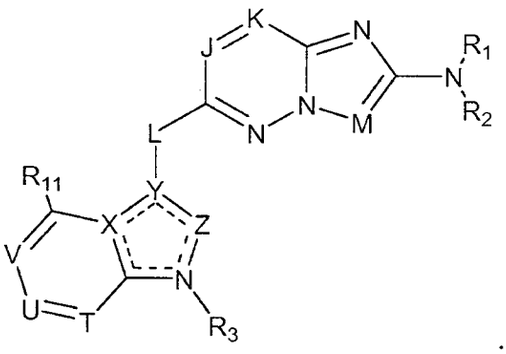
amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{15} is absent when the carbon to which it is bound forms part of a double bond;

R_{16} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{16} is absent when the nitrogen to which it is bound forms part of a double bond; and

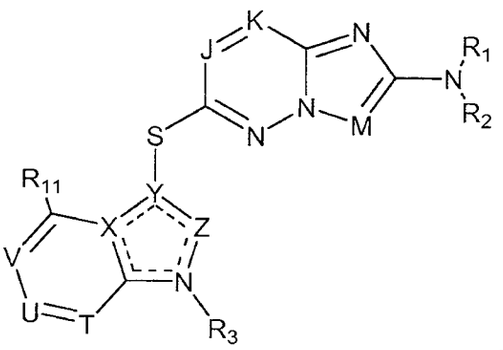
R_{19} selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

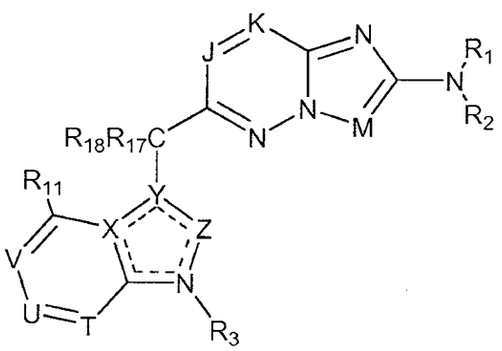
2. The compound according to claim 1 having the formula:



3. The compound according to claim 1 having the formula:



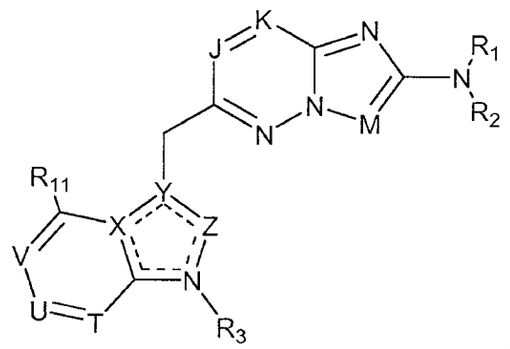
4. The compound according to claim 1 having the formula:



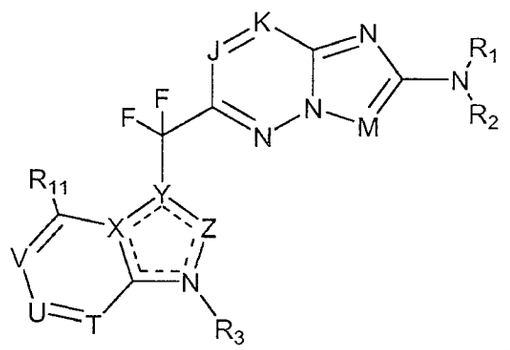
wherein R_{17} and R_{18} are each independently elected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy,

(C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

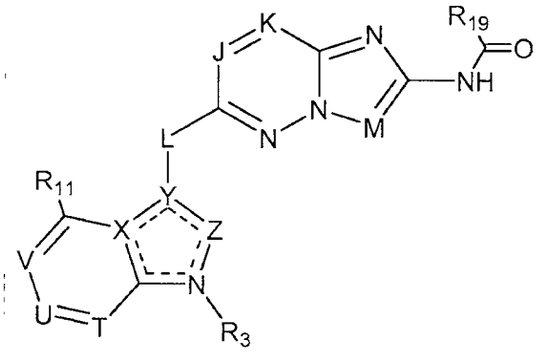
5. The compound according to claim 1 having the formula:



6. The compound according to claim 1 having the formula:

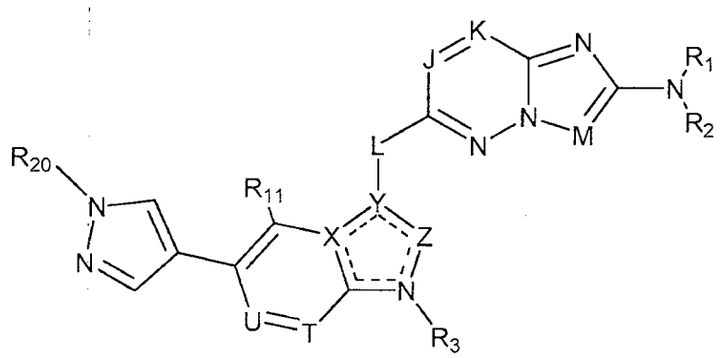


7. The compound according to claim 1 having the formula:



wherein R_{19} selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

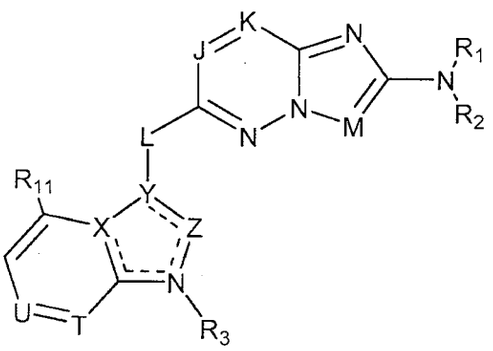
8. The compound according to claim 1 having the formula:



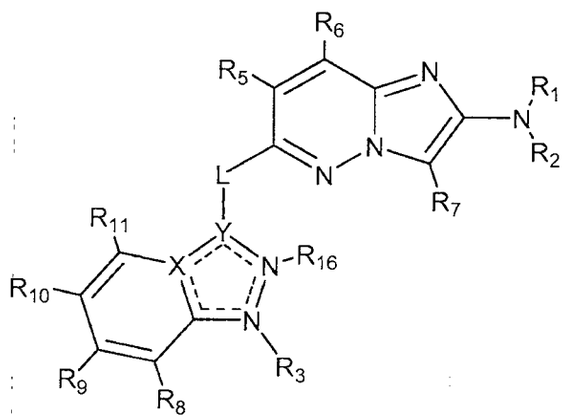
wherein R_{20} selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

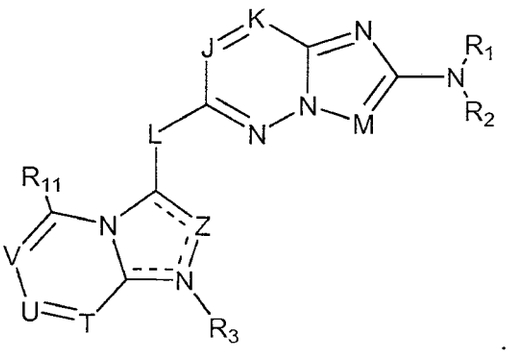
9. The compound according to claim 1 having the formula:



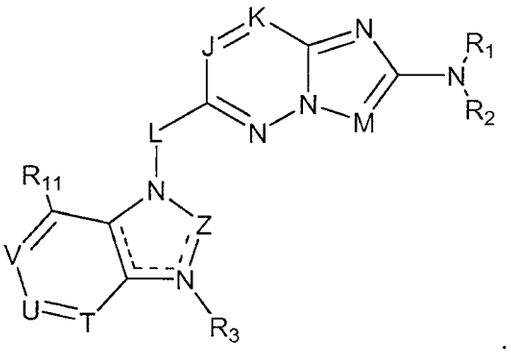
10. The compound according to claim 1 having the formula:



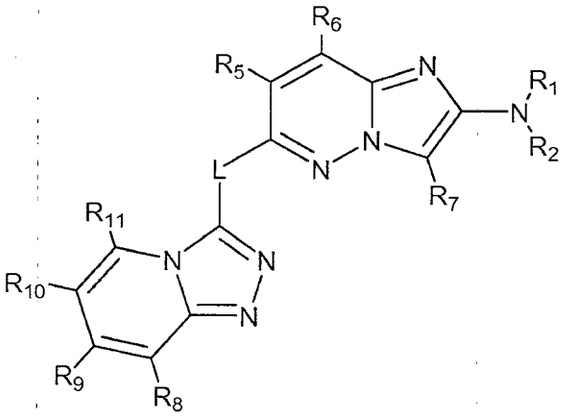
11. The compound according to claim 1 having the formula:



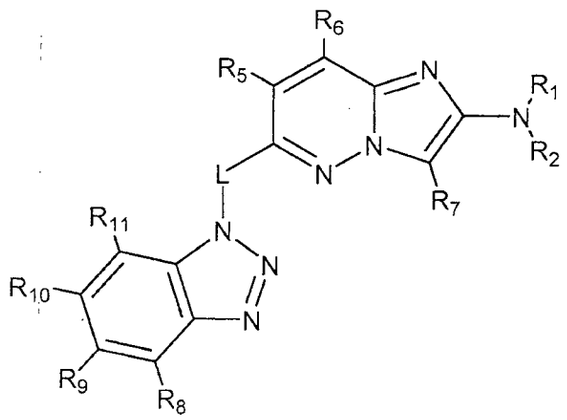
12. The compound according to claim 1 having the formula:



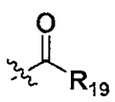
13. The compound according to claim 1 having the formula:



14. The compound according to claim 1 having the formula:



15. The compound according to any one of claims 1-6 and 8-14, wherein R_1 has the formula



wherein R_{19} selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

16. The compound according to any one of claims 1-6 and 8-15, wherein R_2 is hydrogen.

17. The compound according to any one of claims 1-12, 15 and 16, wherein R_3 is absent.

18. The compound according to any one of claims 1 and 15-17, wherein R_4 is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

19. The compound according to any one of claims 1-18, wherein R_5 is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

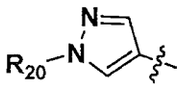
20. The compound according to any one of claims 1-19, wherein R_6 is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

21. The compound according to any one of claims 1-20, wherein R_7 is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

22. The compound according to any one of claims 1-21, wherein R_8 is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

23. The compound according to any one of claims 1-22, wherein R_9 is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

24. The compound according to any one of claims 1-7 and 10-23, wherein R_{10} has the formula



wherein R_{20} 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, aminocarbonyl, 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_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

25. The compound according to any one of claims 1-24, wherein R_{11} is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

26. The compound according to any one of claims 1-10 and 15-25, wherein R_{12} is absent.

27. The compound according to any one of claims 1-10 and 15-26, wherein R_{13} is absent.

28. The compound according to any one of claims 1-9, 11, 12 and 15-27, wherein R_{14} is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

29. The compound according to any one of claims 1-9, 11, 12 and 15-28, wherein R_{15} is absent.

30. The compound according to any one of claims 1-12 and 15-29, wherein R_{16} is absent.

31. The compound according to any one of claims 4 and 15-30, wherein R_{17} is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

32. The compound according to any one of claims 4 and 15-31, wherein R_{18} is selected from the group consisting of hydrogen, halo and a substituted or unsubstituted (C_{1-3})alkyl.

33. The compound according to any one of claims 1-32, wherein R_{19} is a substituted or unsubstituted (C_{1-5})alkyl.

34. The compound according to any one of claims 1-32, wherein R_{19} is a substituted or unsubstituted (C_{3-6})cycloalkyl.

35. The compound according to any one of claims 1-32, wherein R_{19} is a substituted or unsubstituted cyclopropyl.

36. The compound according to any one of claims 8 and 15-35, wherein R_{20} is selected from the group consisting of hydrogen, halo, a substituted or unsubstituted (C_{1-5})alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted (C_{3-12})cycloalkyl, a substituted or unsubstituted hetero(C_{4-10})aryl, a substituted or unsubstituted hydroxy(C_{1-6})alkyl and a substituted or unsubstituted hetero(C_{3-6})cycloalkyl(C_{1-4})alkyl.

37. The compound according to any one of claims 8 and 15-35, wherein R_{20} is hydrogen.

38. The compound according to any one of claims 8 and 15-35, wherein R_{20} is methyl.

39. The compound according to any one of claims 1-38, wherein the compound is in the form of a pharmaceutically acceptable salt.

40. A pharmaceutical composition comprising a compound according to any one of claims 1-39; and a pharmaceutically acceptable excipient.

41. A kit comprising:

a compound of any one of claims 1-39; 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.

42. An article of manufacture comprising:

a compound of any one of claims 1-39; and

packaging materials.

43. A therapeutic method comprising administering a compound of any one of claims 1-39 to a subject.

44. A method of inhibiting cMET comprising contacting cMET with a compound of any one of claims 1-39.

45. A method of inhibiting cMET comprising causing a compound of any one of claims 1-39 to be present in a subject in order to inhibit cMET *in vivo*.

46. A method of inhibiting cMET comprising administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits cMET *in vivo*, the second compound being a compound according to any one of claims 1-39.

47. A method of treating a disease state for which cMET possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising causing a compound of any one of claims 1-39 to be present in a subject in a therapeutically effective amount for the disease state.

48. A method of treating a disease state for which cMET possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising administering a compound of any one of claims 1-39 to a subject, wherein the compound is present in the subject in a therapeutically effective amount for the disease state.

49. A method of treating a disease state for which cMET possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits cMET *in vivo*, the second compound being a compound according to any one of claims 1-39.

50. The method according to any one of claims 47-49, wherein the disease state is selected from the group consisting of cancer, atherosclerosis and fibrosis of the lung.

51. The method according to claim 50, wherein the cancer is selected from the group consisting of gastric cancer, lung cancer, colon cancer, breast cancer and other solid tumors

52. A compound according to any one of claims 1-39 for use as a medicament.

53. Use of a compound according to any one of claims 1-39 for inhibiting cMET.

54. Use of a compound according to any one of claims 1-39 for treating a disease state for which cMET possess activity that contributes to the pathology and/or symptomology of the disease state.

55. Use of a compound according to any one of claims 1-39 for treating cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/053913

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D487/04 C07D519/00 A61K31/437 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/075567 A (JANSSEN PHARMACEUTICA NV [BE]; LU TIANBAO [US]; ALEXANDER RICHARD [US]) 5 July 2007 (2007-07-05) page 1, line 13 - line 15; claim 1	1-55
X	WO 2008/021781 A (INCYTE CORP [US]; ZHUO JINCONG [US]; ZHANG COLIN [US]; XU MEIZHONG [US]) 21 February 2008 (2008-02-21) page 1, line 7 - line 10; claim 1	1-55
X	WO 2008/064157 A (INCYTE CORP [US]; ZHUO JINCONG [US]; METCALF BRIAN [US]; XU MEIZHONG [ ]) 29 May 2008 (2008-05-29) page 1, line 7 - line 11; claim 1	1-55

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2009	04/11/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Seelmann, Ingo

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/053913

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2009/106577 A (NOVARTIS AG [CH]; FURET PASCAL [CH]; MCCARTHY CLIVE [CH]; SCHOEPFER JO) 3 September 2009 (2009-09-03) page 1, line 3 - line 9; examples 153,161	1,16-32, 38,40-55

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/053913

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 2007075567 A	05-07-2007	AR	058703 A1	20-02-2008
		AU	2006331912 A1	05-07-2007
		CA	2634721 A1	05-07-2007
		CN	101374843 A	25-02-2009
		EA	200870085 A1	30-12-2008
		EC	SP088573 A	30-07-2008
		EP	1966214 A1	10-09-2008
		JP	2009525263 T	09-07-2009
		KR	20080085154 A	23-09-2008
		US	2009098181 A1	16-04-2009
		US	2007203136 A1	30-08-2007
		UY	30041 A1	31-05-2007
WO 2008021781 A	21-02-2008	AR	062240 A1	22-10-2008
		CA	2660836 A1	21-02-2008
		EP	2057164 A1	13-05-2009
		US	2008039457 A1	14-02-2008
WO 2008064157 A	29-05-2008	AR	066142 A1	29-07-2009
		AU	2007323725 A1	29-05-2008
		CA	2669991 A1	29-05-2008
		CL	33412007 A1	18-04-2008
		CR	10841 A	30-06-2009
		EC	SP099400 A	31-07-2009
		EP	2099447 A1	16-09-2009
		US	2008167287 A1	10-07-2008
WO 2009106577 A	03-09-2009	US	2009264406 A1	22-10-2009
		UY	31676 A1	30-09-2009

000230

INHIBIDORES DE cMET

CAMPO DE LA INVENCIÓN

La presente invención se refiere a compuestos que se pueden usar para inhibir cMET, así como composiciones de materia, kits y artículos de manufactura que comprenden estos compuestos. La invención también se refiere a métodos para inhibir cMET y métodos de tratamiento que usan compuestos de acuerdo con la presente invención. Además, la invención se refiere a métodos de obtener los compuestos de la presente invención, así como intermediarios útiles en dichos métodos.

ANTECEDENTES DE LA INVENCIÓN

cMET quinasa es un receptor de tirosina quinasa. HGF (factor de crecimiento de hepatocitos, también conocido como un factor de dispersión), el ligando para cMET, es secretado por las células de origen mesodérmico mientras que cMET se expresa predominantemente en las células de origen epitelial/endotelial resultante de la señalización de las células epiteliales–mesenquimáticas paracrinas (Stoker, M. et al., Nature 327: 239–242 (1987)). La unión de HGF a la región extracelular de cMET activa la actividad de tirosina quinasa cMET intracelular. Se considera que cMET participa en los eventos de fosforilación de proteínas que regulan la proliferación, apoptosis, motilidad celular y disociación de las interacciones célula–célula, morfogénesis, angiogénesis, y transición epitelial–mesenquimática. La mala regulación de cMET puede llevar a la proliferación y supervivencia celular no regulada. Se piensa que cMET es un regulador clave del crecimiento invasivo, tumorigénesis cancerosa y progresión a metástasis (Trusolino, T. y Comoglio, P. Nature Reviews Cancer: 2: 289–300 (2002)). Se han detectado amplificación, alteración, mutación del gen cMET y sobreexpresión de proteína o activación del cMET mediante mecanismos autocrinos o paracrinos en una amplia variedad de carcinomas. Por ejemplo, en tejido de cáncer gástrico humano, se halló que cMET se sobreexpresa y amplifica (Smolen, G.A., et al. PNAS 103: 2316–2321, (2006)). En glioblastomas y carcinomas de pulmón, tiroides y mama, se ha hallado que cMET se activa como resultado de los niveles de HGF aumentados y la

señalización autocrina (Birchmeier, C. et al. Rev. Mol. Cell Biol. 4: 915–925, (2003)). EN tejido de cáncer de pulmón humano, se halló que la señalización de cMET se regula por aumento como mecanismo de resistencia a los fármacos (Engelman, J.A., et al. Science 316: 1049–1043, (2007)). Se han informado mutaciones de activación en cMET, si bien no tan comunes, en carcinomas renales papilares esporádicos y hereditarios, carcinomas escamosos de cabeza y cuello así como cánceres gástricos y pulmonares. Por otra parte, el aumento de expresión, la alteración de cMET más común en una amplia variedad de tumores humanos (que incluye, pero sin limitación, cánceres renal, ovárico, hepatocelular, pulmonar de células no pequeñas, hueso, hígado, metástasis de colon, células escamosas orales, esofágico, gástrico, pancreático y prostático) se correlaciona con mal pronóstico (Benvenuti, S. y Comoglio, P.M., J. Cell. Physiol. 213: 316–325, (2007)).

Existe una necesidad continua de hallar nuevos agentes terapéuticos para tratar enfermedades humanas. La inhibición de cMET es un objetivo especialmente atractivo para el descubrimiento de nuevas terapéuticas debido a su función importante en el cáncer y otras enfermedades.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

La presente invención se refiere a compuestos que tienen actividad para inhibir cMET. La presente invención también proporciona composiciones, artículos de manufactura y kits que comprenden estos compuestos. Además, la invención se refiere a métodos de obtener los compuestos de la presente invención, así como intermediarios útiles en dichos métodos.

En una modalidad, se proporciona una composición farmacéutica que comprende un inhibidor de cMET de acuerdo con la presente invención como un ingrediente activo. Las composiciones farmacéuticas de acuerdo con la invención opcionalmente pueden comprender 0.001%–100% de uno o más inhibidores de esta invención. Las composiciones farmacéuticas de acuerdo con la invención opcionalmente pueden comprender uno o más compuestos seleccionados del grupo que consiste en excipientes, diluyentes, lubricantes, aglutinantes, adyuvantes, portadores, agentes humectantes, agentes emulsionantes, agentes solubilizantes y agentes amortiguadores de pH. Las composiciones farmacéuticas

se pueden administrar o coadministrar por una amplia variedad de vías, que incluyen por ejemplo, vía oral, parenteral, intraperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposómica, por medio de inhalación, vaginal, intraocular, por medio de administración local (por ejemplo, por catéter o endoprótesis vascular), subcutánea, intraadiposo, intraarticular, o intratecal. Las composiciones también se pueden administrar o coadministrar en formas de dosificación de liberación lenta.

La invención también se refiere a kits y otros artículos de manufactura para tratar estados de enfermedad asociados con cMET.

En una modalidad, se proporciona un kit que comprende una composición que comprende al menos un inhibidor de cMET de la presente invención en combinación con las instrucciones. Las instrucciones pueden indicar el estado de enfermedad para el que se administra la composición, información de almacenamiento, información de dosis y/o instrucciones respecto de cómo administrar la composición. El kit también puede comprender materiales de envase. El material de envase puede comprender un recipiente para contener la composición. Opcionalmente el kit también puede comprender componentes adicionales, tales como jeringas para la administración de la composición. El kit puede comprender la composición en formas de dosificación únicas o múltiples.

En otra modalidad, se proporciona un artículo de manufactura que comprende una composición que comprende al menos un inhibidor de cMET de la presente invención en combinación con materiales de envase. El material de envase puede comprender un recipiente para contener la composición. El recipiente opcionalmente puede comprender una etiqueta que indica el estado de enfermedad para el que se administra la composición, información de almacenamiento, información de dosis y/o instrucciones respecto de cómo administrar la composición. El kit opcionalmente también puede comprender componentes adicionales, tales como jeringas para la administración de la composición. El kit puede comprender la composición en formas de dosificación únicas o múltiples.

También se proporcionan métodos para preparar compuestos, composiciones y kits de acuerdo con la presente invención. Por ejemplo, se proporcionan varios esquemas de síntesis de la presente para sintetizar los compuestos de acuerdo

con la presente invención.

También se proporcionan métodos para usar compuestos, composiciones, kits y artículos de manufactura de acuerdo con la presente invención.

En una modalidad, los compuestos, composiciones, kits y artículos de manufactura se usan para inhibir cMET.

En otra modalidad, los compuestos, composiciones, kits y artículos de manufactura se usan para tratar un estado de enfermedad para el que cMET posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad.

En otra modalidad, un compuesto de acuerdo con la presente invención se administra a un sujeto en donde la actividad de cMET dentro del sujeto se altera, con preferencia se reduce.

En otra modalidad, un profármaco de un compuesto de acuerdo con la presente invención se administra a un sujeto que se convierte al compuesto *in vivo* donde se inhibe cMET.

En otra modalidad, se proporciona un método para inhibir cMET que comprende poner en contacto un cMET con un compuesto de acuerdo con la presente invención.

En otra modalidad, se proporciona un método para inhibir cMET que comprende causar que un compuesto de acuerdo con la presente invención esté presente en un sujeto a fin de inhibir cMET *in vivo*.

En otra modalidad, se proporciona un método para inhibir un cMET que comprende administrar un primer compuesto a un sujeto que se convierte *in vivo* a un segundo compuesto en donde el segundo compuesto inhibe cMET *in vivo*. Se indica que los compuestos de la presente invención pueden ser los primeros o segundos compuestos.

En otra modalidad, se proporciona un método terapéutico que comprende administrar un compuesto de acuerdo con la presente invención.

En otra modalidad, se proporciona un método para tratar una enfermedad en un paciente que se sabe está mediada por cMET, o que se sabe se trata con inhibidores de cMET, el método que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de acuerdo con la presente invención.

En otra modalidad, se proporciona un método para tratar un estado de enfermedad para el que cMET posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, el método que comprende: producir un compuesto de acuerdo con la presente invención está presente en una cantidad terapéuticamente efectiva para el estado de enfermedad.

En otra modalidad, se proporciona un método para tratar un estado de enfermedad para el que cMET posee actividad que contribuye a 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 de modo que el segundo compuesto esté presente en el sujeto en una cantidad terapéuticamente efectiva para el estado de enfermedad. Se indica que los compuestos de la presente invención pueden ser los primeros o segundos compuestos.

En otra modalidad, se proporciona un método para tratar un estado de enfermedad para el que cMET posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, el método que comprende: administrar un compuesto de acuerdo con la presente invención compuesto esté presente en el sujeto en una cantidad terapéuticamente efectiva para el estado de enfermedad.

En otra modalidad, se proporciona un método para usar un compuesto de acuerdo con la presente invención a fin de fabricar un medicamento para usar en el tratamiento de un estado de enfermedad que se sabe está mediado por cMET, o que se sabe es tratada por los inhibidores de cMET.

Se indica en relación con todas las anteriores modalidades que la presente invención está destinada a incluir todas las formas ionizadas farmacéuticamente aceptable (*por ejemplo*, sales) y solvatos (*por ejemplo*, hidratos) de los compuestos, sin tener en cuenta si dichas formas ionizadas y solvatos especificadas ya que es bien conocido en el arte para administrar agentes farmacéuticos en una forma ionizada y solvatada. También se indica que a menos que especifique una particular estereoquímica, la mención de un compuesto está destinada a abarcar todos los estereoisómeros posibles (*por ejemplo*, enantiómeros o diasterómeros de acuerdo con la cantidad de centros quirales), independiente de si el compuesto está presente como un isómero individual o una mezcla de isómeros. Además, a menos que se especifique de otro modo, la

mención de un compuesto está destinada a incluir todas las posibles formas de resonancia y tautómeros. Con respecto a las reivindicaciones, la frase "compuesto que comprende la formula" "compuesto que tiene la fórmula" y "compuesto de la fórmula" incluye el compuesto y todas las formas ionizadas y solvatos farmacéuticamente aceptables, todos los estereoisómeros posibles, y todas las formas de resonancia y tautómeros posibles a menos que se especifique de otro modo en la reivindicación particular.

Además se indica que también se pueden administrar los profármacos que se alteran *in vivo* y se convierten en un compuesto de acuerdo con la presente invención. Los diversos métodos de usar los compuestos de la presente invención, independientemente de si se especifica la administración de profármaco, incluyen la administración de un profármaco que se convierte *in vivo* a un compuesto de acuerdo con la presente invención. También se indica que ciertos compuestos de la presente invención se pueden alterar *in vivo* antes de inhibir cMET y en consecuencia ellos mismos pueden ser profármacos para otros compuestos. Dichos profármacos de otro compuesto pueden o no ser por sí mismos independientemente tener actividad inhibidora de cMET.

DEFINICIONES

A menos que se indique de otro modo, los siguientes términos usados en la memoria descriptiva y reivindicaciones tienen los siguientes significados para los fines de esta solicitud.

Se indica que, como se usa en la memoria descriptiva y las reivindicaciones anexas, las formas singulares "un" "una" y "el/la" incluye los referentes plurales a menos que el contexto indique claramente lo contrario. Además, las definiciones de términos de química estándares se pueden hallar en los trabajos de referencia, que incluyen Caree Y Sundberg "Advanced Organic Chemistry 4th Ed." Vols. A (2000) y B (2001), Plenum Press, New York. También, a menos que se indique de otro modo, se emplean métodos convencionales de espectroscopia de masa, NMR, HPLC, química de proteínas, bioquímica, técnicas de ADN recombinante y farmacología están dentro de la experiencia del arte.

"Alicíclico" significa un residuo que comprende una estructura anular no aromático. Los residuos alicíclicos pueden ser saturados o parcialmente insaturado con uno,

dos o más dobles o triples enlaces. Los residuos alicíclicos opcionalmente también pueden comprender heteroátomos tales como nitrógeno, oxígeno y azufre. Los átomos de nitrógeno opcionalmente se pueden cuaternizar u oxidar y los átomos de azufre opcionalmente se pueden oxidar. Los ejemplos de los residuos alicíclicos incluyen, pero sin limitación residuos con anillos (C_{3-8}) tales como ciclopropilo, ciclohexano, ciclopentano, ciclopenteno, ciclopentadieno, ciclohexano, ciclohexeno, ciclohexadieno, cicloheptano, cicloheptano, cicloheptadieno, ciclooctano, cicloocteno y ciclooctadieno.

"Alifático" significa un residuo caracterizado por una disposición de cadena lineal o ramificada de átomos de carbono constituyentes y pueden estar saturados o parcialmente insaturados con uno, dos o más dobles o triples enlaces.

"Alquenilo" significa un cadena carbonada lineal o ramificada que contiene al menos un doble enlace carbono–carbono (–CR=CR'– o –CR=CR'R", en donde R, R' y R" son cada uno de modo independiente hidrógeno u otros sustituyentes). Los ejemplos de alquenilo incluyen vinilo, alilo, isopropenilo, pentenilo, hexenilo, heptenilo, 1–propenilo, 2–butenilo, 2–metil–2–butenilo y similares. En modalidades 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}). De modo alternativo, "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).

"Alquenileno" significa una cadena carbonada divalente, lineal o ramificada que tiene uno o más enlaces dobles carbono–carbono (–CR=CR'–, en donde R y R' son cada uno de modo independiente hidrógeno u otros sustituyentes). Los ejemplos de alquenileno incluyen eteno–1,2–diilo, propen–1,3–diilo, metilen–1,1–diilo, y similares. En modalidades particulares, "alqueniloeno," ya sea solo o representado junto con otro radical, pueden 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}). De modo alternativo, "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).

"Alcoxi" significa un residuo oxígeno que tiene un sustituyente alquilo adicional. Los grupos alcoxi de la presente invención pueden estar opcionalmente

000287

sustituidos.

"Alquilo" representado por sí mismo significa un radical alifático, saturado o insaturado, lineal o ramificado que tiene una cadena de átomos de carbono, opcionalmente con uno o más de los átomos de carbono reemplazados con oxígeno (Ver "oxaalquilo"), un grupo carbonilo (Ver "oxoalquilo"), azufre (Ver "tioalquilo"), y/o nitrógeno (Ver "azaalquilo"). Alquilo (C_X) y alquilo (C_{X-Y}) se usan normalmente donde X e Y indican el número de átomos de carbono de la cadena. Por ejemplo, alquilo (C_{1-6}) incluye alquilos que tienen una cadena de entre 1 y 6 carbonos (*por ejemplo*, metilo, etilo, propilo, isopropilo, butilo, *sec*–butilo, isobutilo, *ter*–butilo, vinilo, alilo, 1–propenilo, isopropenilo, 1–butenilo, 2–butenilo, 3–butenilo, 2–metilalilo, etinilo, 1–propinilo, 2–propinilo, y similares). Alquilo representado junto con otro radical (*por ejemplo*, como en arilalquilo, heteroarilalquilo y similares) significa un radical divalente alifático, saturado o insaturado, lineal o ramificado que tiene el número de átomos indicado o cuando no se indican átomos significa un enlace (*por ejemplo*, aril (C_{6-10}) alquilo (C_{1-3}) incluye, bencilo, fenetilo, 1–feniletilo, 3–fenilpropilo, 2–tienilmetilo, 2–piridinilmetilo y similares). En modalidades 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 a un alquilo (C_{1-3}). De modo alternativo, "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).

"Alquileno", a menos que se indique lo contrario, significa radical divalente alifático, saturado o insaturado, lineal o ramificado. Normalmente se usan alquileno (C_X) y alquileno (C_{X-Y}) donde X e Y indican el número de átomos de carbono de 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 modalidades 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}). De modo alternativo, "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).

"Alquilideno" significa un radical alifático, saturado o insaturado, lineal o ramificado

conectado a la molécula original por un doble enlace. Normalmente se usan alquilideno (C_X) y alquilideno (C_{X-Y}) donde X e Y indican el número de átomos de carbono de 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 modalidades particulares, "alquilideno," ya sea solo o representado junto con otro radical, puede ser 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}). De modo alternativo, "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).

"Alquinilo" significa un cadena carbonada lineal o ramificada que contiene al menos un enlace triple carbono–carbono (–C≡C– o –C≡CR, en donde R es hidrógeno o un sustituyente adicional). Los ejemplos de alquinilo incluyen etinilo, propargilo, 3–metil–1–pentinilo, 2–heptinilo y similares. En modalidades 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}). De modo alternativo, "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).

"Alquinileno" significa un cadena carbonada divalente, lineal o ramificado que tiene uno o más enlaces triples carbono–carbono (–CR≡CR'–, en donde R y R' son cada uno de modo independiente hidrógeno u otros sustituyentes). Los ejemplos de alquinileno incluyen etin–1,2–diilo, propin–1,3–diilo, y similares. En modalidades 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}). De modo alternativo, "alquinileno" ya sea solo o representado junto con otro radical, puede ser un alquinileno (C_2), un alquinileno (C_3) o un alquinileno (C_4).

"Amido" significa el radical –C(=O)–NR–, –C(=O)–NRR', –NR–C(=O)– y/o –NR–C(=O)R', en donde cada R y R' son de modo independiente hidrógeno o un sustituyente adicional.

"Amino" significa un residuo nitrógeno que tiene dos sustituyentes adicionales donde, por ejemplo, un átomo de hidrógeno o carbono se une al nitrógeno. Por ejemplo, los grupos amino representativos incluyen $–NH_2$, $–NHCH_3$, –

000289

$N(CH_3)_2$, –NH(alquilo (C_{1-10})), –N(alquilo (C_{1-10}))$_2$, –NH(arilo), –NH(heteroarilo), –N(arilo)$_2$, –N(heteroarilo)$_2$, y similares. Opcionalmente, los dos sustituyentes junto con el nitrógeno también pueden formar un anillo. A menos que se indique lo contrario, los compuestos de la invención que contiene residuos amino puede incluir sus derivados protegidos. Los grupos protectores adecuados para residuos amino incluyen acetilo, *ter*–butoxicarbonilo, benciloxicarbonilo y similares.

"Animal" incluye seres humanos, mamíferos no humanos (*por ejemplo*, perros, gatos, conejos, ganado vacuno, caballos, oveja, cabras, cerdos, ciervo y similares) y no mamíferos (*por ejemplo*, pájaros y similares).

"Aromático" significa un residuo en donde los átomos constituyentes componen un sistema anular insaturado, todos los átomos del sistema anular son sp^2 hibridizados y el número total de los electrones pi es igual a 4n+2. Un anillo aromático puede ser tal que los átomos anulares son solo átomos de carbono o pueden incluir carbono y átomos de no carbono (Ver "heteroarilo").

"Arilo" significa un ensamblaje de anillo monocíclico o policíclico en donde cada anillo es aromático o cuando se fusiona con uno o más anillo forma un ensamblaje de anillo aromático. Si uno o más átomos anulares no es carbono (*por ejemplo*, N, S), el arilo es un heteroarilo. Normalmente se usan arilo (C_X) y arilo (C_{X-Y}) donde X e Y indican el número de átomos de carbono en el anillo. En modalidades 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}). De modo alternativo, "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}).

"Azaalquilo" significa un alquilo, como se definió anteriormente, excepto donde uno o más de los átomos de carbono que forman la cadena alquilo se reemplazan con átomos de nitrógeno sustituido o no sustituido (–NR– o –NRR', en donde R y R' son cada uno de modo independiente 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.

"Bicicloalquilo" significa un ensamblaje de anillo bicíclico, fusionado, espiro o con puente saturado o parcialmente saturado. En modalidades particulares,

000290

"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}). De modo alternativo, "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}).

"Bicicloarilo" significa un ensamblaje de anillo bicíclico, fusionado, espiro o con puente en donde al menos uno de los anillos que comprende el ensamblaje es aromático. Normalmente se usan bicicloarilo (C_X) y bicicloarilo (C_{X-Y}) donde X e Y indican el número de átomos de carbono en el ensamblaje del anillo bicíclico y se une directamente al anillo. En modalidades 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}). De modo alternativo, "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}).

"Anillo con puente" y "anillo unido por puente" como se usa 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 anulares que son comunes en ambos anillos no se unen directamente entre sí. Los 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 puede comprender heteroátomos.

"Carbamoilo" significa el radical –OC(O)NRR', en donde R y R' son cada uno de modo independiente hidrógeno u otros sustituyentes.

"Carbociclo" significa un anillo que consiste en átomos de carbono.

"Carbonilo" significa el radical –C(=O)– y/o –C(=O)R, en donde R es hidrógeno o un sustituyente adicional. Se indica que el radical carbonilo también puede estar sustituido con una variedad de sustituyentes para formar diferentes grupos carbonilo que incluyen ácidos, haluros ácidos, aldehídos, amidas, ésteres y cetonas.

"Carboxi" significa el radical –C(=O)–O– y/o –C(=O)–O, en donde R es hidrógeno o un sustituyente adicional. Se indica que los compuestos de la invención que contienen residuos carboxi pueden incluir sus derivados protegidos, *es decir*, donde el oxígeno está sustituido con un grupo protector. Los grupos protectores

000291

adecuados para los residuos carboxi incluyen bencilo, *ter*–butilo y similares.

Como se usa en la presente, "cMet" es sinónimo con "c–Met", "MET", "Met", "receptor del factor de crecimiento de hepatocitos" y otras denominaciones conocidas por los expertos en el arte.

"Ciano" significa el radical –CN.

"Cicloalquilo" significa un ensamblaje de anillo monocíclico, bicíclico o policíclico, no aromático, saturado o parcialmente insaturado. Normalmente se usan cicloalquilo (C_X) y cicloalquilo (C_{X-Y}) donde X e Y indican el número de átomos de carbono en el ensamblaje del anillo. 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 modalidades 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}). De modo alternativo, "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}).

"Cicloalquileno" significa un ensamblaje de anillo monocíclico, bicíclico o policíclico, divalente, saturado o parcialmente insaturado. Normalmente se usan cicloalquileno (C_X) y cicloalquileno (C_{X-Y}) donde X e Y indican el número de átomos de carbono del ensamblaje anular. En modalidades 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}). De modo alternativo, "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 cicloalquileno (C_8), un cicloalquileno (C_9) o un cicloalquileno (C_{10}).

"Enfermedad" incluye específicamente cualquier condición no saludable de un animal o parte de este e incluye una condición no saludable que puede ser causada por, o incidente a, terapia médica o veterinaria aplicada a ese animal, *es decir*, los "efectos secundarios" de dicha terapia.

"Anillo fusionado" como se usa en la presente se refiere a un anillo que se une a

otro anillo para formar un compuesto que tiene una estructura bicíclica donde los átomos anulares que son comunes a ambos anillos se unen directamente entre sí. Los ejemplos no exclusivos de anillos fusionados comunes incluyen decalina, naftaleno, antraceno, fenantreno, indol, furano, benzofurano, quinolina y similares. Los compuestos que tienen anillos fusionados pueden ser saturados, parcialmente saturados, carbocíclicos, heterocíclicos, aromáticos, heteroaromáticos y similares.

"Halo" significa fluoro, cloro, bromo o yodo.

"Heteroalquilo" significa alquilo, como se definió en esta solicitud, con la condición de que uno o más de los átomos dentro de la cadena alquilo es un heteroátomo. En modalidades 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 (C_{1-3}) o un heteroalquilo (C_{1-2}). De modo alternativo, "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).

"Heteroarilo" significa un grupo aromático monocíclico, bicíclico o policíclico en donde al menos un átomo del anillo es un heteroátomo y los restantes átomos del anillo son carbono. Los grupos heteroarilo monocíclicos incluyen, pero sin limitación, grupos aromáticos cíclicos que tienen cinco o seis átomos anulares, en donde al menos un átomo anular es une heteroátomo y los restantes átomos anulares son carbono. Los átomos de nitrógeno opcionalmente se pueden cuaternizar y los átomos de azufre opcionalmente se pueden oxidar. Los grupos heteroarilo de esta invención incluyen, pero sin limitación, los derivados de furano, imidazol, isotiazol, isoxazol, oxadiazol, oxazol, 1,2,3–oxadiazol, pirazina, pirazol, piridazina, piridina, pirimidina, pirrolina, tiazol, 1,3,4–tiadiazol, triazol y tetrazol. "Heteroarilo" también incluye pero sin limitación, anillos bicíclicos o tricíclicos, en donde el anillo heteroarilo se usa para fusionar a uno o dos anillos seleccionados independientemente del grupo que consiste en un anillo arilo, un anillo cicloalquilo, un anillo cicloalquenilo y otro anillo heteroarilo o heterocicloalquilo monocíclico. Estos heteroarilos bicíclicos o tricíclicos incluyen, pero sin limitación, los derivados 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]indole y 2(1H)–piridinona. Los anillos heteroarilos bicíclicos o tricíclicos pueden estar unidos a la molécula original a través del grupo heteroarilo mismo o el grupo arilo, cicloalquilo, cicloalquenilo o heterocicloalquilo al que se fusiona. Los grupos heteroarilos de esta invención pueden estar sustituidos o no sustituidos. En modalidades 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}). De modo alternativo, "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)arilo, un heteroarilo (C_7), un heteroarilo (C_8) o un heteroarilo (C_9).

"Heteroátomo" se refiere a un átomo que no es un átomo de carbono. Los ejemplos particulares de heteroátomos incluyen, pero sin limitación, nitrógeno, oxígeno, y azufre.

"Residuo de heteroátomo" incluye un residuo donde el átomo al que se une el residuo no es un carbono. Los ejemplos de residuos de heteroátomo incluyen –NR–, $–N^+(O^-)=$, –O–, –S– o $–S(O)_2–$, en donde R es hidrógeno o un sustituyente adicional.

"Heterobicicloalquilo" significa bicicloalquilo, como se definió en esta solicitud, con la condición de que uno o más de los átomos dentro del anillo es un heteroátomo. Por ejemplo heterobicicloalquilo (C_{9-12}) como se usa en esta 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 modalidades 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}). De modo alternativo, "heterobicicloalquilo" ya sea solo o representado junto con otro radical, puede ser un heterobicicloalquilo (C_5), un heterobicicloalquilo (C_6), un heterobicicloalquilo (C_7), un heterobicicloalquilo (C_8) o un heterobicicloalquilo (C_9).

"Heterobicicloarilo" significa bicicloarilo, como se definió en esta solicitud, con la condición de que uno o más de los átomos dentro del anillo es un heteroátomo. Por ejemplo, un heterobicicloarilo (C_{4-12}) como se usa en esta solicitud incluye pero sin limitación, 2–amino–4–oxo–3,4–dihidropteridin–6–ilo, tetrahidroisoquinolinilo, y similares. En modalidades particulares, "heterobicicloarilo," ya sea solo o representado junto con otro radical, puede ser un hetero(C_{1-14})bicicloarilo, a hetero(C_{4-14})bicicloarilo, a hetero(C_{4-9})bicicloarilor a hetero(C_{5-9})bicicloaril. De modo alternativo, "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 heterobicicloarilo (C_9).

"Heterocicloalquilo" significa cicloalquilo, como se definió en esta solicitud, con la condición de que uno o más de los átomos que forman el anillo es un heteroátomo seleccionado de modo independiente de N, O o S. Los 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 modalidades 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}). De modo alternativo, "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), un heterocicloalquilo (C_7), un heterocicloalquilo (C_8) o un heterocicloalquilo (C_9).

"Heterocicloalquileno" significa cicloalquileno, como se definió en esta solicitud, con la condición de que uno o más de los átomos miembros del anillo está reemplazado con un heteroátomo. En modalidades 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}). De modo alternativo, "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), un heterocicloalquileno (C_7), un heterocicloalquileno (C_8) o un heterocicloalquileno (C_9).

"Hidroxi" significa el radical –OH.

"IC_{50}" significa la concentración molar de un inhibidor que produce 50% de inhibición de la enzima objetivo.

"Imino" significa el radical –CR(=NR') y/o –C(=NR')– en donde R y R' son cada uno de modo independiente hidrógeno o un sustituyente adicional.

"Isómeros" significa los compuestos que tienen fórmulas moleculares idénticas pero 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 no son imágenes especulares de otro se denominan "diasterómeros y los estereoisómeros que son imágenes especulares no superponibles se denominan "enantiómeros" o algunas veces "isómeros ópticos". Un átomo de carbono unido a cuatro sustituyentes no idénticos se denomina un "centro quiral". Un compuesto con un centro quiral tiene dos formas enantioméricas de quiralidad opuesta. Una mezcla de dos formas enantioméricas se denomina una "mezcla racémica". Un compuesto que tiene más de un centro quiral tiene 2^{n-1} pares enantioméricos, donde *n* es el número de centros quirales. Los compuestos con más de un centro quiral puede existir como un diastereómero individual o como una mezcla de diasterómeros, denominada una "mezcla diastereomérica". Cuando un centro quiral está presente, un estereoisómero se puede caracterizar por la configuración absoluta del centro quiral. La configuración absoluta se refiere a la disposición en el espacio de los sustituyentes unidos al centro quiral. Los enantiómeros se caracterizan por la por la configuración absoluta de sus centros quirales y se describen con las reglas de secuenciación *R*– y *S*– de Cahn, Ingold y Prelog. Las convenciones para la nomenclatura estereoquímica, métodos para la determinación de estereoquímica y la separación de los estereoisómeros son bien conocidos en el arte (*por ejemplo*, ver "Advanced

Organic Chemistry", 4ta edición, March, Jerry, John Wiley & Sons, New York, 1992).

"Residuo que provee separación de X átomo" y "enlazante que provee separación de X átomos" entre otros dos residuos significa que la cadena de átomos que une directamente los dos otros residuos es X átomos de longitud, Cuando X se da como rango (*por ejemplo*, X_1–X_2), luego la cadena de átomos es al menos X_1 y no más de X_2 átomos de longitud. Se considera que la cadena de átomos se puede formar a partir de una combinación de átomos que incluye, por ejemplo, átomos de carbono, nitrógeno, azufre y oxígeno. Por otra parte, cada átomo se puede unir opcionalmente a uno o más sustituyentes, según lo permitan las valencias. Además, la cadena de átomos puede formar parte de un anillo. Por consiguiente, en una modalidad, un residuo que provee separación de X átomos entre otros dos residuos (R y R') se puede representar con R–$(L)_x$–R' donde cada L es de modo independiente seleccionado del grupo que consiste en CR''R''', NR'''', O, S, CO, CS, C=NR'''''', SO, SO_2, y similares, donde dos o más de R'', R''', R'''' y R'''''' se pueden tomar juntos para formar un anillo sustituido o no sustituido.

"Nitro" significa el radical –NO_2.

"Oxaalquilo" significa un alquilo, como se definió anteriormente, excepto que se reemplazan uno o más de los átomos de carbono que forman la cadena alquilo con átomos de oxígeno (–O– o –O, en donde R es hidrógeno o un sustituyente adicional). Por ejemplo, un oxaalquilo (C_{1-10}) se refiere a una cadena que comprende entre 1 y 10 carbonos y uno o más átomos de oxígeno.

"Oxoalquilo" significa un alquilo, como se definió anteriormente, excepto que se reemplazan uno o más de los átomos de carbono que forman la cadena alquilo con grupos carbonilo (–C(=O)– o –C(=O)–R, en donde R es hidrógeno o un sustituyente adicional). 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.

"Oxi" significa el radical –O– o –O, en donde R es hidrógeno o un sustituyente adicional. Por consiguiente, se indica que el radical oxi también puede estar sustituido con una variedad de sustituyentes para formar diferentes grupos oxi que incluyen hidroxi, alcoxi, ariloxi, heteroariloxi o carboniloxi.

000297

"Farmacéuticamente aceptable" significa que es útil para preparar una composición farmacéutica que es generalmente seguro, no tóxico y ni biológicamente ni de otro modo no deseable e incluye que sea aceptable para uso veterinario así como uso farmacéutico humano.

El término "excipiente farmacéuticamente aceptable" se refiere a los que se usan normalmente para preparar composiciones farmacéuticas y deben ser farmacéuticamente puros y no tóxicos en las cantidades usadas. Estos generalmente son un material sólido, semisólido o líquido que puede actuar como un vehículo o medio para el ingrediente activo o un auxiliar para la conservación, administración o manufactura de la composición. Algunos ejemplos de excipientes farmacéuticamente aceptables se hallan en Remington's Pharmaceutical Sciences and the Handbook of Pharmaceutical Excipients e incluyen diluyentes, vehículos, bases de ungüentos, aglutinantes, desintegrantes, lubricantes, deslizantes, edulcorantes, agentes saborizantes, bases de gel, matrices de liberación sostenida, agentes estabilizantes, conservadors, solventes, agentes de suspensión, amortiguadores, emulsionantes, colorantes, propelentes, agentes de recubrimiento y otros.

"Sales farmacéuticamente aceptables" significan sales de los compuestos de la presente invención que son farmacéuticamente aceptables, como se definió anteriormente, y que poseen la actividad farmacológica deseada. Dichas sales incluyen sales de adición con ácidos 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 masónico, ácido succínico, ácido málico, ácido maleico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido *o*–(4–hidroxibenzoil)benzoico, ácido cinámico, ácido mandélico, ácido metansulfónico, ácido etansulfónico, ácido 1,2–etandisulfónico, ácido 2–hidroxietansulfónico, ácido bencensulfónico, ácido *p*–clorobencensulfónico, ácido 2–naftalensulfónico, ácido *p*–toluensulfónico, ácido canforsulfónico, ácido 4–metilbiciclo[2.2.2]oct–2–eno–1–carboxílico, ácido glucoheptónico, ácido 4,4'–metilenbis(3–hidroxi–2–eno–1–carboxílico), ácido 3–fenilpropiónico, ácido trimetilacético, ácido terbutilacético, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido

000298

salicílico, ácido esteárico, ácido mucónico y similares.

Las sales farmacéuticamente aceptables también incluyen sales de adición con base que 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 aceptables incluyen etanolamina, dietanolamina, trietanolamina, trometamina, *N*–metilglucamina y similares.

"Anillo policíclico" incluye anillos bicíclicos y multicíclicos. Los anillos individuales que comprenden el anillo policíclico pueden ser anillos fusionados, espiro o que forman puente.

"Profármaco" significa un compuesto que se convierte *in vivo* en forma metabólica en un inhibidor de acuerdo con la presente invención. El profármaco mismo también puede o no puede tener actividad con respecto a una proteína objetivo dada. Por ejemplo, un compuesto que comprende un grupo hidroxi se puede administrar como 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, metilen–bis–b–hidroxinaftoatos, gentisatos, isetionatos, di–*p*–toluoiltartratos, metansulfonatos, etansulfonatos, bencensulfonatos, p–toluensulfonatos, ciclohexilsulfamatos, quinatos, ésteres de aminoácidos y similares. De modo similar, un compuesto que comprende un grupo amino se puede administrar como una amida que se convierte por hidrólisis *in vivo* al compuesto amina.

"Derivados protegidos" significa derivados de los inhibidores en los que un sitio o sitios reactivos se bloquean con grupos protectores. Los derivados protectores pueden ser útiles en la preparación de inhibidores o ellos mismos pueden ser activos como inhibidores. Una lista exhaustiva de grupos protectores adecuados se pueden hallar en T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Anillo" y "ensamblaje anular" significa un sistema carbocíclico o heterocíclico e incluye sistemas aromáticos y no 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,

espiro o que forman puente.

"Sujeto" y "paciente" incluyen seres humanos, mamíferos no humanos (*por ejemplo*, perros, gatos, conejos, ganado vacuno, caballos, ovejas, cabras, cerdos, ciervos, y similares) y no mamíferos (*por ejemplo*, pájaros y similares).

"Sustituyente convertible a hidrógeno *in vivo*" significa cualquier grupo que sea convertible a un átomo de hidrógeno por medios enzimológicos o químicos, que incluyen pero sin limitación, hidrólisis e hidrigenólisis. Los ejemplos incluyen grupos hidrolizables, tales como grupos acilo, grupos que tienen un grupo oxicarbonilo, residuos de aminoácido, residuos de péptido, o–nitrofenilsulfenilo, trimetilsililo, tetrahidro–piranilo, difenilfosfinilo y similares. Los ejemplos de grupos acilo incluyen formilo, acetilo, trifluoroacetilo, y similares. Los ejemplos de grupos que tienen un grupo oxicarbonilo incluyen etoxicarbonilo, t–butoxicarbonilo [$(CH_3)_3C–OCO–$], benciloxicarbonilo, p–metoxibenciloxicarbonilo, viniloxicarbonilo, β–(p–toluensulfonil)etoxicarbonilo y similares. Los ejemplos de residuos de aminoácidos adecuados incluyen residuos de aminoácidos *per se* y residuos de aminoácidos que se protegen con un grupo protector. Los residuos de 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), Phe (fenilalanina), Pro (prolina), Ser (serina), Thr (treonina), Trp (triptofano), Tyr (tirosina), Val (valina), Nva (norvalina), Hse (homoserina), 4–Hyp (4–hidroxiprolina), 5–Hil (5–hidroxilisina), Orn (ornitina) y β–Ala. Los ejemplos de grupo protectores adecuados incluyen los normalmente empleados en la síntesis de péptidos, 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 de péptidos que comprenden dos a cinco, y opcionalmente dos a tres de los residuos de aminoácidos mencionados anteriormente. Los ejemplos de dichos residuos de péptidos incluyen, pero sin limitación, residuos de dichos péptidos como 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 y Ala–Leu. Los residuos de estos

aminoácidos o péptidos pueden estar presentes en configuraciones estereoquímicas de la forma D, la forma L o sus mezclas. Además, los residuos de aminoácidos o péptidos pueden tener un átomo de carbono asimétrico. Los ejemplos de residuos de aminoácidos adecuados que tienen un átomo de carbono asimétrico incluyen los residuos de Ala, Leu, Phe, Trp, Nva, Val, Met, Ser, Lys, Thr y Tyr. Los residuos de péptidos que tienen un átomo de carbono asimétrico incluyen los residuos de péptidos que tienen uno o más residuos de aminoácidos constituyentes que tienen un átomo de carbono asimétrico. Los ejemplos de los grupos protectores de amino adecuados incluyen los que se emplean normalmente en la síntesis de péptidos, que incluyen 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 "convertible a hidrógeno *in vivo*" incluyen los grupos hidrogenolizable que se pueden eliminar en forma reductora. Los ejemplos de grupos hidrogenolizable que se pueden eliminar en forma reductora adecuados incluyen, pero sin limitación, grupos arilsulfonilo (tales como o–toluensulfonilo); 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).

"Sustituido o no sustituido" significa que un residuo dado puede consistir en solo sustituyentes hidrógeno a través de valencias disponibles (no sustituido) o también puede comprender uno o más sustituyentes no hidrógeno a través a través de valencias disponibles (sustituido) que no se especifican de otro modo por el nombre del residuo dado. Por ejemplo, isopropilo es un ejemplo de residuo etileno que está sustituido con $–CH_3$. En general, un sustituyente no hidrógeno puede ser cualquier sustituyente que pueda unirse a un átomo del residuo dado que se especifica que está sustituido. Los ejemplos de sustituyentes incluyen, pero sin limitación, residuos aldehído, alicíclico, alifático, alquilo ($C_{1–10}$), alquileno, alquilideno, amida, amino, aminoalquilo, aromático, arilo, bicicloalquilo, bicicloarilo, carbamoilo, carbociclilo, carboxilo, grupo carbonilo, cicloalquilo, cicloalquileno, éster, halo, heterobicicloalquilo, heterocicloalquileno, heteroarilo, heterobicicloarilo, heterocicloalquilo, oxo, hidroxi, iminocetona, cetona, nitro, oxaalquilo, y oxoalquilo,

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cada uno de los cuales opcionalmente también puede estar sustituido o no sustituido. En una modalidad particular, los 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, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})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 por sí mismo opcionalmente sustituido con un sustituyente adicional. En una modalidad particular, los ejemplos de sustituyentes adicionales 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, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})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}).

"Sulfinilo" significa el radical –SO– y/o –SO–R, en donde R es hidrógeno o un sustituyente adicional. Se indica que el radical sulfinilo también puede estar sustituido con una variedad de sustituyentes para formar diferentes grupos sulfinilo que incluyen ácidos sulfínicos, sulfinamidas, ésteres de sulfinilo y sulfóxidos.

"Sulfonilo" significa el radical $–SO_2–$ y/o $–SO_2–R$, en donde R es hidrógeno o un sustituyente adicional. Se indica que el radical sulfonilo también puede estar sustituido con una variedad de sustituyentes para formar diferentes grupos sulfonilo que incluye ácidos sulfónicos, sulfonamidas, ésteres de sulfonato y sulfonas.

"Cantidad terapéuticamente efectiva" significa que la cantidad, que se administra a un animal para tratar una enfermedad, es suficiente para efectuar dicho tratamiento para la enfermedad.

"Tio" indica reemplazo de un oxígeno con un azufre e incluye pero sin limitación, grupos que contienen –SR, –S– y =S.

"Tioalquilo" significa un alquilo, como se definió anteriormente, excepto que uno o más de los átomos de carbono que forman la cadena alquilo se reemplazan con átomos de azufre (–S– o –S–R, en donde R es hidrógeno o un sustituyente adicional). 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.

"Tiocarbonilo" significa el radical –C(=S)– y/o –C(=S)–R, en donde R es hidrógeno o un sustituyente adicional. Se indica que el radical tiocarbonilo también se puede sustituir con una variedad de sustituyentes para formar grupos tiocarbonilo diferentes que incluyen tioácidos, tioamidas, tioésteres y tiocetonas.

"Tratamiento" o "que trata" significa una administración de un compuesto de la presente invención e incluye:

(1) prevenir que la enfermedad aparezca en un animal que puede estar predispuesto a la enfermedad pero que aún no experimenta o exhibe la patología o sintomatología de la enfermedad,

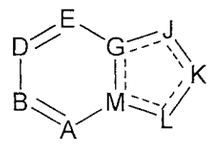
(2) inhibir la enfermedad en un animal que experimenta o exhibe la patología o sintomatología de la enfermedad (*es decir*, detener el posterior desarrollo de la patología y/o sintomatología), o

(3) mejorar la enfermedad en un animal que está experimentado o exhibiendo la patología o sintomatología de la enfermedad (*es decir*, revertir la patología y/o sintomatología).

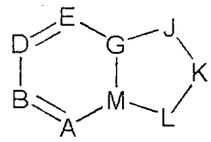
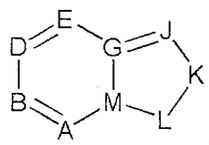
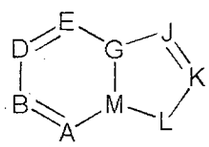
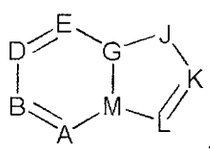
En consideración de todas las definiciones provistas en la presente se indica que las definiciones se deberían interpretar como abiertas en el sentido que pueden incluir otros sustituyentes más allá de los especificados. En consecuencia, un alquilo C_1 indica que existe un átomo de carbono pero no indica cuáles son los sustituyentes del átomo de carbono. En consecuencia, un alquilo (C_1) comprende metilo (*es decir*, $–CH_3$) así como –CRR'R" donde R, R', y R" pueden ser de modo independiente hidrógeno o un sustituyente adicional donde el átomo unido al carbono es un heteroátomo o ciano. En consecuencia, CF_3, CH_2OH y CH_2CN, por

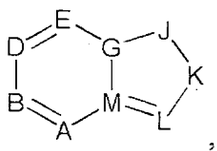
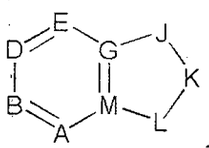
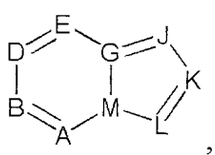
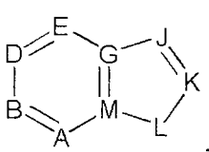
ejemplo, son alquilos (C_1). De modo similar, los términos tales como alquilamino y similares comprenden dialquilamino y similares.

Un compuesto que tiene una fórmula que se representa con una línea de puntos está destinado a incluir las fórmulas que opcionalmente tienen cero, uno o más dobles enlaces, como se ejemplifica y se muestra a continuación:



representa

 ,  ,  ,  ,

 ,  ,  ,  , etc.

Además, los átomos que constituyen los compuestos de la presente invención incluyen todas las formas isotópicas de dichos átomos. Los isótopos, como se usa en la presente, incluyen los átomos que tienen el mismo número atómico pero diferentes números másicos. 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

La presente invención se refiere a compuestos que se pueden usar para inhibir cMET. La presente invención también se refiere a composiciones farmacéuticas, kits y artículos de manufactura que comprenden dichos compuestos. Además, la presente invención se refiere a métodos e intermediarios útiles para preparar los compuestos. Por otra parte, la presente invención se refiere a métodos de uso de dichos compuestos. Se indica que los compuestos de la presente invención también pueden poseer actividad para otros miembros de la misma familia de proteínas y en consecuencia se pueden usar para dirigirse a estados de enfermedad asociados con otros miembros de la familia.

cMET pertenece a la familia de enzimas fosforil transferasa que transfieren grupos

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que contienen fósforo de un sustrato a otro. Por las convenciones expuestas por el comité de nomenclatura de enzimas de la International Union of Biochemistry and Molecular Biology (IUBMB) de este tipo tienen los números de la Enzyme Commission (EC) comenzando con 2.7.–.– (*Ver*, Bairoch A., base de datos ENZYME en Nucleic Acids Res. 28:204–305 (2000)). Las quinasas son una clase de enzimas que actúan en la catálisis de la transferencia de fosforilo. Las proteína quinasas constituyen una de las más grandes subfamilias de fosforil transferasas relacionadas estructuralmente y son responsables del control de una amplia variedad de procesos de transducción de señales celulares. (*Ver*, Hardie, G. y Hanks, S. (1995) The Protein Kinase Facts Book, I y II, Academic Press, San Diego, CA).

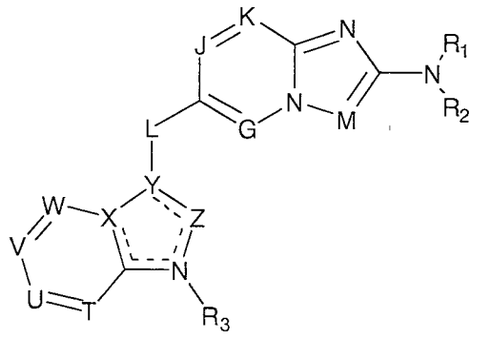
La desregulación de cMET está implicada en dichas enfermedades como cánceres (que incluyen carcinomas (*por ejemplo*, vejiga, mamas, cervical, colangiocarcinoma, colorrectal, esofágico, gástrico, cabeza y cuello, riñón, hígado, pulmón, nasofaríngeo, ovárico, pancreático, próstata y tiroides); sarcomas musculoesqueléticos (*por ejemplo*, osteosarcoma, sarcoma sinovial y rabdomiosarcoma); sarcomas de tejido blando (*por ejemplo*, MFH/fibrosarcoma, leiomiosarcoma, y sarcoma de Kaposi); neoplasias hematopoyéticas (*por ejemplo*, mieloma múltiple, linfomas, leucemia de células T adultas, leucemia mielógena aguda y leucemia mieloide crónica); y otros neoplasmas (*por ejemplo*, glioblastomas, astrocitomas, melanoma, mesotelioma, y tumor de Wilm)); y enfermedades proliferativas (*por ejemplo*, trastornos mieloproliferativos, aterosclerosis y fibrosis pulmonar).

Se indica que los compuestos de la presente invención también pueden poseer actividad inhibidora para otros miembros de la familia del receptor de tirosina quinasa y en consecuencia se pueden usar para tratar estados de enfermedad asociados con estos otros miembros de familia. En particular, los compuestos de la presente invención se pueden usar para modular la actividad de otras proteínas de la subfamilia de Met (*por ejemplo*, Ron y Sea).

Inhibidores de cMET

En uno de sus aspectos, la presente invención se refiere a compuestos que son útiles como inhibidores de cMET. En una modalidad, los inhibidores de cMET de la

presente invención comprenden:



o uno de sus polimorfos, solvatos, ésteres, tautómeros, enantiómeros, sales o profármacos farmacéuticamente aceptables, en donde

G se selecciona del grupo que consiste en CR_4 y N;

J se selecciona del grupo que consiste en CR_5 y N;

K se selecciona del grupo que consiste en CR_6 y N;

M se selecciona del grupo que consiste en CR_7 y N;

L está ausente o un enlazante que provee 1, 2, 3, 4, 5 o 6 átomos de separación entre los anillos a los que se une L, en donde los átomos del enlazante que proporciona la separación se seleccionan del grupo que consiste en carbono, oxígeno, nitrógeno, y azufre;

T se selecciona del grupo que consiste en CR_8 y N;

U se selecciona del grupo que consiste en CR_9 y N;

V se selecciona del grupo que consiste en CR_{10} y N;

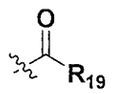
W se selecciona del grupo que consiste en CR_{11} y N;

X se selecciona del grupo que consiste en CR_{12} y N;

Y se selecciona del grupo que consiste en CR_{13} y N;

Z se selecciona del grupo que consiste en $CR_{14}R_{15}$ y NR_{16}; R_1 se selecciona del grupo que consiste en hidrógeno, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, alquilcarbonilo (C_{1-10}), cicloalquil (C_{3-12})carbonilo (C_{1-5}), heterocicloalquil (C_{3-12})carbonilo (C_{1-10}), arilcarbonilo (C_{1-10}), heteroaril(C_{1-10}) carbonilo (C_{1-5}), bicicloaril (C_{9-12})carbonilo (C_{1-5}), heterobicicloaril (C_{8-12})carbonilo (C_{1-5}), amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido o R_1 tiene la formula



R_2 es hidrógeno o un sustituyente convertible *in vivo* al hidrógeno;

R_3 se selecciona del grupo que consiste en hidrógeno, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_3 está ausente cuando el nitrógeno al que está unido forma parte de un doble enlace;

R_4 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}),

heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), aril (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_5 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_7 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}),

cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_8 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_9 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, amido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}), haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}), carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), aminoalquilo (C_{1-10}), amidoalquil (C_{1-10})aminoalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) carbonilarilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo,

oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, amido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}), haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}), carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), aminoalquilo (C_{1-10}), amidoalquil (C_{1-10})aminoalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) carbonilarilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_{11} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo

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(C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_{12} está ausente cuando el carbono al que está unido forma parte de un doble enlace;

R_{13} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_{13} está ausente cuando el carbono al que está unido forma parte de un doble enlace;

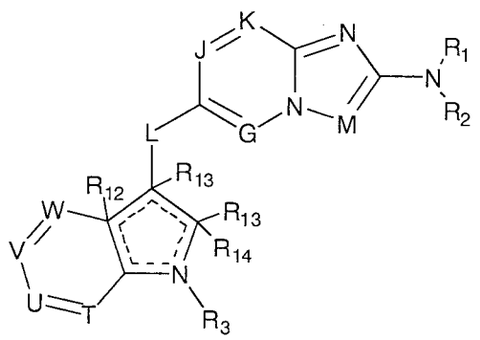
R_{14} y R_{15} se selecciona de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, imino, sulfonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_{15} está ausente cuando el carbono al que está unido forma parte de un doble enlace;

R_{16} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}), haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}),

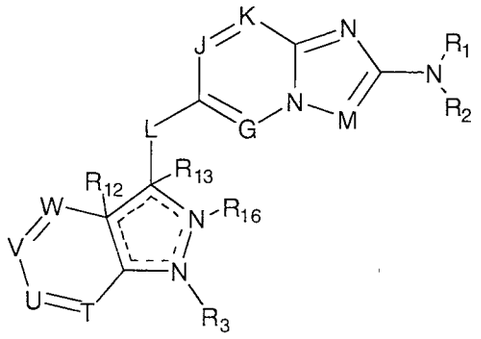
carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_{16} está ausente cuando el nitrógeno al que se une forma parte de un doble enlace, y

R_{19} se selecciona del grupo que consiste en hidrógeno, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

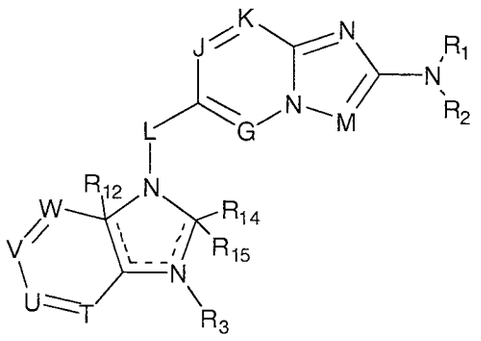
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



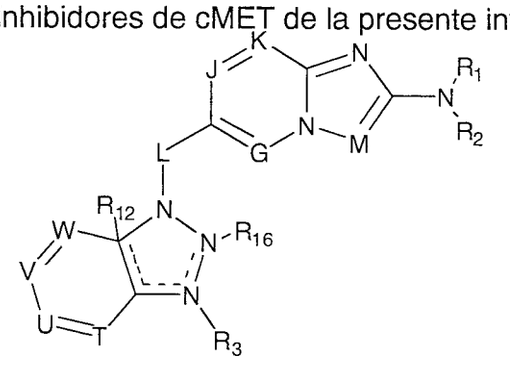
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



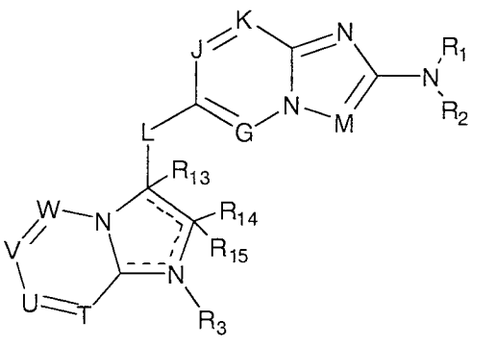
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



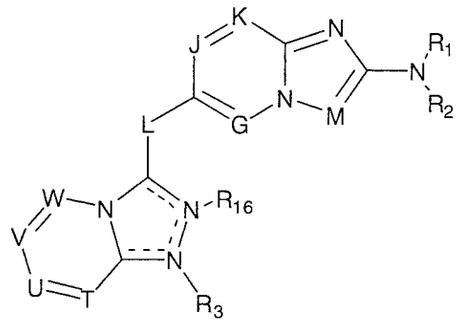
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



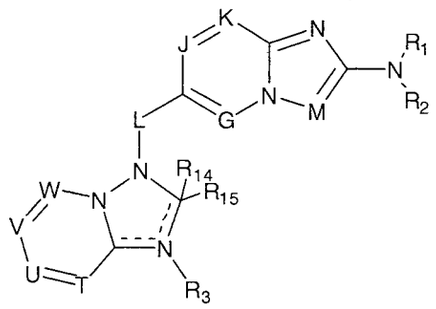
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



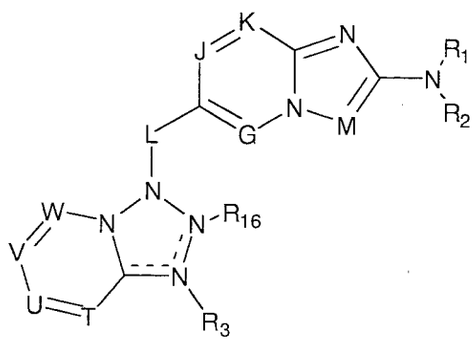
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



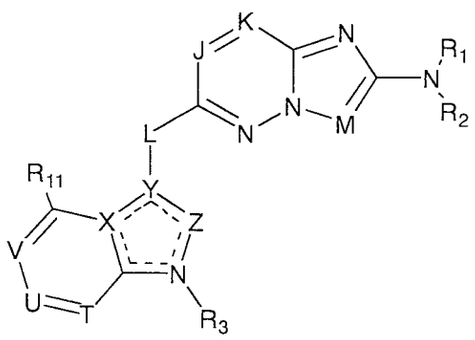
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



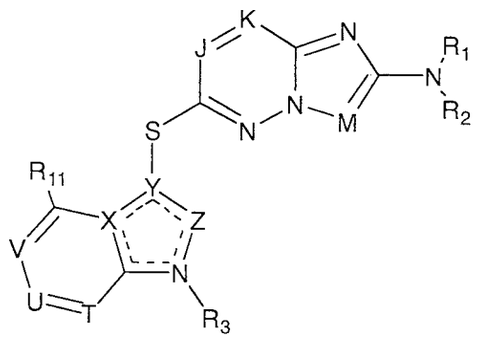
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



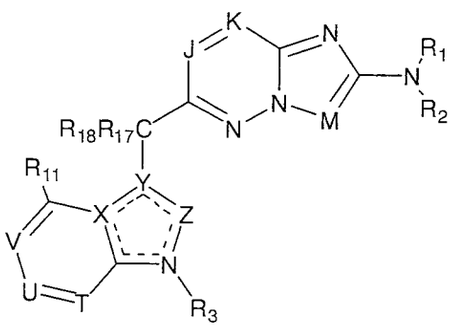
En una modalidad adicional, los inhibidores de cMET de la presente invención comprenden:



En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:

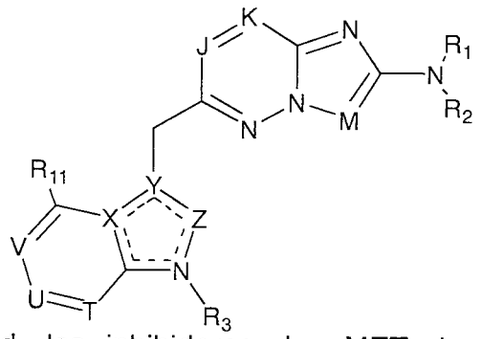


En una modalidad más, los inhibidores de cMET de la presente invención comprenden:

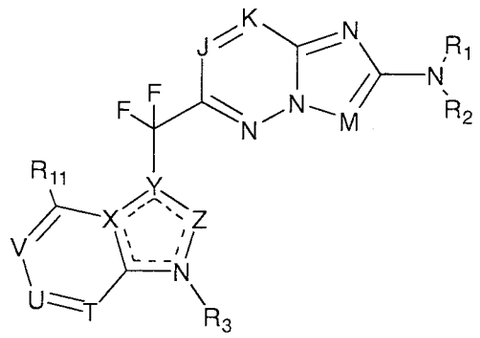


en donde R_{17} y R_{18} se seleccionan de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, amino, alquilamino (C_{1-10}), sulfonamido, imino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

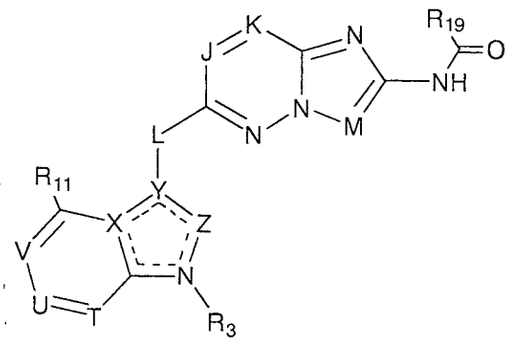
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



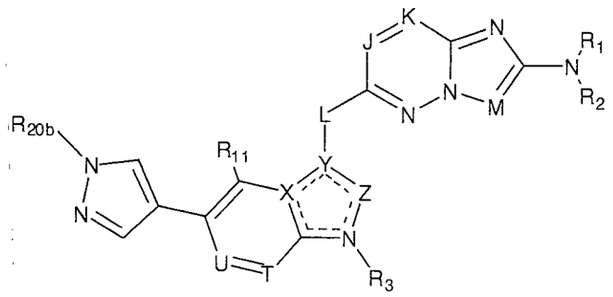
En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



en donde R_{19} se selecciona del grupo que consiste en hidrógeno, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo

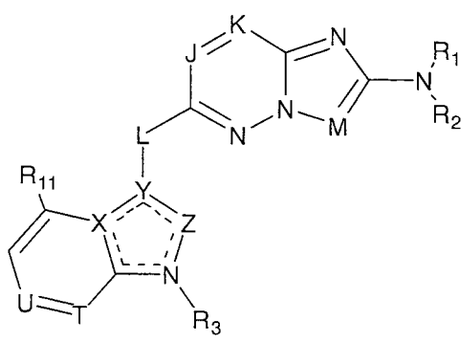
(C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una modalidad adicional, los inhibidores de cMET de la presente invención comprenden:

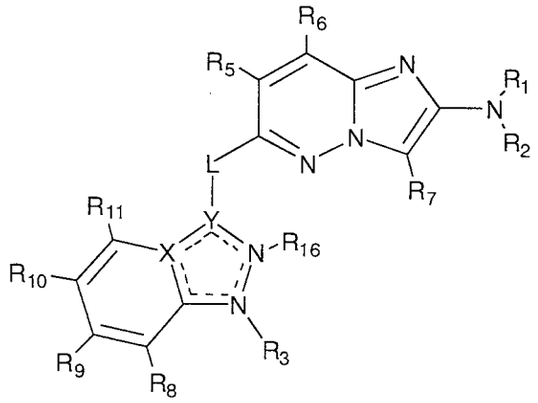


en donde R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, amino, alquilamino (C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

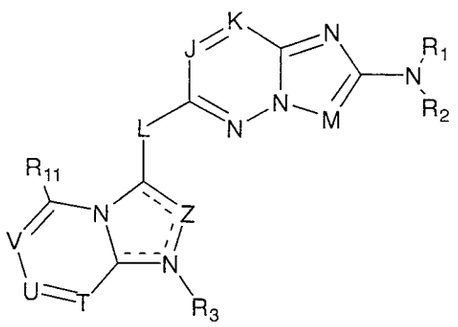
En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



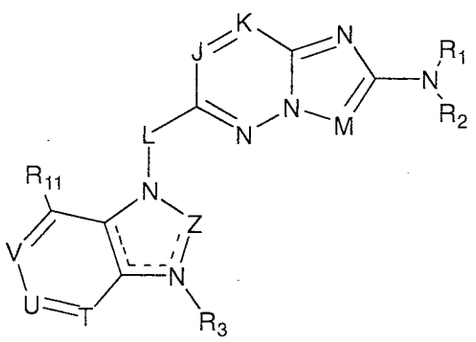
En una modalidad más, los inhibidores de cMET de la presente invención comprenden:



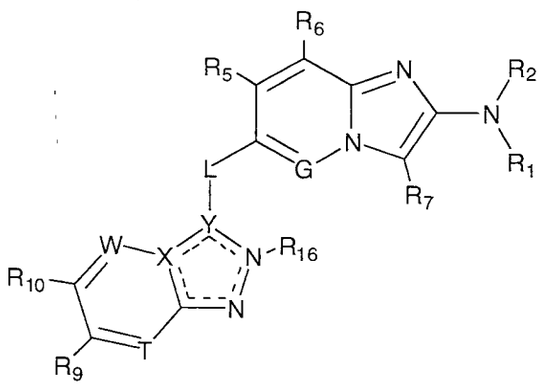
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:

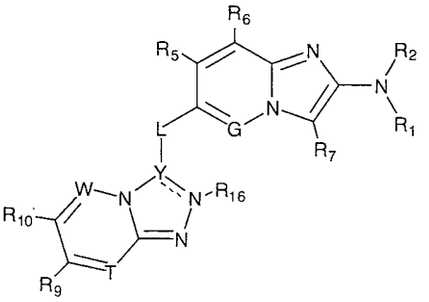


En una modalidad adicional, los inhibidores de cMET de la presente invención comprenden:

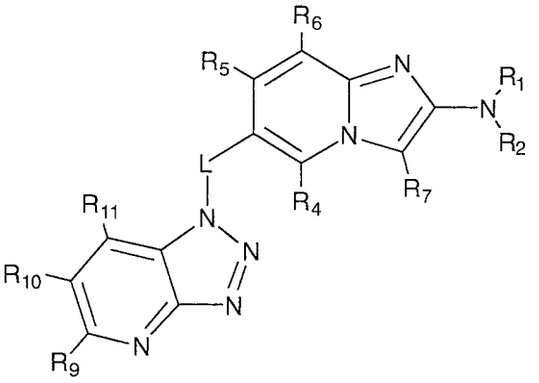


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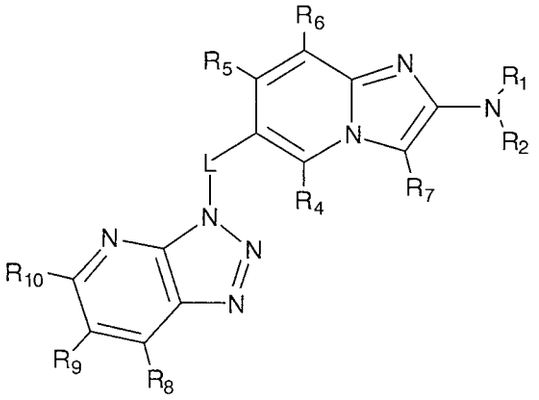
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



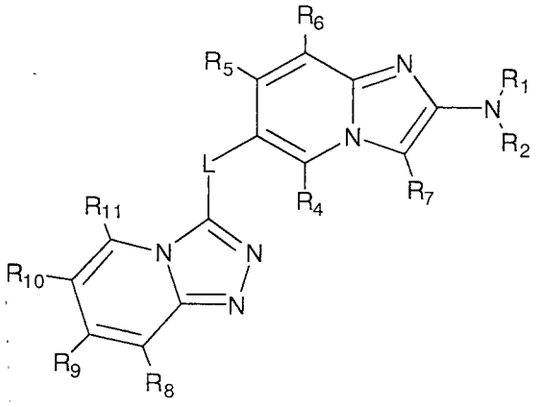
En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



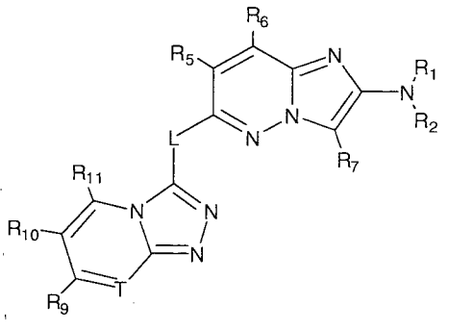
En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



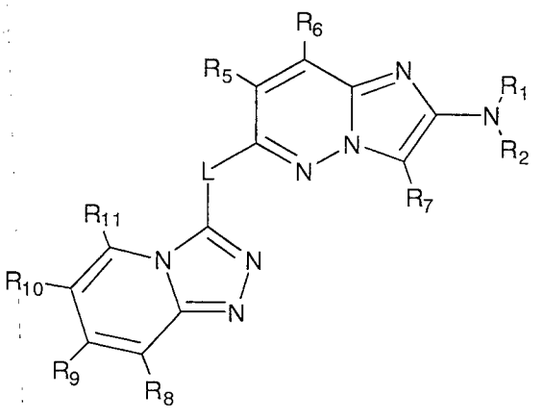
En una modalidad adicional, los inhibidores de cMET de la presente invención comprenden:



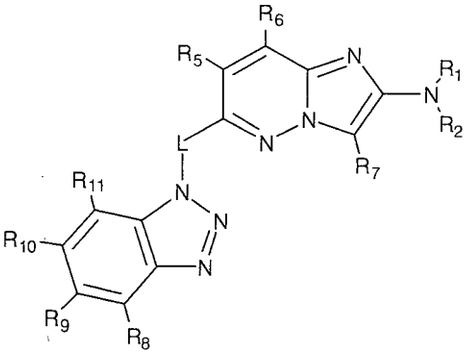
En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



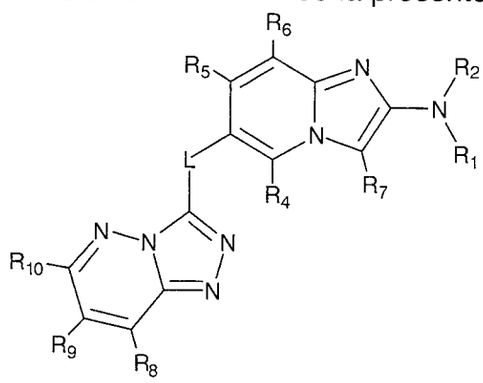
En una modalidad más, los inhibidores de cMET de la presente invención comprenden:



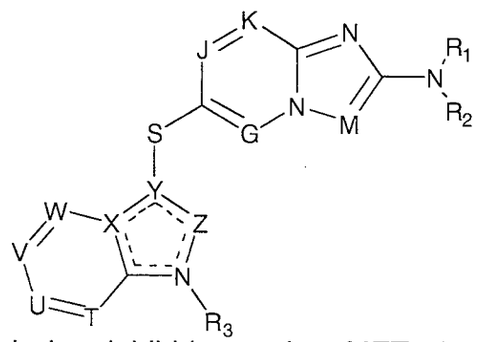
En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



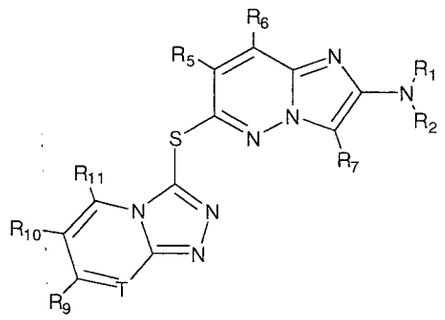
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



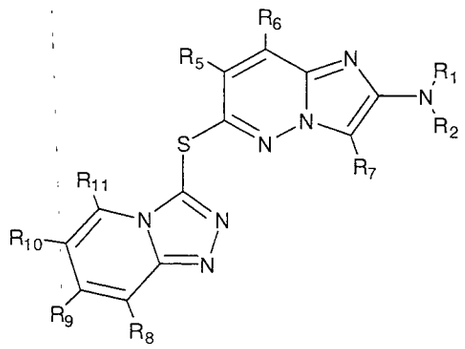
En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



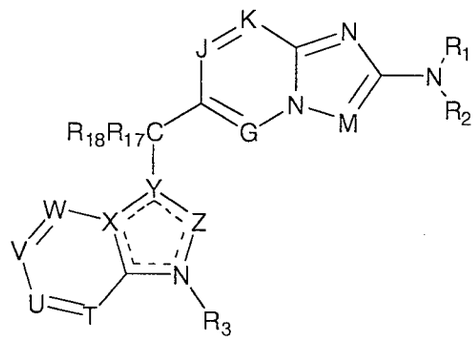
En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



En una modalidad adicional, los inhibidores de cMET de la presente invención comprenden:

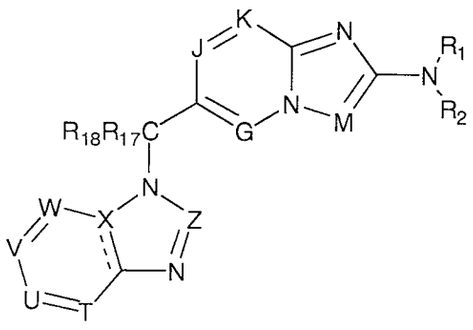


En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



en donde R_{17} y R_{18} se seleccionan de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una modalidad más, los inhibidores de cMET de la presente invención comprenden:

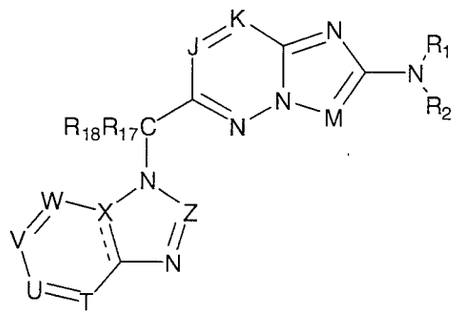


en donde R_{17} y R_{18} se seleccionan de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, amino, alquilamino (C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}),

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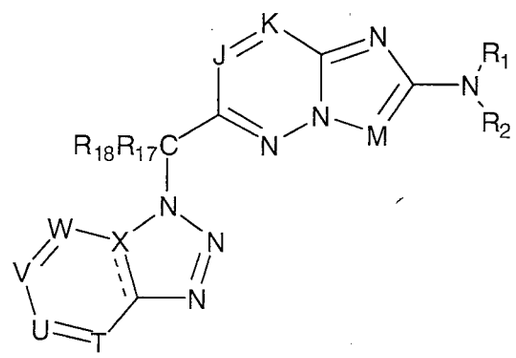
haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}), carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



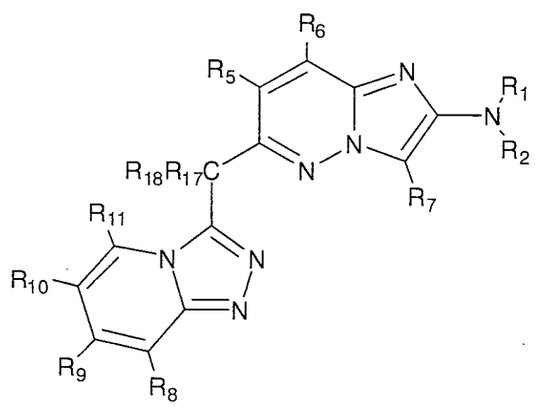
en donde R_{17} y R_{18} se seleccionan de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, amino, alquilamino (C_{1-10}), sulfonamido, imino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



en donde R_{17} y R_{18} se seleccionan de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

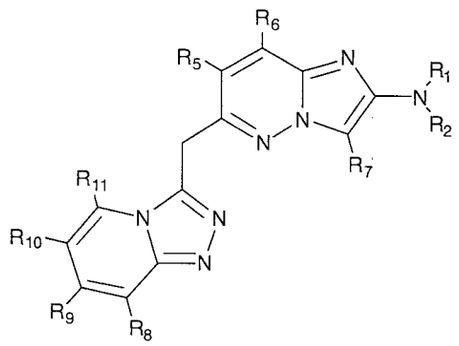
En una modalidad adicional, los inhibidores de cMET de la presente invención comprenden:



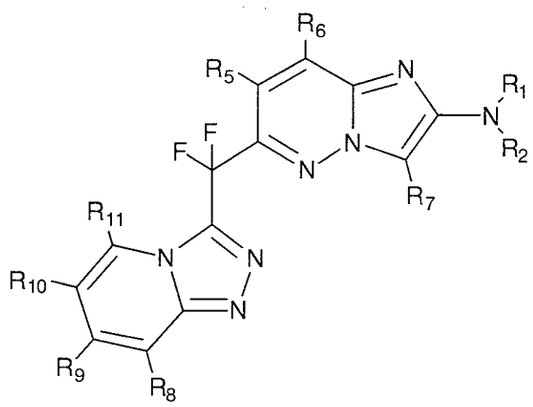
en donde R_{17} y R_{18} se seleccionan de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, amino, alquilamino (C_{1-10}), sulfonamido, imino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

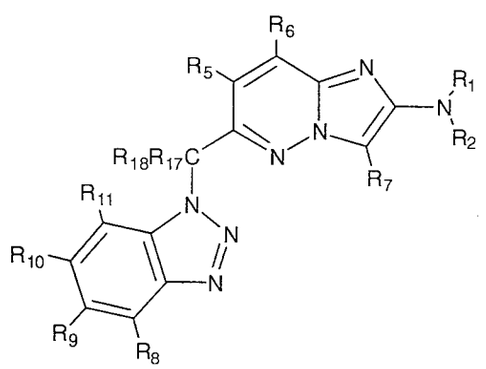
En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:

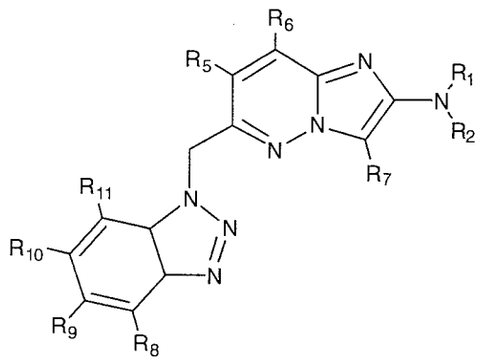


En aún otra modalidad, los inhibidores de cMET de la presente invención comprenden:



en donde R_{17} y R_{18} se seleccionan de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra modalidad, los inhibidores de cMET de la presente invención comprenden:



En otro de sus aspectos, la presente invención se refiere a métodos de preparar compuestos que son útiles como inhibidores de cMET.

En aún otro de sus aspectos, la presente invención se refiere a intermediarios que son útiles para preparar inhibidores de cMET.

En una variación de cada uno de las anteriores modalidades y variaciones, G es CR_4. En otra variación de cada una de las anteriores modalidades y variaciones, G es N.

En aún otra variación de cada una de las anteriores modalidades y variaciones, J es CR_5. En aún otra variación de cada una de las anteriores modalidades y variaciones, J es N.

En una variación adicional de cada una de las anteriores modalidades y variaciones, K es CR_6. En otra variación más de cada una de las anteriores modalidades y variaciones, K es N.

En otra variación más de cada una de las anteriores modalidades y variaciones, M es CR_7. En otra variación de cada una de las anteriores modalidades y variaciones, M es N.

En otra variación de cada una de las anteriores modalidades y variaciones,

L es un enlazante seleccionado del grupo que consiste en $-(CR_{27}R_{28})_r-$, –CO–, –CS–, $-C(=NR_{29})-$, $-NR_{30}-$, –O–, –S–, –SO–, $-SO_2-$ y sus combinaciones;

r se selecciona del grupo que consiste en 1, 2 y 3;

R_{27} se selecciona del grupo que consiste en 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroarilo (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_{28} se selecciona del grupo que consiste en 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_{29} se selecciona del grupo que consiste en hidrógeno, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, amino,

000327

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}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (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}), cada uno sustituido o no sustituido; y

R_{30} se selecciona del grupo que consiste en hidrógeno, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, 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}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (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}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, L es un alquilo (C_{1-5}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, L es $-CH_2-$. En una variación adicional de cada una de las anteriores modalidades y variaciones, L es $-CH(CH_3)-$. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, L es $-C(CH_3)_2-$. En aún otra variación adicional de cada una de las anteriores modalidades y variaciones, L es $-CF_2-$. En una variación adicional de cada una de las anteriores modalidades y variaciones, L es –S–. En otra variación de cada una de las anteriores modalidades y variaciones, L es –SO–. En aún otra variación de cada una de las anteriores modalidades y variaciones, L es $-SO_2-$. En aún otra variación de cada una de las anteriores modalidades y variaciones L es –CO–. En otra variación de cada una de las anteriores modalidades y variaciones, L es –O–. En aún otra variación de cada una de las anteriores

000328

modalidades y variaciones, L es –NH–. En aún otra variación de cada una de las anteriores modalidades y variaciones L es $–CH_2–$. En una variación adicional de cada una de las anteriores modalidades y variaciones, L es –CO–NH–. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, L es –NH–CO–. En aún otra variación adicional de cada una de las anteriores modalidades y variaciones, L es $–SO_2–NH–$. En otra variación de cada una de las anteriores modalidades y variaciones, L es $–NH–SO_2–$. En aún otra variación de cada una de las anteriores modalidades y variaciones, L es –NH–NH–. En aún otra variación de cada una de las anteriores modalidades y variaciones L es –CO–O–. En una variación adicional de cada una de las anteriores modalidades y variaciones, L es –O–CO–.

En otra variación más de cada una de las anteriores modalidades y variaciones, T es CR_8. En otra variación más de cada una de las anteriores modalidades y variaciones, T es N.

En otra variación de cada una de las anteriores modalidades y variaciones, U es CR_9. En aún otra variación de cada una de las anteriores modalidades y variaciones, U es N.

En aún otra variación de cada una de las anteriores modalidades y variaciones, V es CR_{10}. En una variación adicional de cada una de las anteriores modalidades y variaciones, V es N.

En otra variación más de cada una de las anteriores modalidades y variaciones, W es CR_{11}. En otra variación más de cada una de las anteriores modalidades y variaciones, W es N.

En otra variación de cada una de las anteriores modalidades y variaciones, X es CR_{12}. En aún otra variación de cada una de las anteriores modalidades y variaciones, X es N.

En aún otra variación de cada una de las anteriores modalidades y variaciones, Y es CR_{13}. En una variación adicional de cada una de las anteriores modalidades y variaciones, Y es N.

En otra variación más de cada una de las anteriores modalidades y variaciones, Z es $CR_{14}R_{15}$. En otra variación más de cada una de las anteriores modalidades y variaciones, Z es NR_{16}.

En otra variación de cada una de las anteriores modalidades y variaciones, T, E Y

Z son cada uno N. En aún otra variación de cada una de las anteriores modalidades y variaciones, G es CR_4, J es CR_5, K es CR_6, M es CR_7, T es CR_8, U es CR_9, V es CR_{10}, W es CR_{11}, X es CR_{12} e Y es CR_{13}. En aún otra variación de cada una de las anteriores modalidades y variaciones, G es CR_4, J es CR_5, K es CR_6, M es CR_7, T es CR_8, U es CR_9, V es CR_{10}, W es CR_{11} e Y es CR_{13}. En una variación adicional de cada una de las anteriores modalidades y variaciones, G, J, K, M, U, V, W, y X son cada uno CH. En otra variación más de cada una de las anteriores modalidades y variaciones, W, E Y Z son cada uno N. En otra variación más de cada una de las anteriores modalidades y variaciones, G, J, K, M, T, U, V, y X son cada uno CH. En otra variación de cada una de las anteriores modalidades y variaciones, G, X y Z son cada uno N. En aún otra variación de cada una de las anteriores modalidades y variaciones, J, K, M, T, U, V, W e Y son cada uno CH. En aún otra variación de cada una de las anteriores modalidades y variaciones, X y Z son cada uno N. En una variación adicional de cada una de las anteriores modalidades y variaciones, G, J, K, M, T, U, V, W e Y son cada uno CH. En otra variación más de cada una de las anteriores modalidades y variaciones, en donde T es CR_8, U es CR_9, V es CR_{10}, W es CR_{11}, X es CR_{12}, Y es N y Z es $CR_{14}R_{15}$. En otra variación más de cada una de las anteriores modalidades y variaciones, T es CR_8, U es CR_9, V es CR_{10}, W es CR_{11}, X es N, Y es CR_{13} y Z es NR_{16}. En otra variación de cada una de las anteriores modalidades y variaciones, en donde G es N, J es CR_5, K es CR_6 y M es CR_7. En una variación adicional de cada una de las anteriores modalidades y variaciones, J es CR_5, K es CR_6, T es CR_8, U es CR_9, V es CR_{10} y Z es NR_{16}. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, uno y solo uno de G y W es N. En otra variación de cada una de las anteriores modalidades y variaciones, G es N y W es CR_{11}. En aún otra variación de cada una de las anteriores modalidades y variaciones, G es CR_4 y W es N. En aún otra variación adicional de cada una de las anteriores modalidades y variaciones, uno y solo uno de W y Z es N. En otra variación de cada una de las anteriores modalidades y variaciones, uno y solo uno de W y X es N. En aún otra variación de cada una de las anteriores modalidades y variaciones, uno y solo uno de W, X y Z es N. En una variación adicional de cada una de las anteriores modalidades y variaciones, G es N; y J, K, M, T, U, V y W son CH. En aún una variación adicional de cada una de las anteriores

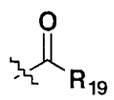
000330

modalidades y variaciones, G es N, J; K, M, T, U y W son CH; y V es CR_{10}. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, G es N, J; K, M, T, U y W son CH; y V es CR_{10}, en donde R_{10} es un heteroarilo (C_{1-10}) sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, CR_5, CR_6, CR_7, CR_8 y CR_9 son hidrógeno.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_1 se selecciona del grupo que consiste en hidrógeno, carbonilo, oxicarbonilo, aminocarbonilo, alquil (C_{1-10})carbonilo, cicloalquil (C_{3-12})carbonilo (C_{1-5}), heterocicloalquil (C_{3-12}) carbonilo (C_{1-10}), aril(C_{1-10})carbonilo, heteroaril (C_{1-10})carbonilo (C_{1-5}), bicicloaril (C_{9-12})carbonilo (C_{1-5}), heterobicicloaril (C_{8-12})carbonilo (C_{1-5}), 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_1 es hidrógeno. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_1 tiene la fórmula



en donde R_{19} se selecciona del grupo que consiste en hidrógeno, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo

000331

(C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_2 es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_2 es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_2 es un alquilo (C_{1-3}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_2 es metilo.

En aún otra variación adicional de cada una de las anteriores modalidades y variaciones, R_3 está ausente. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_3 es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_3 es un alquilo (C_{1-3}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_3 es metilo.

En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_4 es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_4 es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_4 es un alquilo (C_{1-3}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_4 es metilo.

En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_5 es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_5 es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_5 es un alquilo (C_{1-3}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_5 es metilo.

En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_6 es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_6 es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_6 es un alquilo (C_{1-3}) sustituido o no

sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_6 es metilo.

En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_7 es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_7 es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_7 es un alquilo (C_{1-3}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_7 es metilo.

En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_8 es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_8 es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_8 es un alquilo (C_{1-3}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_8 es metilo.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula $-C(=O)-NHR_{20}$ en donde R_{20} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula $-((C_{1-3})alquil)-NHR_{20a}$ en donde R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

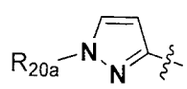
En aún otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula $-CH_2-NHR_{20a}$ en donde R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula $-NHR_{20a}$ en donde R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, en donde R_9 tiene la fórmula $-NH-C(=O)R_{20a}$ en donde R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_9 un alcoxi (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_9 es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_9 es halo. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_9 es un alquilo (C_{1-3}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_9 es metilo. En otra variación de cada una de las anteriores modalidades y variaciones, R_9 es $-CF_3$.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula

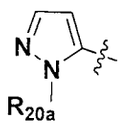


en donde R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, imino, sulfonilo, sulfinilo, alquilo (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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo

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(C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

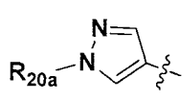
En aún otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



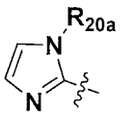
en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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

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(C_{1-10}), azaalquilo (C_{1-10}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

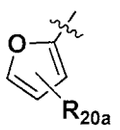
En otra variación más de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula

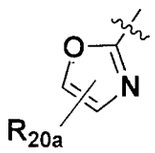


en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

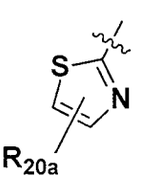
En otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula

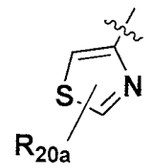


en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi,

hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

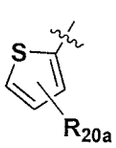
En aún otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula

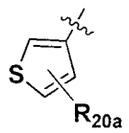


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en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

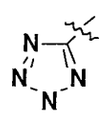
En otra variación más de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



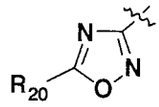
en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



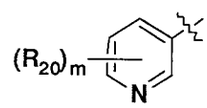
En otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



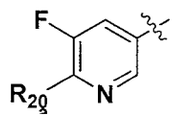
en donde

m se selecciona del grupo que consiste en 0, 1, 2, 3 y 4; y

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo

(C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

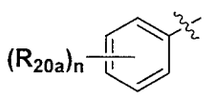
En aún otra variación de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



en donde

R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_9 tiene la fórmula



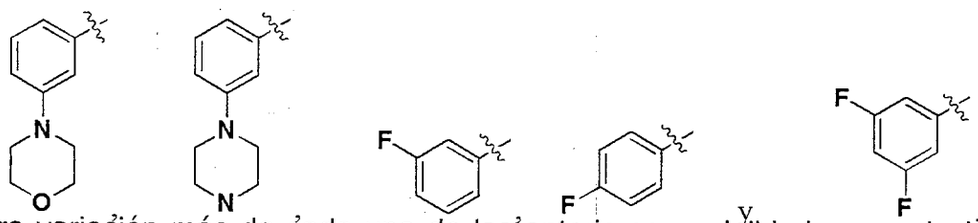
en donde

n se selecciona del grupo que consiste en 0, 1, 2, 3, 4 y 5; y

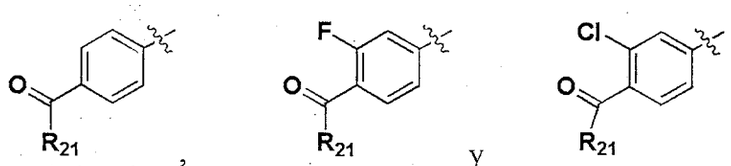
R_{20a} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}), 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}),

heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_9 has a formula se selecciona del grupo que consiste en



En otra variación más de cada una de las anteriores modalidades y variaciones, R_9 has a formula se selecciona del grupo que consiste en



en donde R_{21} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula $-C(=O)-NHR_{20b}$ en donde R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula $-((C_{1-3})alquil)-NHR_{20b}$ en donde R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula $-CH_2-NHR_{20b}$ en donde R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

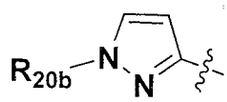
En otra variación más de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula $-NHR_{20b}$ en donde R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula $-NH-C(=O)R_{20b}$ en donde R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} es hidrógeno. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} es halo. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} se selecciona del grupo que consiste en Cl, Br y I. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{10} es un alquilo (C_{1-3}) sustituido o no sustituido. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} es metilo.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{10} es $-CF_3$. En otra variación de cada una de las anteriores modalidades y variaciones, R_{10} un alcoxi (C_{1-3}) sustituido o no sustituido. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} es ciano.

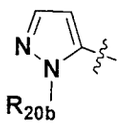
En otra variación más de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



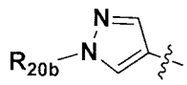
en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo

000346

(C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

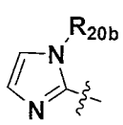
En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



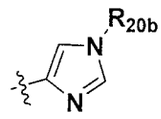
en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}),

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cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

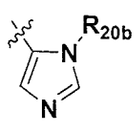
En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación de cada una de las anteriores modalidades y variaciones, R_{10} es un heteroarilo (C_{1-10}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} es un heteroarilo (C_{1-5}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones R_{10} es un heterocicloalquilo (C_{3-12}) sustituido o no sustituido. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} es un heterocicloalquilo (C_{3-6}) sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} es un grupo heteroarilo de 5 miembros sustituido que tiene 1–3 heteroátomos, en donde el anillo heteroarilo tiene al menos un grupo oxo del anillo o al menos un sustituyente hidroxi. En una variación particular, el grupo heteroarilo tiene 1–3 átomos de nitrógeno.

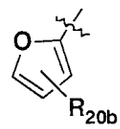
En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} es un grupo heterocicloalquilo de 5 miembros sustituido que tiene 1–3 heteroátomos, en donde el anillo heterocicloalquilo tiene al menos un grupo oxo en el anillo o al menos un sustituyente hidroxi. En una variación particular, el grupo heterocicloalquilo tiene 1–3 átomos de nitrógeno.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} es un grupo heteroarilo de 6 miembros sustituido que tiene 1–3 heteroátomos, en donde el anillo heteroarilo tiene al menos un grupo oxo en el anillo o al menos un sustituyente hidroxi. En una variación particular, el grupo heteroarilo tiene 1–3 átomos de nitrógeno.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} es un grupo heterocicloalquilo de 6 miembros sustituido que tiene 1–3 heteroátomos, en donde el anillo heterocicloalquilo tiene al menos un grupo oxo en el anillo o al menos un sustituyente hidroxi. En una variación particular, el

grupo heterocicloalquilo tiene 1–3 átomos de nitrógeno.

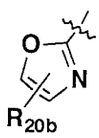
En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula

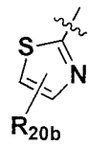


en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo

(C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

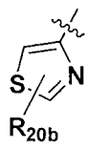
En otra variación más de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



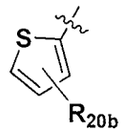
en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}),

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heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

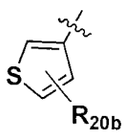
En otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula

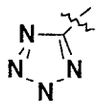


en donde

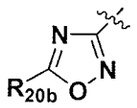
R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}), 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}),

heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



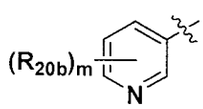
En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



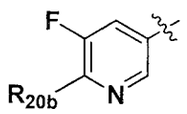
en donde

m se selecciona del grupo que consiste en 0, 1, 2, 3 y 4; y

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo,

oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

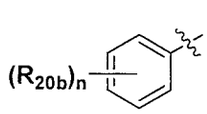
En otra variación más de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



en donde

R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación de cada una de las anteriores modalidades y variaciones, R_{10} tiene la fórmula



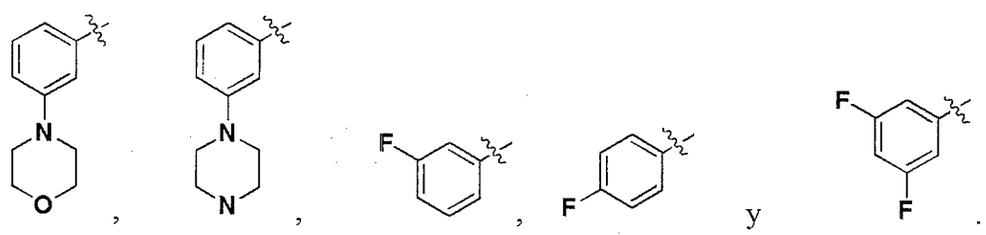
en donde

n se selecciona del grupo que consiste en 0, 1, 2, 3, 4 y 5; y

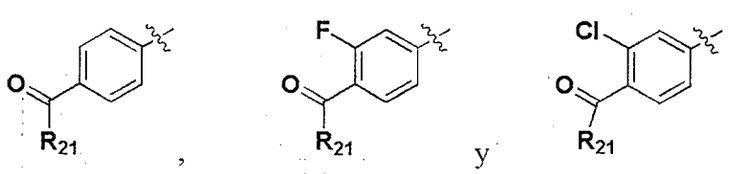
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R_{20b} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} has a formula se selecciona del grupo que consiste en



En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{10} has a formula se selecciona del grupo que consiste en



en donde

R_{21} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}),

heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{11} es hidrógeno. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{11} es halo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{11} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{11} es metilo.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{12} está ausente. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{12} es hidrógeno. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{12} es halo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{12} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{12} es metilo.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{13} está ausente. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{13} es hidrógeno. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{13} es halo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{13} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{13} es metilo.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{14} es hidrógeno. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{14} es halo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{14} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{14} es metilo.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{15} está ausente. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{15} es hidrógeno. En otra variación más de cada una

de las anteriores modalidades y variaciones, R_{15} es halo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{15} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{15} es metilo.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{16} está ausente. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{16} es hidrógeno. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{16} es halo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{16} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{16} es metilo.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{17} es hidrógeno. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{17} es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_{17} es fluoro. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{17} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{17} es metilo. En una variación de cada uno de las anteriores modalidades y variaciones que contiene R_{17}, R_{17} no está sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{18} es hidrógeno. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{18} es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_{18} es fluoro. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{18} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{18} es metilo. En una variación de cada uno de las anteriores modalidades y variaciones que contiene R_{18}, R_{18} no está sustituido.

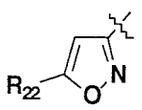
En otra variación de cada una de las anteriores modalidades y variaciones, R_{19} se selecciona del grupo que consiste en hidrógeno, amino, alquilamino (C_{1-10}), sulfonamido, alquilo (C_{1-10}), haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}), carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo

000357

(C_{1-10}), arilalquilo (C_{1-10}), heteroarilo (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación de cada una de las anteriores modalidades y variaciones, R_{19} es un alquilo (C_{1-5}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{19} es metilo. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{19} es trifluorometilo. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{19} es isopropilo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{19} es butilo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{19} es un cicloalquilo (C3–6) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{19} es ciclopropilo. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{19} es ciclopentilo. En otra variación de cada una de las anteriores modalidades y variaciones, R_{19} es un heterocicloalquilo (C_{3-12}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{19} es un arilo (C_{4-12}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{19} es un heteroarilo C_{4-10}) sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{19} tiene la fórmula



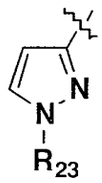
en donde

R_{22} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo

000358

(C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

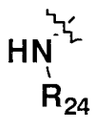
En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{19} tiene la fórmula



en donde

R_{23} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{19} tiene la fórmula



en donde

R_{24} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

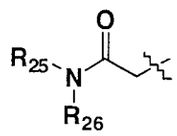
En una variación de cada uno de las anteriores modalidades y variaciones que contiene R_{19}, R_{19} no está sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{20a} se selecciona del grupo que consiste en hidrógeno, carbonilo, oxicarbonilo, aminocarbonilo, alquil (C_{1-10})carbonilo, cicloalquil (C_{3-12})carbonilo (C_{1-5}), heterocicloalquil (C_{3-12}) carbonilo (C_{1-10}), aril(C_{1-10})carbonilo, heteroarilo (C_{1-10})carbonilo (C_{1-5}), bicicloarilo (C_{9-12})carbonilo (C_{1-5}), heterobicicloaril (C_{8-12})carbonilo (C_{1-5}), 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{20a} es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_{20a} es un alquilo (C_{1-5}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{20a} es metilo. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{20a} es etilo. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{20a} es propilo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{20a} es un arilo sustituido o no sustituido. En otra variación más de cada una de las anteriores modalidades y

variaciones, R_{20a} es un fenilo sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{20a} es un cicloalquilo (C_{3-12}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{20a} es un ciclohexilo (C_{3-12}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{20a} es un heteroarilo (C_{4-10}) sustituido o no sustituido. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{20a} es un alquilo (C_{1-6}) sustituido o no sustituido. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{20a} es hidroxietilo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{20a} es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_{20a} es fluoro. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{20a} es un heterocicloalquilo (C_{3-6}) alquilo (C_{1-4}) sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{20a} tiene la fórmula



en donde

R_{25} y R_{26} se selecciona de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloarilo (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación de cada uno de las anteriores modalidades y variaciones que contiene R_{20a}, R_{20a} no está sustituido.

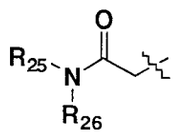
En una variación adicional de cada una de las anteriores modalidades y

variaciones, R_{20b} se selecciona del grupo que consiste en hidrógeno, carbonilo, oxicarbonilo, aminocarbonilo, alquil (C_{1-10})carbonilo, cicloalquil (C_{3-12})carbonilo (C_{1-5}), heterocicloalquil $(C_{3-12})(C_{1-10})$carbonilo, aril(C_{1-10})carbonilo, heteroarilo (C_{1-10})carbonilo (C_{1-5}), bicicloarilo (C_{9-12})carbonilo (C_{1-5}), heterobicicloaril (C_{8-12})carbonilo (C_{1-5}), 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

En aún otra variación adicional de cada una de las anteriores modalidades y variaciones, R_{20b} es hidrógeno. En otra variación de cada una de las anteriores modalidades y variaciones, R_{20b} es un alquilo (C_{1-5}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{20b} es metilo. En aún otra variación de cada una de las anteriores modalidades y variaciones R_{20b} es etilo. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{20b} es propilo. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_{20b} es un arilo sustituido o no sustituido. En aún otra variación adicional de cada una de las anteriores modalidades y variaciones, R_{20b} es un fenilo sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{20b} es un cicloalquilo (C_{3-12}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{20b} es un ciclohexilo sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones R_{20b} es un heteroarilo (C_{4-10}) sustituido o no sustituido. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{20b} es un hidoxialquilo (C_{1-6}) sustituido o no sustituido. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_{20b} es hidroxietilo. En aún otra variación adicional de cada una de las anteriores modalidades y

variaciones, R_{20b} es halo. En otra variación de cada una de las anteriores modalidades y variaciones, R_{20b} es fluoro. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{20b} es un heterocicloalquil (C_{3-6}) alquilo (C_{1-4}) sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones R_{20b} tiene la fórmula



en donde

R_{25} y R_{26} se seleccionan de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

En una variación de cada una de las anteriores modalidades y variaciones que contienen R_{20b}, R_{20b} está no sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{21} es un alquilamino (C_{1-5}) sustituido o no sustituido. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{21} es CH_3NH–. En una variación de cada uno de las anteriores modalidades y variaciones que contiene R_{21}, R_{21} no está sustituido.

En otra variación más de cada una de las anteriores modalidades y variaciones, R_{22} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{22} es metilo. En una variación de cada uno de las anteriores modalidades y variaciones que contiene R_{22}, R_{22} no está sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{23} es un alquilo (C_{1-3}) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{23} es metilo. En una variación de cada uno de las anteriores modalidades y variaciones que contiene R_{23}, R_{23} no está sustituido.

En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{24} es un alquilo (C_{1-5}) sustituido o no sustituido. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{24} es isopropilo. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{24} es ter–butilo. En otra variación de cada una de las anteriores modalidades y variaciones, R_{24} es un cicloalquilo (C3–6) sustituido o no sustituido. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{24} es ciclopropilo. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{24} es ciclopentilo. En otra variación de cada una de las anteriores modalidades y variaciones, R_{24} es un arilo sustituido o no sustituido. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{24} es un fenilo sustituido o no sustituido. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{24} es un heterocicloalquilo (C_{3-12}) sustituido o no sustituido. En otra variación más de cada una de las anteriores modalidades y variaciones, R_{24} es un pirrolidinilo sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{24} es un piperidinilo sustituido o no sustituido. En una variación de cada uno de las anteriores modalidades y variaciones que contiene R_{24}, R_{24} no está sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{25} es hidrógeno. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_{25} es halo. En aún otra variación adicional de cada una de las anteriores modalidades y variaciones, R_{25} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{25} es metilo. En una variación de cada una de las anteriores modalidades y variaciones que contienen R_{25}, R_{25} está no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones R_{26} es hidrógeno. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_{26} es halo. En aún otra variación adicional de cada

una de las anteriores modalidades y variaciones, R_{26} es un alquilo (C_{1-3}) sustituido o no sustituido. En otra variación de cada una de las anteriores modalidades y variaciones, R_{26} es metilo. En una variación de cada una de las anteriores modalidades y variaciones que contienen R_{26}, R_{26} está no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones R_{27} es hidrógeno. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{27} es halo. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_{27} es un alquilo (C_{1-3}) sustituido o no sustituido.

En aún otra variación de cada una de las anteriores modalidades y variaciones R_{28} es hidrógeno. En una variación adicional de cada una de las anteriores modalidades y variaciones, R_{28} es halo. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, R_{28} es un alquilo (C_{1-3}) sustituido o no sustituido.

En aún otra variación adicional de cada una de las anteriores modalidades y variaciones, R_{29} es hidrógeno. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{29} es un alquilo (C_{1-3}) sustituido o no sustituido.

En otra variación de cada una de las anteriores modalidades y variaciones, R_{30} se selecciona del grupo que consiste en hidrógeno, carbonilo, oxicarbonilo, 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}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (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}), cada uno sustituido o no sustituido. En aún otra variación adicional de cada una de las anteriores modalidades y variaciones, R_{30} es hidrógeno. En aún otra variación de cada una de las anteriores modalidades y variaciones, R_{30} es un alquilo (C_{1-3}) sustituido o no sustituido.

En una variación adicional de cada una de las anteriores modalidades y

variaciones, n es 1. En aún una variación adicional de cada una de las anteriores modalidades y variaciones, n es 2. En aún otra variación de cada una de las anteriores modalidades y variaciones, r es 1. En aún otra variación de cada una de las anteriores modalidades y variaciones r es 2.

En otra variación más de cada una de las anteriores modalidades y variaciones, m es 1. En otra variación de cada una de las anteriores modalidades y variaciones, m es 2.

Se indica que los compuestos de la presente invención pueden estar en la forma de una sal farmacéuticamente aceptable, éster, solvato, hidrato o profármaco de este. Por ejemplo, el compuesto opcionalmente comprende un sustituyente que se convierte *in vivo* a un sustituyente diferente tal como hidrógeno. Los ejemplos de los sustituyentes que se pueden convertir *in vivo* a un compuesto biológicamente activo incluyen, pero sin limitación, residuos biohidrolizables tales como ésteres biohidrolizables, amidas biohidrolizables y carbamatos biohidrolizables.

También cabe indicar que el compuesto puede estar presente como una mezcla de estereoisómeros, o el compuesto puede estar presente como un único estereoisómero.

En otro de sus aspectos, se proporciona una composición farmacéutica que comprende como un compuesto de acuerdo con cualquiera de las anteriores modalidades y variaciones y uno o más excipientes farmacéuticamente aceptables. En una variación particular, la composición es una formulación sólida adaptada para la administración oral. En otra variación particular, la composición es una formulación líquida adaptada para administración oral. En aún otra variación particular, la composición es un comprimido. En aún otra variación particular, la composición es una formulación líquida adaptada para administración parenteral.

La presente invención también proporciona una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las anteriores modalidades y variaciones, en donde la composición está adaptada para la administración por una vía seleccionada del grupo que consiste en oral, parenteral, intraperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposómica, por medio de inhalación, vaginal, intraocular, por medio de administración local (por ejemplo, por catéter o

000366

stent), subcutánea, intraadiposa, intraarticular y intratecal.

En aún otro de sus aspectos, se proporciona un kit que comprende a compuesto de cualquiera de las anteriores modalidades y variaciones; e instrucciones que comprenden una o más formas de información seleccionada del grupo que consiste en indicación de un estado de enfermedad para el que se administra la composición, información de almacenamiento para la composición, información de dosificación e instrucciones respecto de cómo administrar la composición. En una variación particular, el kit comprende el compuesto en una forma de dosificación múltiple.

En aún otro de sus aspectos, se proporciona un artículo de manufactura que comprende un compuesto de cualquiera de las anteriores modalidades y variaciones; y materiales de envase. En una variación, el material de envase comprende un recipiente para contener el compuesto. En una variación particular, el recipiente comprende una etiqueta que indique uno o más miembros del grupo que consiste en un estado de enfermedad para la que se administra el compuesto, información de almacenamiento, información de dosis y/o instrucciones respecto de cómo administrar el compuesto. En otra variación, el artículo de manufactura comprende el compuesto en una forma de dosificación múltiple.

En otro de sus aspectos, se proporciona un método terapéutico que comprende administrar un compuesto de cualquiera de las anteriores modalidades y variaciones a un sujeto.

En otro de sus aspectos, se proporciona un método para inhibir cMET que comprende poner en contacto cMET con un compuesto de cualquiera de las anteriores modalidades y variaciones.

En aún otro de sus aspectos, se proporciona un método para inhibir cMET que comprende causar que un compuesto de cualquiera de las anteriores modalidades y variaciones esté presente en un sujeto esté presente a fin de inhibir cMET in vivo.

En otro de sus aspectos, se proporciona un método para inhibir cMET que comprende administrar un primer compuesto a un sujeto que se convierte in vivo a un segundo compuesto en donde el segundo compuesto inhibe cMET in vivo, el segundo compuesto es un compuesto de acuerdo con cualquiera de las anteriores modalidades y variaciones.

000367

En otro de sus aspectos, se proporciona un método para tratar un estado de enfermedad para el que cMET posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, el método que comprende producir que un compuesto de cualquiera de las anteriores modalidades y variaciones esté presente en un sujeto en una cantidad terapéuticamente efectiva para el estado de enfermedad.

En aún otro de sus aspectos, se proporciona un método para tratar un estado de enfermedad para el que cMET posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, el método que comprende administrar un compuesto de cualquiera de las anteriores modalidades y variaciones a un sujeto, en donde el compuesto está presente en el sujeto en una cantidad terapéuticamente efectiva para el estasdo de enfermedad.

En otro de sus aspectos, se proporciona un método para tratar un estado de enfermedad para el que cMET posee actividad que contribuye a 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 en donde el segundo compuesto inhibe cMET in vivo, el segundo compuesto es un compuesto de acuerdo con cualquiera de las anteriores modalidades y variaciones.

En una variación de cada uno de los anteriores métodos, el estado de enfermedad es cáncer. En variaciones particulares, el cáncer se selecciona del grupo que consiste en carcinomas (*por ejemplo*, vejiga, mamas, cervical, colangiocarcinoma, colorrectal, esofágico, gástrico, cabeza y cuello, riñón, hígado, pulmón, nasofaríngeo, ovárico, pancreático, próstata y tiroides); sarcomas musculoesqueléticos (*por ejemplo*, osteosarcoma, sarcoma sinovial y rabdomiosarcoma); sarcomas de tejido blando (*por ejemplo*, MFH/fibrosarcoma, leiomiosarcoma, y sarcoma de Kaposi); neoplasias hematopoyéticas (*por ejemplo*, mieloma múltiple, linfomas, leucemia de células T adultas, leucemia mielógena aguda y leucemia mieloide crónica); y otros neoplasmas (*por ejemplo*, glioblastomas, astrocitomas, melanoma, mesotelioma, y tumor de Wilm). En otras variaciones particulares, el cáncer se selecciona del grupo que consiste en cáncer gástrico, cáncer de pulmón, cáncer de colon, cáncer de mama y otros tumores sólidos.

En otra variación de cada uno de los anteriores métodos, el estado de enfermedad es una enfermedad proliferativa. En variaciones particulares, las enfermedades proliferativas se selecciona del grupo que consiste en trastornos mieloproliferativos, aterosclerosis, y fibrosis del pulmón.

Sales, Hidratos y Profármacos de los Inhibidores de cMET

Se debe reconocer que los compuestos de la presente invención pueden estar presentes y opcionalmente se administran en la forma de sales, hidratos y profármacos 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 farmacéuticamente aceptables derivadas de diversos ácidos y bases orgánicos e inorgánicos de acuerdo con procedimientos bien conocidos en el arte.

Cuando los compuestos de la presente invención poseen una forma de base libre, los compuestos se pueden preparar como una sal de adición de ácido farmacéuticamente aceptable por la reacción de la forma de base libre del compuesto con un ácido inorgánico u orgánico farmacéuticamente aceptable, *por ejemplo*, halogenohidratos tales como clorhidrato, bromhidrato, yodhidrato; otros ácidos minerales y sus sales correspondientes tales como sulfato, nitrato, fosfato, etc.; y alquil y monoarilsulfonatos tales como etansulfonato, toluensulfonato y bencensulfonato; y otros ácidos orgánicos y sus sales correspondientes tales como acetato, tartrato, maleato, succinato, citrato, benzoato, salicilato y ascorbato. Otras sales de adición de ácidos de la presente invención incluyen, pero sin limitación: adipato, alginato, arginato, aspartato, bisulfato, bisulfito, bromuro, butirato, canforato, canforsulfonato, caprilato, cloruro, clorobenzoato, ciclopentanopropionato, digluconato, difosfato ácido, dinitrobenzoato, dodecilsulfato, fumarato, galacterato (a partir de ácido múcico), galacturonato, glucoheptonato, gluconato, glutamato, glicerofosfato, hemisuccinato, hemisulfato, heptanoato, hexanoato, hipurato, clorhidrato, bromhidrato, yodhidrato, 2–hidroxietansulfonato, yoduro, isetionato, iso–butirato, lactato, lactobionato, malato, malonato, mandelato, metafosfato, metansulfonato, metilbenzoato, monofosfato ácido, 2–naftalensulfonato, nicotinato, nitrato, oxalato, oleato, pamoato, pectinato, persulfato, fenilacetato, 3–fenilpropionato, fosfato, fosfonato y ftalato. Se deberá

reconocer que las formas de base libre normalmente diferirás de sus respectivas formas de sal en algunas propiedades físicas tales como solubilidad en solventes polares, pero de otro modo las sales son equivalentes a sus respectivas formas de base libre para los fines de la presente invención.

Cuando los compuestos de la presente invención poseen una forma de ácido libre, una sal de adición de base farmacéuticamente aceptable se pueden preparar por la reacción de la forma de ácido libre del compuesto co una base inorgánica u orgánica farmacéuticamente aceptable. Los ejemplos de dichas bases son hidróxidos de metales alcalinos que incluyen hidróxidos de potasio, sodio y litio; hidróxidos de metales alcalinotérreos tales como hidróxidos de bario y calcio; alcóxidos de metales alcalino, *por ejemplo*, etanolato de potasio y propanolato de sodio; y varias bases orgánicas tales como hidróxido de amonio, piperidina, dietanolamina y N–metilglutamina. También se incluyen las sales de aluminio de los compuestos de la presente invención. Otras sales básicas de la presente invención incluyen, pero sin limitación: sales de cobre, férrico, ferroso, litio, magnesio, mangánico, manganoso, potasio, sodio y zinc. Las sales básicas orgánicas incluyen, pero sin limitación, sales de aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen aminas sustituidas naturales, aminas cíclicas y resinas de intercambio iónico básico, *por ejemplo*, arginina, betaína, cafeína, cloroprocaína, colina, N,N'–dibenciletilendiamina (benzatina), diciclohexilamina, dietanolamina, 2–dietilaminoetanol, 2–dimetilaminoetanol, etanolamina, etilendiamina, N–etilmorfolina, N–etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, iso–propilamina, lidocaína, lisina, meglumina, N–metil–D–glucamina, morfolina, piperazina, piperidina, resinas de poliamina, procaína, purinas, teobromina, trietanolamina, trietilamina, trimetilamina, tripropilamina y tris–(hidroximetil)–metilamina (trometamina). Se debe reconocer que las formas de ácido libre normalmente diferirán de sus formas de sales respectivas en algunas propiedades físicas tales como solubilidad en solventes polares, pero de otro modo las sales son equivalentes a sus respectivas formas de ácido libre para los fines de la presente invención.

La presente invención también se refiere a los N-óxidos de los compuestos de acuerdo con la presente invención. Los N–óxidos de los compuestos de acuerdo con la presente invención se pueden preparar por métodos conocidos por los

expertos en el arte. Por ejemplo, los N–óxidos se pueden preparar por el tratamiento de una forma no oxidada del compuesto con un agente oxidante (*por ejemplo*, ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido meta–cloroperoxibenzoico, o similares) en un solvente orgánico inerte adecuado (*por ejemplo*, un hidrocarburo halogenado tales como diclorometano) a aproximadamente 0 °C. De modo alternativo, los N–óxidos de los compuestos se pueden preparar a partir del N–óxido de un material de partida apropiado. Se entiende que los N–óxidos se pueden preparar por procesos metabólicos *in vitro* e *in vivo*.

Los derivados del profármaco de los compuestos de acuerdo con la presente invención se pueden preparar por la modificación de los sustituyentes de los compuestos de la presente invención que luego se convierten in vivo a un sustituyente diferente. Se indica que en muchos casos, los profármacos de por sí también se incluyen en el alcance de la variedad de compuestos de acuerdo con la presente invención. Por ejemplo, los profármacos se pueden preparar por la reacción de un compuesto con un agente de carbamilación (*por ejemplo*, 1,1–aciloxialquilcarbonocloridato, carbonato de para–nitrofenilo, o similares) o un agente acilante. Otros s ejemplos de métodos de preparación de profármacos se describen en Saulnier et al. (1994), Bioorganic y Medicinal Chemistry Letters, Vol. 4, p. 1985.

Los derivados protegidos de los compuestos de la presente invención también se pueden preparar. Los 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, 3rd edición, John Wiley & Sons, Inc. 1999.

Los compuestos de la presente invención también se pueden preparar de modo conveniente, o formar durante el proceso de la invención, como solvatos (*por ejemplo*, hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar de modo conveniente por la recristaliación de una mezcla de solventes acuoso/orgánico, usando solventes orgánicos tales como dioxina, tetrahidrofurano o metanol.

Una "sal farmacéuticamente aceptable", como se usa en la presente, abarca cualquier compuesto de acuerdo con la presente invención que se utiliza en su forma de sal, especialmente cuando la sal confiere al compuesto mejores

propiedades farmacocinéticas en comparación con la forma libre del compuesto o una forma de sal diferente del compuesto. La forma de sal farmacéuticamente aceptable también puede conferir inicialmente propiedades farmacocinéticas deseables al compuesto que no poseía previamente e incluso puede afectar positivamente la farmacodinámica del compuesto con respecto a su actividad terapéutica en el cuerpo. Un ejemplo de una propiedad farmacocinética que puede afectar favorablemente es la manera en que el compuesto se transporta a través de las membranas celulares, que a su vez pueden afectar directa y positivamente la absorción, distribución, biotransformación y excreción del compuesto. Si bien la vía de administración de la composición farmacéutica es importante y diversos factores anatómicos, fisiológicos y patológicos pueden afectar críticamente la biodisponibilidad, la solubilidad del compuesto usualmente depende del carácter de su forma de sal particular, que se utiliza. Los expertos en el arte apreciarán que una solución acuosa del compuesto proveerá la más rápida absorción del compuesto en el cuerpo de un sujeto tratado, mientras que las soluciones y suspensiones de lípidos, así como las formas de dosificación sólidas, producirán absorción menos rápida del compuesto.

Composiciones Que Comprenden Inhibidores de cMET

Una amplia variedad de composiciones y métodos de administración se puede usar en conjunto con los compuestos de la presente invención. Dichas composiciones pueden incluir, además de los compuestos de la presente invención, excipientes farmacéuticos convencionales, y otros agentes farmacéuticamente inactivos convencionales. En forma adicional, las composiciones pueden incluir agentes activos además de los compuestos de la presente invención. Estos agentes activos adicionales incluyen compuestos de acuerdo con la invención adicionales y/o uno o más agentes farmacéuticamente activos.

Las composiciones pueden estar en forma gaseosa, líquida, semilíquida o sólida, formulado de manera adecuada para la vía de administración usada. Para la administración oral, normalmente se usan cápsulas u comprimidos. Para la administración parenteral, normalmente se usa la reconstitución de un polvo liofilizado, preparado como se describió en la presente.

000372

Las composiciones que comprenden compuestos de la presente invención se pueden administrar o coadministrar por vía oral, parenteral, intraperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposómica, por medio de inhalación, vaginal, intraocular, por medio de administración local (por ejemplo, por catéter o stent), subcutánea, intraadiposa, intraarticular o intratecal. Los compuestos y/o las composiciones de acuerdo con la invención también se pueden administrar o coadministrar en las formas de dosificación de liberación lenta.

Los inhibidores de cMET y las composiciones que los comprenden se pueden administrar o coadministrar en cualquier forma de dosificación convencional. La coadministración en el contexto de esta invención significa la administración de más de un agente terapéutico, uno de los cuales incluye un inhibidor de cMET, en el curso de un tratamiento coordinado para obtener un resultado clínico mejor. Dicha coadministración también puede ser coincidente, es decir, que ocurre durante períodos superpuestos de tiempo.

Las soluciones o suspensiones usadas para la aplicación parenteral, intradérmica, subcutánea o tópico opcionalmente puede incluir uno o más de los siguientes componentes: un diluyente estéril, tal como agua para inyección, solución salina, aceite fijo, polietilenglicol, glicerina, propilenglicol u otro solvente sintético; agentes antimicrobianos, tales como alcohol bencílico y metil parabenos; antioxidantes, tales como ácido ascórbico y bisulfito de sodio; agentes quelantes, tales como ácido etilendiamintetraacético (EDTA); amortiguadores, tales como acetatos, citratos y fosfatos; agentes para el ajuste de tonicidad tales como cloruro o dextrosa de sodio, y agentes para el ajuste de acidez y alcalinidad de la composición, tales como agentes alcalinos y acidificantes o amortiguador como carbonatos, bicarbonatos, fosfatos, ácido clorhídrico, y ácidos orgánicos como ácido acético y cítrico. Las preparaciones parenterales opcionalmente se pueden encapsular en ampollas, jeringas desechables o viales de dosis únicas o múltiples hechas de vidrio, plástico u otro material adecuado.

Cuando los compuestos de acuerdo con la presente invención exhiben solubilidad insuficiente, se pueden usar métodos para solubilizar los compuestos. Dichos métodos son conocidos para los expertos en este arte, e incluyen, pero sin limitación, usando cosolventes, tales como dimetilsulfóxido (DMSO), usando

tensioactivos, tales como TWEEN, o disolución en bicarbonato de sodio acuoso. Los derivados de los compuestos, tales como los profármacos de los compuestos también se pueden usar en la formulación de composiciones farmacéuticas efectivas.

Después de mezclar o agregar compuestos de acuerdo con la presente invención a una composición, se puede formar una solución, suspensión, emulsión o similares. La forma de la composición resultante dependerá de numerosos factores, que incluyen el modo deseado de administración, y la solubilidad del compuesto en portador o vehículo seleccionado. La concentración efectiva necesaria para mejorar la enfermedad tratada se puede determinar empíricamente.

Las composiciones de acuerdo con la presente invención opcionalmente son provistas para la administración a seres humanos y animales en formas de dosificación unitarias, tales como comprimidos, cápsulas, pastillas, polvos, polvos secos para inhaladores, gránulos, soluciones o suspensiones parenterales estériles, y soluciones o suspensiones orales, y emulsiones aceite-agua que contienen cantidades adecuadas de los compuestos, en particular sales farmacéuticamente aceptables, con preferencia sus sales de sodio. Los compuestos farmacéutica y terapéuticamente activos y sus derivados se formulan normalmente y se administran en formas de dosificación unitarias o formas de dosificación múltiples. Las formas de dosificación unitarias, como se usa en la presente, se refieren a unidades físicamente diferenciadas adecuadas para sujetos humanos y animales y envasados de forma individual como se conoce en el arte. Cada dosis unitaria contiene una cantidad predeterminada del compuesto terapéuticamente activo suficiente para producir el efecto terapéutico deseado, en asociación con el portador, vehículo o diluyente farmacéutico requerido. Los ejemplos de formas de dosificación unitarias incluyen ampollas y jeringas, comprimidos o cápsulas envasados individualmente. Las formas de dosificación unitarias se pueden administrar en fracciones o múltiplos de esta. Una forma de dosificación múltiple es una pluralidad de formas de dosificación unitarias idénticas envasadas en un recipiente único para administrarse en forma de dosis unitarias separadas. Los ejemplos de formas de dosificación múltiples incluyen viales, frascos de comprimidos o cápsulas o frascos de pinta o galones. En

consecuencia, la forma de dosificación múltiple es un múltiplo de dosis unitarias que no se separan en el envase.

Además de uno o más compuestos de acuerdo con la presente invención, la composición puede comprender: un diluyente tales como lactosa, sacarosa, fosfato de dicalcio o carboximetilcelulosa; un lubricante, tal como estearato de magnesio, estearato de calcio y talco; y un aglutinante tal como almidón, gomas naturales, tales como goma de acacia, gelatina, glucosa, melazas, polvinilpirrolidina, celulosas y sus derivados, povidona, crospovidonas y otros de estos aglutinantes conocidos por los expertos en el arte. Las composiciones líquidas administrables farmacéuticamente, por ejemplo, se pueden preparar por la disolución, dispersión o mezclar de otro modo 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 administrada también puede contener cantidades menores de sustancias auxiliares tales como, agentes humectantes, agentes emulsionantes o agentes solubilizantes, agentes amortiguadores de pH y similares, por ejemplo, acetato, citrato de sodio, derivados de ciclodextrina, monolaurato de sorbitano, acetato de trietanolamina sódica, oleato de trietanolamina y otros de estos agentes. Los métodos reales de preparar dichas formas de dosificación son conocidas en el arte, o serán evidentes para los expertos en este arte; por ejemplo, ver Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edición, 1975. La composición o formulación administrada, en cualquier caso, contendrá una cantidad suficiente de un inhibidor de la presente invención para reducir la actividad de cMET in vivo, por ende para tratar el estado de enfermedad del sujeto.

Las formas de dosificación o composiciones opcionalmente pueden comprender uno o más compuestos de acuerdo con la presente invención en el rango de 0.005% a 100% (peso/peso) con el equilibrio que comprende sustancias adicionales tales como los que se describen en la presente. Para la administración oral, una composición farmacéuticamente aceptable opcionalmente puede comprender alguno o más excipientes empleados comúnmente, tales como, por ejemplo calidades farmacéuticas de manitol, lactosa, almidón, estearato de

000375

magnesio, talco, derivados de celulosa, croscarmelosa sódica, glucosa, sacarosa, carbonato de magnesio, sacarina sódica, talco. Dichas 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 microencapsulada, y polímeros biocomtibles, biodegradables, tales como colágeno, acetato de etilenvinilo, polianhídridos, ácido poliglicólico, poliortoésteres, ácido poliláctico y otros. Los métodos para preparar estas formulaciones son conocidas para los expertos en el arte. Las composiciones opcionalmente pueden contener 0.01%–100% (peso/peso) de uno o más inhibidores de cMET, opcionalmente 0.1–95%, y opcionalmente 1–95%.

Las sales, con preferencia sales de sodio, de los inhibidores se pueden preparar con portadores que protegen el compuesto contra la eliminación rápida del cuerpo, tales como formulaciones o recubrimientos de liberación con el tiempo. Las formulaciones además pueden incluir otros compuestos activos para obtener combinaciones de propiedades deseadas.

Formulaciones Para Administración Oral

Las formas de dosificación farmacéuticas orales pueden ser como un sólido, gel o líquido. Los ejemplos de formas de dosificación sólidas incluyen, pero sin limitación comprimidos, cápsulas, gránulos y polvos a granel. Los ejemplos más específicos de comprimidos orales incluyen pastillas y comprimidos masticables, comprimidos que pueden tener un recubrimiento entérico, recubrimiento de azúcar o recubrimiento de película. Los ejemplos de cápsulas incluyen cápsulas de gelatina dura o blanda. Los gránulos y polvos se pueden proveer en formas no efervescentes o efervescentes. Cada uno se puede combinar con otros ingredientes conocidos por los expertos en el arte.

En ciertas modalidades, los compuestos de acuerdo con la presente invención se proveen como formas de dosificación sólidas, con preferencia cápsulas o comprimidos. Los comprimidos, pastillas, cápsulas, pastillas y similares opcionalmente pueden contener uno o más de los siguientes ingredientes, o compuestos de una naturaleza similar: un aglutinante; un diluyente; un agente desintegrante; un lubricante; un deslizante; un agente edulcorante; y un agente

saborizante.

Los ejemplos de aglutinantes que se pueden usar incluyen, pero sin limitación, celulosa microcristalina, goma de tragacanto, solución de glucosa, mucílago de acacia, solución de gelatina, sacarosa, y pasta de almidón.

Los ejemplos de lubricantes que se pueden usar incluyen, pero sin limitación, talco, almidón, estearato de magnesio o calcio, licopodio y ácido esteárico.

Los ejemplos de diluyentes que se pueden usar incluyen, pero sin limitación, lactosa, sacarosa, almidón, caolín, sal, manitol, y fosfato de dicalcio.

Los ejemplos de deslizantes que se pueden usar incluyen, pero sin limitación, dióxido de silicio coloidal.

Los ejemplos de agentes desintegrantes que se pueden usar incluyen, pero sin limitación, croscarmelosa sódica, glicolato de almidón sódico, ácido algínico, almidón de maíz, almidón de papa, bentonita, metilcelulosa, agar y carboximetilcelulosa.

Los ejemplos de agentes colorantes que se pueden usar incluyen, pero sin limitación, cualquiera de los colorantes FD y C hidrosolubles certificados aprobados y sus mezclas; y colorantes FD y C insolubles en agua suspendidos en hidrato de alúmina.

Los ejemplos de agentes edulcorantes que se pueden usar incluyen, pero sin limitación, sacarosa, lactosa, manitol y agentes edulcorantes artificiales tales como ciclamato de sodio y sacarina, y numerosos sabores secos por aspersión.

Los ejemplos de agentes saborizantes que se pueden usar incluyen, pero sin limitación, sabores naturales extraídos de plantas tales como frutas y mezclas sintéticas de compuestos que producen una sensación agradable, tales como, pero sin limitación menta y salicilato de metilo.

Los ejemplos de agentes humectantes que se pueden usar incluyen, pero sin limitación, propilenglicol monoestearato, monooleato de sorbitano, monolaurato de dietilenglicol, y lauriléter de polioxietileno.

Los ejemplos de recubrimientos anti–eméticos que se pueden usar incluyen, pero sin limitación, ácidos grasos, grasas, ceras, goma laca, goma laca amoniada y ftalatos de acetato de celulosa.

Los ejemplos de recubrimientos de película que se pueden usar incluyen, pero sin limitación, hidroxietilcelulosa, carboximetilcelulosa sódica, polietilenglicol 4000 y

ftalato de acetato de celulosa.

Si se desea la administración oral, la sal del compuesto opcionalmente puede ser provista en una composición que la protege del ambiente ácido del estómago. Por ejemplo, la composición se puede formular en un recubrimiento entérico que mantenga si integridad en el estómago y libera el compuesto activo en el intestino. La composición también se puede formular en combinación con un antiácido u otro ingrediente.

Cuando la forma de dosificación unitaria es una cápsula, opcionalmente puede comprender en forma adicional un portador líquido tal como un aceite graso. Además, las formas de dosificación unitarias opcionalmente pueden comprender en forma adicional varios otros materiales que modifican la forma física de la unidad de dosis, por ejemplo, recubrimientos de azúcar y otros agentes entéricos.

Los compuestos de acuerdo con la presente invención también se pueden administrar como un componente de un elíxir, suspensión, jarabe, oblea, espolvoreo, goma masticable o similares. Un jarabe opcionalmente puede comprender, además de los compuestos activos, sacarosa como agente edulcorante y ciertos conservadors, tinturas y colorantes y sabores.

Los compuestos de la presente invención también se pueden mezclar con otros materiales activos que no alteran la acción deseada, o con materiales que suplementan la acción deseada, tales como antiácidos, bloqueantes de H2, y diuréticos. Por ejemplo, si un compuesto se usa para tratar asma o hipertensión, se puede usar con otros broncodilatadores y agentes antihipertensivos, respectivamente.

Los ejemplos de portadores farmacéuticamente aceptables 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 con recubrimiento entérico, debido a que el recubrimiento entérico resiste la acción del ácido estomacal y disuelve o desintegra en los intestinos neutros o alcalinos. Los comprimidos con recubrimiento de azúcar pueden ser comprimidos prensados en los que se aplican diferentes capas de sustancias farmacéuticamente aceptables. Los comprimidos con recubrimiento de película pueden ser comprimidos prensados que han sido recubiertos con

polímeros u otros recubrimientos adecuados. Los comprimidos prensados múltiples pueden ser comprimidos prensados obtenidos por más un ciclo de compresión que utiliza las sustancias farmacéuticamente aceptables previamente mencionadas. Los agentes colorantes también se pueden usar en los comprimidos. Los agentes saborizantes y edulcorantes se pueden usar en comprimidos, y son especialmente útiles en la formación de comprimidos y pastillas masticables.

Los ejemplos de formas de dosificación orales líquidas s que se pueden usar incluyen, pero sin limitación, soluciones, emulsiones, suspensiones acuosas, soluciones y/o suspensiones reconstituidas a partir de gránulos no efervescentes y preparaciones efervescentes reconstituidas a partir gránulos efervescentes.

Los ejemplos de soluciones acuosas que se pueden usar incluyen, pero sin limitación, elíxires y jarabes. Como se usa en la presente, los elíxires se refieren a preparaciones hidroalcohólicas, edulcoradas y transparentes. Los ejemplos de portadores farmacéuticamente aceptables que se pueden usar en los elíxires incluyen, pero sin limitación solventes. Los ejemplos particulares de solventes que se pueden usar incluyen glicerina, sorbitol, alcohol etílico y jarabe. Como se usa en la presente, los jarabes se refieren a soluciones acuosas concentradas de un azúcar, por ejemplo, sacarosa. Los jarabes opcionalmente también pueden comprender un conservador.

Las emulsiones se refieren a sistemas de dos fases en los que un líquido se dispersa en forma de pequeños glóbulos en todo el otro líquido. Las emulsiones opcionalmente puede ser aceite en agua o agua en aceite. Los ejemplos de portadores farmacéuticamente aceptables que se pueden usar en las emulsiones incluyen, pero sin limitación líquidos no acuosos, agentes emulsionantes y conservadors.

Los ejemplos de sustancias farmacéuticamente aceptables que se pueden usar en gránulos efervescentes, reconstituirse en una forma de dosificación líquida, incluyen diluyentes, edulcorantes y agentes humectantes.

Los ejemplos de sustancias farmacéuticamente aceptables que se pueden usar en gránulos efervescentes, reconstituidos en una forma de dosificación oral líquida, incluyen ácidos orgánicos y una fuente de dióxido de carbono.

Los agentes colorantes y saborizantes opcionalmente se pueden usar en todas las

000379

formas de dosificación sólidas.

Los ejemplos particulares de conservadors que se pueden usar incluyen glicerina, metil y propilparabeno, ácido benzoico, benzoato de sodio y alcohol.

Los ejemplos particulares de líquidos no acuosos que se pueden usar en emulsiones incluyen aceite mineral y aceite de semilla de algodón.

Los ejemplos particulares de agentes emulsionantes que se pueden usar incluyen gelatina, acacia, tragacanto, bentonita, y tensioactivos tales como monooleato de polioxietilen sorbitano.

Los ejemplos particulares de agentes de suspensión que se pueden usar incluyen carboximetilcelulosa de sodio, pectina, tragacanto, Veegum y acacia. Los diluyentes incluyen lactosa y sacarosa. Los agentes edulcorantes incluyen sacarosa, jarabes, glicerina y agentes edulcorantes artificiales tales como ciclamato y sacarina de sodio.

Los ejemplos particulares de agentes humectantes que se pueden usar incluyen monostearato de propilenglicol, monooleato de sorbitano, monolaurato de dietilenglicol, y polioxietilen lauril éter.

Los ejemplos particulares de ácidos orgánicos que se pueden usar incluyen ácido cítrico y tartárico.

Las fuentes de dióxido de carbono que se pueden usar en composiciones efervescentes incluyen bicarbonato de sodio y carbonato de sodio. Los agentes colorantes incluyen alguno de los colorantes FD y C hidrosolubles certificados aprobados y sus mezclas.

Los ejemplos particulares de agentes saborizantes que se pueden usar incluyen sabores naturales extraídos de plantas y frutas, y mezclas sintéticas de compuestos que producen una sensación de sabor agradable.

Para una forma de dosificación sólida, la solución o suspensión, en por ejemplo carbonato de propileno, aceites vegetales o triglicéridos, con preferencia está encapsulada en una cápsula de gelatina. Dichas soluciones y su preparación y encapsulación, se describen en las patentes U.S. Nos. 4.328.245; 4.409.239; y 4.410.545. Para una forma de dosificación líquida, la solución, *por ejemplo*, por ejemplo, en un polietilenglicol, se puede diluir en una cantidad suficiente de un portador líquido farmacéuticamente aceptable, *por ejemplo*, agua, para ser medido fácilmente para la administración.

De modo alternativo, las formulaciones orales líquidas o semisólidas se pueden preparar por la disolución o dispersión del compuesto activo o sal en aceites vegetales, glicoles, triglicéridos, ésteres de propilenglicol (*por ejemplo*, carbonato de propileno) y otros de estos portadores, y la encapsulado de estas soluciones o suspensiones en cápsulas duras o blandas de goma laca y gelatina. Otras formulaciones incluyen las expuestas en las patentes Nos. Re 28.819 y 4.358.603.

Inyectables, Soluciones y Emulsiones

La presente invención también se refiere a composiciones diseñadas para administrar los compuestos de la presente invención por administración parenteral, generalmente caracterizada por inyección subcutánea, intramuscular o intravenosa. Los inyectables se pueden preparar en cualquier forma convencional, por ejemplo como soluciones o suspensiones líquidas, formas sólidas adecuadas para solución o suspensión en líquido antes de la inyección, o como emulsiones. Los ejemplos de excipientes que se pueden usar en conjunto con los inyectables de acuerdo con la presente invención incluyen, pero sin limitación agua, solución salina, dextrosa, glicerol o etanol. Las composiciones inyectables opcionalmente también pueden comprender cantidades menores de sustancias auxiliares no tóxicas tales como agentes humectantes o emulsionantes, agentes amortiguadores de pH, estabilizantes, potenciadores de la solubilidad y otros de estos agentes, tales como por ejemplo, acetato de sodio, monolaurato de sorbitano, oleato de trietanolamina y ciclodextrinas. La implantación de un sistema de liberación lenta o liberación sostenida, de modo de mantener un nivel de dosificación constante (ver, *por ejemplo*, Patente U.S. No. 3.710.795) también está contemplado en la presente. El porcentaje de compuesto activo contenido en dichas composiciones parenterales es altamente dependiente de su naturaleza específica, así como la actividad del compuesto y las necesidades del sujeto.

La administración parenteral de las formulaciones incluye las administraciones intravenosa, subcutánea e intramuscular. Las preparaciones para la administración parenteral incluyen soluciones estériles listas para la inyección, productos solubles secos estériles, tales como los polvos liofilizados descritos en la presente, listos para combinarse con un solvente inmediatamente antes de usar, que incluyen comprimidos hipodérmicos, suspensiones estériles listas para

inyección, productos insolubles secos estériles listos para combinarse con un vehículo inmediatamente antes de usar y emulsiones estériles. Las soluciones pueden ser acuosas o no acuosas.

Cuando se administra por vía intravenosa, los ejemplos de portadores adecuados incluyen, pero sin limitación solución salina fisiológica o solución salina amortiguada con fosfato (PBS), y soluciones que contienen agentes espesantes y solubilizantes, tales como glucosa, polietilenglicol, y polipropilenglicol y sus mezclas.

Los ejemplos de portadores farmacéuticamente aceptables que se pueden usar opcionalmente en las preparaciones parenterales incluyen, pero sin limitación vehículos acuosos, vehículos no acuosos, agentes antimicrobianos, agentes isotónicos, amortiguadores, antioxidantes, anestésicos locales, agentes de suspensión y dispersión, agentes emulsionantes, agentes secuestrantes o quelantes y otras sustancias farmacéuticamente aceptables.

Los ejemplos de vehículos acuosos que se pueden usar opcionalmente incluyen inyección de cloruro de sodio, inyección de Ringer, inyección dextrosa isotónica, inyección de agua estéril, inyección de dextrosa y Ringer lactada.

Los ejemplos de vehículos parenterales no acuosos que se pueden usar opcionalmente incluyen aceites fijos de origen vegetal, aceite de algodón, aceite de maíz, aceite de sésamo y aceite de maní.

Los agentes antimicrobianos en concentraciones bacteriostáticas o fungistáticas se pueden agregar a preparaciones parenterales, en particular cuando las preparaciones se envasan en recipientes de múltiples dosis y en consecuencia se diseñan para almacenar y se extraen múltiples alícuotas. Los ejemplos de agentes antimicrobianos que se pueden usar incluyen fenoles o cresoles, mercuriales, alcohol bencílico, clorobutanol, ésteres de ácido metil y propil p–hidroxibenzoico, timerosal, cloruro de benzalconio y cloruro de bencetonio.

Los ejemplos de agentes isotónicos que se pueden usar incluyen cloruro de sodio y dextrosa. Los ejemplos de amortiguadores que se pueden usar incluyen fosfato y citrato. Los ejemplos de antioxidantes que se pueden usar incluyen bisulfato de sodio. Los ejemplos de anestésicos locales que se pueden usar incluyen clorhidrato de procaína. Los ejemplos de agentes de suspensión y dispersión que se pueden usar incluyendo carboximetilcelulosa sódica, hidroxipropilmetilcelulosa

y polivinilpirrolidona. Los ejemplos de agentes emulsionantes que se pueden usar incluyen Polisorbato 80 (TWEEN 80). Un agente secuestrante o quelante de iones metálicos incluye EDTA.

Portadores farmacéuticos opcionalmente también pueden incluir alcohol etílico, polietilenglicol y propilenglicol para los vehículos miscibles en agua e hidróxido de sodio, ácido clorhídrico, ácido cítrico o ácido láctico para el ajuste de pH.

La concentración de un inhibidor en la formulación parenteral se puede ajustar de modo que una inyección administra una cantidad farmacéuticamente efectiva suficiente para producir el efecto farmacológico deseado. La concentración exacta de un inhibidor y/o dosis usada dependerá en última instancia de la edad, peso y condición del paciente o animal como es sabido en el arte.

Las preparaciones parenterales de dosis unitaria se pueden envasar en una ampolla, un vial o una jeringa con una aguja. Todas las preparaciones para la administración parenteral deberían ser estériles, como es sabido y practicado en el arte.

Los inyectables se pueden diseñar para administración local y sistémica. Normalmente una dosis terapéuticamente efectiva se formula para contener una concentración de al menos aproximadamente 0.1% p/p hasta aproximadamente 90% p/p o más, con preferencia más de 1% de p/p del inhibidor de cMET a los tejidos tratados. El inhibidor se puede administrar de una vez, o se puede dividir en numerosas dosis más pequeñas administradas a intervalos de tiempo. Se considera que la dosis exacta y la duración del tratamiento será una función de la localización de donde la composición se administra por vía parenteral, el portador y otras variables que se pueden determinar empíricamente usando protocolos de ensayo conocidos o por extrapolación de los datos de ensayo in vivo o in vitro. Cabe mencionar que los valores de concentraciones y dosis también pueden variar con la edad del individuo tratado. También se considera que para un sujeto particular, los regímenes de dosis específicos pueden necesitar ajustarse respecto del tiempo de acuerdo con la necesidad individual y el criterio profesional de la persona que administra o supervisa la administración de las formulaciones. En consecuencia, los rangos de concentración expuestos en la presente son ejemplares y no están destinados a limitar el alcance o práctica de las formulaciones reivindicadas

El inhibidor de cMET opcionalmente se puede suspender en forma micronizada u otra forma adecuada o se puede derivar para producir un producto activo más soluble o producir un profármaco. La forma de la mezcla resultante depende de diversos factores, que incluyen el modo de administración deseado y la solubilidad del compuesto en el portador o vehículo seleccionado. La concentración efectiva es suficiente para mejorar los síntomas del estado de enfermedad y se puede determinar empíricamente.

Polvos Liofilizados

Los compuestos de la presente invención también se pueden preparar como polvos liofilizados, que se pueden reconstituir para la administración como soluciones, emulsiones y otras mezclas. Los polvos liofilizados también se pueden formular como sólidos o geles.

El polvo liofilizado estéril se puede preparar por la disolución del compuesto en un amortiguador de fosfato de sodio que contiene dextrosa u otro excipiente adecuado. La filtración estéril posterior de la solución seguido por la liofilización en condiciones estándares conocidos por los expertos en el arte proporciona la formulación deseada. En breves palabras, el polvo liofilizado opcionalmente se puede preparar por la disolución de 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 amortiguador adecuado, tal como citrato de sodio o fosfato de potasio u otro amortiguador conocido por los expertos en el arte, normalmente pH aproximadamente neutro. Luego, se agrega un inhibidor de cMET a la mezcla resultante, con preferencia por encima de la temperatura ambiente, con más preferencia a aproximadamente 30–35 °C, y se agita hasta disolverlo. La mezcla resultante se diluye por el agregado de más amortiguador a una concentración deseada. La mezcla resultante se filtra en forma estéril o se trata para eliminar los particulados y para asegurar la esterilidad, y repartieron en viales para la liofilización. Cada vial puede contener una dosis única o dosis múltiples del inhibidor.

Administración Tópica

Los compuestos de la presente invención también se pueden administrar como

000384

mezclas tópicas. Las mezclas tópicas se pueden usar para la administración local y sistémica. La mezcla resultante puede ser una solución, suspensión, emulsiones o similares y se formulan como cremas, geles, ungüentos, emulsiones, soluciones, elíxires, lociones, suspensiones, tinturas, pastas, espumas, aerosoles, irrigaciones, spray, supositorios, vendajes, parches dérmicos o cualquier otra de las formulaciones adecuadas para administración tópica.

Los inhibidores de cMET se pueden formular como aerosoles para aplicación tópica, tal como por inhalación (ver, Patentes U.S. Nos. 4.044.126, 4.414.209, y 4.364.923, que describe aerosoles para administración de un estereoide útil para el tratamiento de enfermedades inflamatorias, en particular asma). Estas formulaciones para la administración al aparato respiratorio pueden estar en forma de un aerosol o solución para un nebulizador, o como un polvo microfino para la insuflación, solo o en combinación con un portador inerte tal como lactosa. En tal caso, las partículas de la formulación normalmente tendrán diámetros de menos de 50 micrones, con preferencia menos de 10 micrones.

Los inhibidores también se pueden formular para la aplicación local o tópica, tal como para aplicación tópica en la piel y membranas mucosas, tales como en el ojo, en forma de geles, cremas y lociones y para aplicación ocular o para aplicación intracisternal o intraespinal. La administración tópica está contemplada para la administración transdérmica y también para administración en los ojos o mucosa, o para terapias de inhalación. También se pueden administrar soluciones nasales del inhibidor de cMET solo o en combinación con otros excipientes farmacéuticamente aceptables.

Formulaciones Para Otras Vías de Administración

De acuerdo con el estado de enfermedad que se trata, también se pueden usar otras vías de administración, tales como aplicación tópica, parches transdérmicos y administración rectal. Por ejemplo, las formas de dosificación farmacéuticas para administración rectal son supositorios rectales, cápsulas y comprimidos para el efecto sistémico. Los supositorios rectales usados en la presente significan cuerpos sólidos para la inserción en el recto que funde o se ablanda a temperatura corporal liberando uno o más ingredientes farmacológicamente o terapéuticamente activos. Las sustancias farmacéuticamente aceptables utilizadas en supositorios

rectales son bases o vehículos y agentes para elevar el punto de fusión. Los ejemplos de bases incluyen manteca de cacao (aceite de teobroma), glicerina–gelatina, carbowax, (polioxietilenglicol) y mezclas apropiadas de mono, di y triglicéridos de ácidos grasos. Se pueden usar combinaciones de diversas bases. Los agentes para elevar el punto de fusión de los supositorios incluyen esperma y cera. Los supositorios rectales se pueden preparar por el método de compresión o por moldeado. El peso típico de un supositorio rectal es aproximadamente 2 a 3 gm. Los comprimidos y cápsulas para la administración rectal se pueden fabricar usando la misma sustancia farmacéuticamente aceptable y por los mismos métodos para las formulaciones para administración oral.

Ejemplos de Formulaciones

Los siguientes son ejemplos particulares de formulaciones orales, intravenosas y de comprimido que se pueden usar opcionalmente con los compuestos de la presente invención. Se indica que estas formulaciones pueden variar de acuerdo con el compuesto particular usado y la indicación para la que se va a usar la formulación.

FORMULACIÓN ORAL

Compuesto de la presente invención	10–100 mg
Ácido cítrico monohidrato	105 mg
Hidróxido de sodio	18 mg
Saborizante	
Agua	c.s. a 100 ml

FORMULACIÓN INTRAVENOSA

Compuesto de la presente invención	0.1–10 mg
Monohidrato de dextrosa	c.s. para hacer isotónica
Monohidrato de ácido cítrico	1.05 mg
Hidróxido de sodio	0.18 mg
Agua para inyección	c.s. a 1.0 ml

000386

FORMULACIÓN DE COMPRIMIDO

Compuesto de la presente invención	1%
Celulosa microcristalina	73%
Ácido esteárico	25%
Sílice coloidal	1%.

Kits Que Comprenden Inhibidores de cMET

La invención también se refiere a kits y otros artículos de manufactura para tratar enfermedades asociadas con cMET. Se indica que las enfermedades están destinadas a cubrir todas las patologías en las que el cMET posee actividad que contribuye a la patología y/o sintomatología de la condición.

En una modalidad, se proporciona un kit que comprende una composición que comprende al menos un inhibidor de la presente invención en combinación con las instrucciones. Las instrucciones pueden indicar el estado de enfermedad para el que se administra la composición, información de almacenamiento del compuesto, información de dosis y/o instrucciones respecto de cómo administrar la composición. El kit también puede comprender materiales de envase. El material de envase puede comprender un recipiente para contener la composición. El kit opcionalmente también puede comprender componentes adicionales, tales como jeringas para la administración de la composición. El kit puede comprender la composición en formas de dosificación únicas o múltiples.

En otra modalidad, se proporciona un artículo de manufactura que comprende una composición que comprende al menos un inhibidor de la presente invención en combinación con materiales de envase. El material de envase puede comprender un recipiente para contener la composición. El recipiente puede comprender opcionalmente una etiqueta que indica el estado de enfermedad para el que se administra la composición, información de almacenamiento del compuesto, información de dosis y/o instrucciones respecto de cómo administrar la composición. El kit opcionalmente también puede comprender componentes adicionales, tales como jeringas para la administración de la composición. El kit puede comprender la composición en formas de dosificación únicas o múltiples.

Se indica que el material de envase usado en los kits y artículos de manufactura de acuerdo con la presente invención puede formar una pluralidad de recipientes

000387

divididos tales como un frasco dividido o un paquete de hojas divididas. El recipiente puede estar en cualquier forma o configuración convencional conocida en el arte que se obtiene de un material farmacéuticamente aceptable material, por ejemplo, una caja de papel o cartón, un frasco o botella de vidrio o plástico, una bolsa resellable (por ejemplo, para contener un "recarga" de comprimidos para colocación en un diferente recipiente), o un envase blister con dosis individual para presionar fuera del paquete de acuerdo con un esquema terapéutico. El recipiente que se emplea dependerá de la forma de dosificación exacta involucrada, por ejemplo no se debería usar una caja de cartón convencional para contener una suspensión líquida. Es factible usar más de un recipiente en conjunto en un paquete único para comercializar una forma de dosificación única. Por ejemplo, los comprimidos pueden estar contenidos en un frasco que está a su vez contenido en una caja. Normalmente el kit incluye directivas para la administración de los componentes separados. La forma del kit es particularmente ventajosa cuando los componentes separados se administran con preferencia en formas de dosificación diferentes (*por ejemplo*, oral, tópica, transdérmica y parenteral), se administran en intervalos de dosis diferentes, o cuando la titulación de los componentes individuales de la combinación es la deseada por la prescripción del médico.

Un ejemplo particular de un kit de acuerdo con la presente invención es el llamado envase blister. Los envases blister son bien conocidos en la industria del envasado y son ampliamente usados para el envasado de formas de dosificación unitarias farmacéuticas (comprimidos, cápsulas y similares). Los envases blister generalmente consisten en una lámina de material relativamente rígido cubierto por una hoja con preferencia de un material plástico transparente. Durante el proceso de envasado se forman cavidades en la hoja de plástico. Las cavidades tienen el tamaño y forma de los comprimidos o las cápsulas individuales que se van a envasar o puede tener el tamaño y la forma para acomodar múltiples comprimidos y/o cápsulas por envasar. Después, los comprimidos o las cápsulas se colocan en las cavidades y la lámina de material relativamente rígido se sella contra la hoja de plástico en la cara de la hoja que está opuesto a la dirección en que se formaron las cavidades. Como resultado, los comprimidos o las cápsulas se sellan individualmente i se sellan colectivamente, según se desee en las cavidades entre la hoja de plástico y la lámina. Con preferencia, la resistencia de

la lámina es tal que los comprimidos o las cápsulas se pueden extrae del envase blister por la aplicación manual de presión en las cavidades por la cual se forma una abertura en la lámina en el lugar de las cavidades. Los comprimidos o las cápsulas luego se pueden extraer por medio de dicha abertura.

Otra modalidad específica de un kit es un dispensador diseñado para dispensar dosis diarias una por una en el orden de su uso previsto. Con preferencia, el dispensador está equipado con un ayuda memoria, de modo de facilitar el cumplimiento con el régimen. Un ejemplo de dicho ayuda memoria es un contado mecánico que indica el número de dosis diarias que se han dispensado. Otro ejemplo de dicho ayuda memoria es una memoria de microchip que funciona con batería acoplado con una lectura de cristal líquido, o una señal de recuerdo audible que, por ejemplo, lee la fecha en que se tomó la última dosis diaria y/o recuerda a uno cuando se debe tomar la próxima dosis.

Dosis, Huésped y Seguridad

Los compuestos de la presente invención son estables y se pueden usar con seguridad. En particular, los compuestos de la presente invención son útiles como inhibidores de cMET para una variedad de sujetos (*por ejemplo*, humanos, mamíferos no humanos y no mamíferos). La dosis óptima puede variar de acuerdo con dichas condiciones como, por ejemplo, el tipo de sujeto, el peso corporal del sujeto, la vía de administración, y las propiedades específicas del compuesto particular usado. 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 1 a 200 mg. Se apreciará que la dosis diaria se puede dar en una administración única o en múltiples porciones al día (*por ejemplo*, 2 o 3).

Terapias de Combinación

Una amplia variedad de agentes terapéuticos puede tener un efecto aditivo o sinérgico terapéutico con los inhibidores de la presente invención. Las terapias de combinación que comprenden uno o más compuestos de la presente invención con uno o más agentes terapéuticos se pueden usar, por ejemplo, para: 1) potenciar el efecto terapéutico de uno o más compuestos de la presente invención

y/o uno o más agentes terapéuticos diferentes; 2) reducir los efectos secundarios exhibidos por uno o más compuestos de la presente invención y/o uno o más agentes terapéuticos diferentes; y/o 3) reducir la dosis efectiva de uno o más compuestos de la presente invención y/o uno o más agentes terapéuticos diferentes. Por ejemplo, dichos agentes terapéuticos pueden combinar en forma aditiva o sinérgica con los inhibidores de la presente invención para inhibir el crecimiento celular no deseable, tales como crecimiento celular inapropiado que producen patologías benignas no deseables o crecimiento tumoral.

En una modalidad, se proporciona un método para tratar un estado de enfermedad proliferativa celular que comprende tratar células con un compuesto de acuerdo con la presente invención en combinación con un agente antiproliferativo, en donde las células se tratan con el compuesto de acuerdo con la presente invención antes, al mismo tiempo y/o después de tratar las células con un agente antiproliferativo, mencionado en la presente como terapia de combinación. Se indica que el tratamiento de un agente antes de otro se denomina en la presente como terapia secuencial, incluso si los agentes también se administran juntos. Se indica que terapia de combinación tiene por objeto cubrir cuando los agentes se administran antes o después del otro (terapia secuencial) así como cuando los agentes se administran al mismo tiempo.

Los ejemplos de agentes terapéuticos que se pueden usar en combinación con los inhibidores de la presente invención incluyen, pero sin limitación, agentes anticáncer, agentes alquilantes, agentes antibióticos, agentes antimetabólicos, agentes hormonales, agentes derivados de plantas, y agentes biológicos.

Los agentes alquilantes son compuestos polifuncionales que tienen la capacidad de sustituir grupos alquilo con iones hidrógeno. Los ejemplos de agentes alquilantes incluyen, pero sin limitación, biscloroetilaminas (mostazas nitrogenadas, por ejemplo clorambucilo, ciclofosfamida, ifosfamida, mecloretamina, melfalan, mostaza de uracilo), aziridinas (por ejemplo tiotepa), sulfonato de alquil alcona (por ejemplo busulfan), nitrosoureas (por ejemplo carmustina, lomustina, estreptozocina), agentes alquilantes no clásicos (altretamina, dacarbazina y procarbazina), compuesto de platino (carboplatino y cisplatino). Estos compuestos reaccionan con grupos fosfato, amino, hidroxilo, sulfhidrilo, carboxilo, e imidazol. En condiciones fisiológicas, estos fármacos se

ionizan y producen iones cargados positivamente que se unen a ácidos nucleicos y proteínas sensibles, que llevan a la detención del ciclo celular y/o muerte celular. La terapia de combinación que incluye un inhibidor de la presente invención y un agente alquilante puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos quimioagentes terapéuticos.

Los agentes antibióticos son un grupo de fármacos que se producen de manera similar a los antibióticos como una modificación de los productos naturales. Los ejemplos de agentes antibióticos incluyen, pero sin limitación, antraciclinas (por ejemplo doxorrubicina, daunorrubicina, epirrubicina, idarrubicina y antracenediona), mitomicina C, bleomicina, dactinomicina, plicatomicina. Estos agentes antibióticos interfieren en el crecimiento celular al dirigirse a diferentes componentes celulares Por ejemplo, en general se considera que las antraciclinas interfieren en la acción de ADN topoisomerasa II en las regiones del ADN transcripcionalmente activo, que produce las escisiones de la cadena de ADN. En general se considera que bleomicina quela al hierro y forma un complejo activado, que luego se une a las bases de ADN, lo que causa escisiones de cadena y muerte celular. La terapia de combinación que incluye un inhibidor de la presente invención y un agente antibiótico puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos quimioagentes terapéuticos.

Los agentes antimetabólicos son un grupo de fármacos que interfieren en procesos metabólicos vitales para la fisiología y proliferación de las células cancerosas. Las células cancerosas con proliferación activa requieren síntesis continua de grandes cantidades de ácidos nucleicos, proteínas, lípidos y otros constituyentes vitales. Muchos de los antimetabolitos inhiben la síntesis de nucleótidos de purina o pirimidina o inhiben las enzimas de la replicación del ADN. Algunos antimetabolitos también interfieren en la síntesis de ribonucleótidos y ARN y/o también en metabolismo de aminoácidos y síntesis de proteínas. Al interferir en la síntesis de constituyentes celulares vitales, los antimetabolitos pueden retrasar o detener el crecimiento de las células cancerosas. Los ejemplos de agentes antimetabólicos incluyen, pero sin limitación, fluorouracilo (5–FU), floxuridina (5–FUdR), metotrexato, leucovorina, hidroxiurea, tioguanina (6–TG), mercaptopurina (6–MP), citarabina, pentostatina, fosfato de fludarabina, cladribina

000391

(2–CDA), asparaginasa, y gemcitabina. La terapia de combinación que incluye un inhibidor de la presente invención y un agente antimetabólico puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos quimioagentes terapéuticos.

Los agentes hormonales son un grupo de fármacos que regulan el crecimiento y desarrollo de sus órganos objetivo. La mayoría de los agentes hormonales son estereoides sexuales y sus derivados y sus análogos, tales como estrógenos, andrógenos y progestinas. Estos agentes hormonales pueden actuar como antagonistas de los receptores para los estereoides sexuales para regular por disminución la expresión del receptor y la transcripción de los genes vitales. Los ejemplos de dichos agentes hormonales son estrógenos sintéticos (por ejemplo dietilstibestrol), antiestrógenos (por ejemplo tamoxifeno, toremifeno, fluoximesterol y raloxifeno), antiandrógenos (bicalutamida, nilutamida y flutamida), inhibidores de aromatasa (por ejemplo, aminoglutetimida, anastrozol y tetrazol), ketoconazol, acetato de goserelina, leuprolida, acetato de megestrol y mifepristona. La terapia de combinación que incluye un inhibidor de la presente invención y un agente hormonal puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos quimioagentes terapéuticos.

Los agentes derivados de plantas son un grupo de fármacos que derivan de plantas o modificados sobre la base de la estructura molecular de los agentes. Los ejemplos de agentes derivados de plantas incluyen, pero sin limitación, alcaloides de vinca (por ejemplo, vincristina, vinblastina, vindesina, vinzolidina y vinorelbina), podofilotoxinas (por ejemplo, etopósido (VP–16) y tenipósido (VM–26)), y taxanos (por ejemplo, paclitaxel y docetaxel). Estos agentes derivados de plantas generalmente actúan como agentes antimitóticos que se unen a la tubulina e inhiben la mitosis. Se cree que las podofilotoxinas tales como etopósido interfieren en la síntesis de ADN por la interacción con topoisomerasa II, lo que lleva a la escisión de la cadena de ADN. La terapia de combinación que incluye un inhibidor de la presente invención y un agente derivado de planta puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos quimioagentes terapéuticos.

Los agentes biológicos son un grupo de biomoléculas que estimulan la regresión del cáncer/tumor cuando se usa solo o en combinación con quimioterapia y/o

radioterapia. Los ejemplos de agentes biológicos incluyen, pero sin limitación, proteínas inmunomoduladoras tales como citoquinas, anticuerpos monoclonales contra antígenos tumorales, genes supresores de tumores y vacunas del cáncer. La terapia de combinación que incluye un inhibidor de la presente invención y un agente biológico puede tener efectos sinérgicos terapéuticos sobre el cáncer, aumentar las respuestas inmunes del paciente a las señales tumorigénicas y reducir los potenciales efectos secundarios asociados este agente quimioterapéutico.

Las citoquinas poseen profunda actividad inmunomoduladora. Algunas citoquinas tales como interleucina–2 (IL–2, aldesleucina) e interferón han demostrado actividad antitumoral y han sido aprobadas para el tratamiento de pacientes con carcinoma de células renales metastático y melanoma maligno metastático. IL–2 es un factor de crecimiento de células T que es central para las respuestas inmunes mediadas por células T. Se considera que los efectos antitumorales selectivos de IL–2 en algunos pacientes son el resultado de una respuesta inmune mediada por célula que discrimina entre propias y no propias. Los ejemplos de interleucinas que se pueden usar en conjunto con los inhibidores de la presente invención incluyen, pero sin limitación, interleucina 2 (IL–2), y interleucina 4 (IL–4), interleucina 12 (IL–12).

Los interferones incluyen más de 23 subtipos relacionados con actividades superpuestas, todos los subtipos de IFN están dentro del alcance de la presente invención. IFN ha demostrado actividad contra muchas neoplasias sólidas y hematológicas, está última parece ser particularmente sensibles.

Otras citoquinas que se pueden usar en conjunto con los inhibidores de la presente invención incluyen las citoquinas que ejercen efectos profundos sobre la hematopoyesis y funciones inmunes. Los ejemplos de dichas citoquinas incluyen, pero sin limitación eritropoyetina, granulocito–CSF (filgrastina), y granulocito, macrófago–CSF (sargramostim). Estas citoquinas se pueden usar en conjunto con un inhibidor de la presente invención para reducir la toxicidad mielopoyética inducida por la quimioterapia.

También se pueden usar otros agentes inmunomoduladores diferentes de las citoquinas en conjunto con los inhibidores de la presente invención para inhibir el crecimiento celular anormal. Los ejemplos de dichos agentes inmunomoduladores

000393

incluyen, pero sin limitación bacilos Calmette–Guerin, levamisol y octreotide, un octapéptido de acción prolongada que simula los efectos de la somatostatina hormonal natural.

Los anticuerpos monoclonales contra antígenos tumorales son anticuerpos estimulados contra los antígenos expresados por los tumores, con preferencia antígenos específicos del tumor. Por ejemplo, el anticuerpo monoclonal HERCEPTIN® (Trastruzumab) se origina contra el receptor 2 del factor de crecimiento epidérmico humano (HER2) que se sobreexpresa en algunos tumores mamarios que incluyen cáncer de mama metastático. La sobreexpresión de la proteína de HER2 se asocia con la enfermedad más agresiva y el peor pronóstico en la clínica. HERCEPTIN® se usa como un agente único para el tratamiento de pacientes con cáncer de mama metastático cuyos tumores sobreexpresan la proteína de HER2. La terapia de combinación que incluye un inhibidor de la presente invención y HERCEPTIN® puede tener efectos sinérgicos terapéuticos en tumores, en especial en los cánceres metastáticos.

Otro ejemplo de anticuerpos monoclonales contra antígenos tumorales es RITUXAN® (Rituximab) que se origina contra CD20 de las células del linfoma y reduce selectivamente las células $CD20^+$ pre–B y B maduras normales y malignas. RITUXAN® se usa como agente único para el tratamiento de pacientes con recaídas o grado refractario bajo o folicular, CD20+, linfoma de células B no Hodgkin. La terapia de combinación que incluye un inhibidor de la presente invención y RITUXAN® puede tener efectos sinérgicos terapéuticos no solo en el linfoma sino también en otras formas y tipos de tumores malignos.

Los genes supresores de tumor son genes que actúan para inhibir los ciclos de crecimiento y división celular, por ende se impide el desarrollo de la neoplasia. Las mutaciones de los genes supresores de tumor causan que la célula ignore uno o más de los componentes de la red de señales inhibidoras, que superan los puntos de revisión del ciclo celular y dan como resultado una mayor tasa de crecimiento celular—cáncer controlado. Los ejemplos de los genes supresores de tumor incluyen, pero sin limitación, DPC–4, NF–1, NF–2, RB, p53, WT1, BRCA1, y BRCA2.

DPC–4 está involucrado en el cáncer pancreático y participa en la vía citoplásmica que inhibe la división celular. NF–1 codifica una proteína que inhibe Ras, una

proteína inhibidora citoplasmica. NF–1 está involucrado en neurofibroma y feocromocitomas del sistema nervioso y leucemia mieloide. NF–2 codifica una proteína nuclear que está involucrada en el meningioma, schwanoma, y ependimoma del sistema nervioso. RB codifica la proteína de pRB, una proteína nuclear que es un importante inhibidor del ciclo celular. RB está involucrado en el retinoblastoma así como cáncer de hueso, vejiga, pulmones de células pequeñas y de mama. P53 codifica la proteína p53 que regula la división celular y puede inducir apoptosis. La mutación y/o inacción de p53 se halla en una amplia variedad de cánceres. WT1 está involucrado en el tumor de Wilms de los riñones. BRCA1 está involucrado en cáncer de mamas y ovario, y BRCA2 está involucrado en cáncer de mama. El gen supresor de tumor se puede transferir a las células tumorales donde ejerce sus funciones de supresión de tumor. La terapia de combinación que incluye un inhibidor de la presente invención y un supresor de tumor puede tener efectos sinérgicos terapéuticos en los pacientes que sufren de varias formas de cánceres.

Las vacunas del cáncer son un grupo de agentes que inducen la respuesta inmune específica del cuerpo a los tumores. La mayoría de las vacunas del cáncer bajo investigación y desarrollo son antígenos asociados a tumores (TAA). Los TAA son estructuras (es decir proteínas, enzimas o carbohidratos) que están presentes en las células tumorales y relativamente ausentes o disminuidas en las células normales. En virtud de ser relativamente únicas para la célula tumoral, los TAA proporcionan objetivos para que el sistema inmune los reconozca y cause su destrucción. Los ejemplos de TAA incluyen, pero sin limitación gangliósidos (GM2), antígeno específico de próstata (PSA), alfa–fetoproteína (AFP), antígeno carcinoembrionaria (CEA) (producido por cánceres de colon y otros adenocarcinomas, por ejemplo cáncer de mamas, pulmón, gástrico, y páncreas), antígenos asociados al melanoma (MART–1, gp100, MAGE 1,3 tirosinasa), fragmentos de papillomavirus E6 y E7, células enteras o porciones/lisados de células tumorales autólogas y células tumorales alogeneicas.

Se puede usar un adyuvante para aumentar la respuesta inmune a los TAA. Los ejemplos de adyuvantes incluyen, pero sin limitación, bacilo Calmette–Guerin (BCG), lipopolisacáridos de endotoxina, hemocianina de lapa (GKLH), interleucina–2 (IL–2), factor estimulante de colonia de granulocitos–macrófagos

(GM–CSF) y citoxano, un agente quimioterapéutico que se considera que reduce la supresión inducida por el tumor cuando se administra en dosis bajas.

EJEMPLOS

Preparación de Inhibidores de cMET

Se pueden usar varios métodos para sintetizar los compuestos de acuerdo con la presente invención. Los métodos representativos para sintetizar estos compuestos se proporcionan en los Ejemplos. Cabe mencionar, sin embargo, que los compuestos de la presente invención también se pueden sintetizar por otras vías de síntesis que otros puedan diseñar.

Se reconocerá con facilidad que ciertos compuestos de acuerdo con la presente invención tienen átomos con ligaduras a otros átomos que confieren una particular estereoquímica al compuesto (*por ejemplo*, centros quirales). Se reconoce que la síntesis de los compuestos de acuerdo con la presente invención puede originar la creación de mezclas de diferentes estereoisómeros (*es decir*, enantiómeros y diasterómeros). A menos que se especifique una estereoquímica particular, se considera que la mención de compuesto abarca todos los diferentes estereoisómeros posibles.

Varios métodos para separar mezclas de diferentes estereoisómeros son conocidos en el arte. Por ejemplo, una mezcla racémica de un compuesto puede reaccionar con un agente de resolución óptimamente activo para formar un par de compuestos diasteroisoméricos. Los diasterómeros luego se pueden separar a fin de recuperar los enantiómeros óptimamente puros. Los complejos disociables también se pueden usar para resolver enantiómeros (*por ejemplo*, sales diasteroisoméricas cristalinas). Los diasterómeros normalmente tienen propiedades físicas suficientemente diferentes (*por ejemplo*, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.) y se pueden separar fácilmente aprovechando la ventaja de esta clase de desigualdades. Por ejemplo, los diasterómeros se pueden separar normalmente por cromatografía o por técnicas de separación/resolución basadas en las diferencias de solubilidad. Una descripción más detallada de las técnicas que se pueden usar para resolver estereoisómeros de compuestos a partir de su mezcal racémica se pueden hallar en Jean Jacques Andre Collet, Samuel H. Wilen, Enantioners, Racemates y

Resolutions, John Wiley & Sons, Inc. (1981).

Los compuestos de acuerdo con la presente invención también se pueden preparar como una sal de adición de ácido farmacéuticamente aceptable por la reacción de la forma de base libre del compuesto con un ácido inorgánico u orgánico farmacéuticamente aceptable. De modo alternativo, una sal de adición de base farmacéuticamente aceptable de un compuesto se puede preparar por la reacción de la forma de ácido libre del compuesto con una base inorgánica u orgánica farmacéuticamente aceptable. Los ácidos y bases inorgánicos y orgánicos adecuados para la preparación de sales farmacéuticamente aceptable de los compuestos se exponen en la sección de definiciones de esta solicitud. De modo alternativo, las formas de sal de los compuestos se pueden preparar usando sales de los materiales de partida o intermediarios.

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 se puede convertir en la base libre correspondiente por el tratamiento con una base adecuada (*por ejemplo*, solución de hidróxido de amonio, hidróxido de sodio, y similares). Un compuesto en una forma de sal de adición de base se puede convertir en el correspondiente ácido libre por el tratamiento con un ácido adecuado (*por ejemplo*, ácido clorhídrico, etc.).

Los N–óxidos de los compuestos de acuerdo con la presente invención se pueden preparar por métodos conocidos por los expertos en el arte. Por ejemplo, los N–óxidos se pueden preparar por tratamiento de una forma no oxidada del compuesto con un agente oxidante (*por ejemplo*, ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido meta–cloroperoxibenzoico o similares) en un solvente orgánico inerte adecuado (*por ejemplo*, un hidrocarburo halogenado tal como diclorometano) a aproximadamente 0 °C. De modo alternativo, los N–óxidos de los compuestos se pueden preparar a partir del N–óxido de un material inicial apropiado.

Los compuestos en forma no oxidada se pueden preparar a partir de N–óxidos de los compuestos por tratamiento con un agente reductor (*por ejemplo*, azufre, dióxido de azufre, trifenil fosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fósforo, tribromuro o similares) en un solvente orgánico inerte

000397

adecuado (*por ejemplo*, acetonitrilo, etanol, dioxano acuoso, o similares) a 0 ato 80 °C.

Los derivados del profármaco de los compuestos se pueden preparar por métodos conocidos por los expertos en el arte (*por ejemplo*, para mayores detalles ver Saulnier et al.(1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). Por ejemplo, los profármacos apropiados se pueden preparar por la reacción de un compuesto no derivatizado con un agente carbamilante adecuado (*por ejemplo*, 1,1–aciloxialquilcarbonocloridato, carbonato de para–nitrofenilo, o similares).

Los derivados protegidos de los compuestos se pueden obtener por métodos conocidos por los expertos en el arte. Una descripción detallada de las técnicas aplicables a la creación de grupos protectores y su eliminación se puede hallar en T.W. Greene, Protecting Groups in Organic Synthesis, 3rd edición, John Wiley & Sons, Inc. 1999.

Los compuestos de acuerdo con la presente invención se pueden preparar de modo conveniente, o formar durante el proceso de la invención, como solvatos (*por ejemplo*, hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar de modo conveniente por recristalización en una mezcla de solvente acuoso/orgánico, mediante solventes orgánicos tales como dioxina, tetrahidrofurano o metanol.

Los compuestos de acuerdo con la presente invención también se pueden preparar como sus estereoisómeros individuales por la reacción de una mezcla racémica del compuesto con un agente de resolución óptimamente activo para formar un par de compuestos diasteroisoméricos, separar los diasterómeros y recuperar el enantiómero ópticamente puro. Si bien la resolución de enantiómeros se puede llevar a cabo usando derivados diastereoméricos covalentes de los compuestos, se prefieren los complejos disociables (*por ejemplo*, sales diastereoisoméricas cristalinas). Los diasterómeros tienen propiedades físicas distintas (*por ejemplo*, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.) y se pueden separar fácilmente aprovechando estas desigualdades. Los diasterómeros se pueden separar por cromatografía o, con preferencia, por técnicas de separación/resolución sobre la base de las diferencias de solubilidad. El enantiómero ópticamente puro luego se recupera, junto con el agente de resolución, por cualquier práctica significa que no debería producir

racemización. Una descripción más detallada de las técnicas aplicable a la resolución de 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).

Como se usa en la presente los símbolos y convenciones usados en estos procesos, esquemas de reacción y ejemplos son compatibles con los usados en la bibliografía científica contemporánea, por ejemplo, el Journal of the American Chemical Society o el Journal of Biological Chemistry. Las abreviaturas de una letra o tres letras estándares generalmente se usan para diseñar residuos de aminoácidos, que se asumen en la configuración L a menos que se indique de otro modo. A menos que se indique de otro modo, todos los materiales iniciales se obtuvieron de proveedores comerciales y se usaron sin purificación posterior.

Todas las referencias a éter o Et_2O son a éter dietílico; y salmuera se refiere a una solución acuosa saturada de NaCl. A menos que se indique de otro modo, todas las temperaturas se expresan en °C (grados centígrados). Todas las reacciones se realizan en una atmósfera inerte a RT a menos que se indique de otro modo

Se registraron los espectros ^1H NMR en un Bruker Avance 400. Los cambios químicos se expresan en partes por millón (ppm). Las constantes de acoplamiento están en unidades de Hertz (Hz). Los patrones de división describen multiplicidades evidentes y se denominan como s (singlete), d (doblete), t (triplete), q (cuarteto), m (multiplete), br (ancho).

Se obtuvieron espectros de masa de resolución baja (MS) y datos de pureza del compuesto en un sistema cuadripolar único Waters ZQ LC/MS equipado con fuente de ionización por electroaspersión (ESI), detector de UV (220 y 254 nm), y detector de dispersión de luz evaporativa (ELSD). La cromatografía en placa fina se realizó en placas de gel de sílice de 0.25 mm E. Merck (60F–254), se visualizó con luz UV, 5% de solución de ninhidrina o p–anisaldehído en ácido fosfomolíbdico etanólico. La cromatografía en columna flash se realizó en gel de sílice (230–400 mesh, Merck).

Los materiales iniciales y reactivos usados para preparar estos compuestos están disponibles en proveedores comerciales tales como Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), o se pueden preparar por métodos bien conocidos por los expertos en el arte, siguiendo los

procedimientos descritos en dichas referencias estándares como Fieser y Fieser's Reagents for Organic Synthesis, vols. 1–17, John Wiley and Sons, New York, NY, 1991; Rodd's Chemistry of Carbon Compound, vols. 1–5 y supps., Elsevier Science Publishers, 1989; Organic Reaccións, 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; y Larock: Comprehensive Organic Transformations, VCH Publishers, New York, 1989.

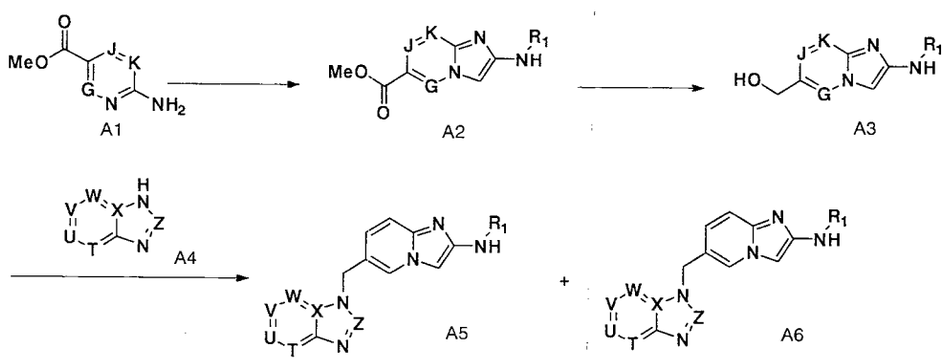
Las descripciones completas de todos los documentos mencionados a lo largo de esta solicitud se incorporan en la presente como referencia.

Esquemas de Síntesis para los Compuestos de la Presente Invención

Los compuestos de acuerdo con la presente invención se pueden sintetizar de acuerdo con los esquemas de reacción que se muestran a continuación. Otros esquemas de reacción podrían ser diseñados fácilmente por los expertos en el arte. También se debería apreciar que una variedad de solventes diferentes, temperaturas y otras condiciones de reacción se pueden variar para optimizar los rendimientos de las reacciones.

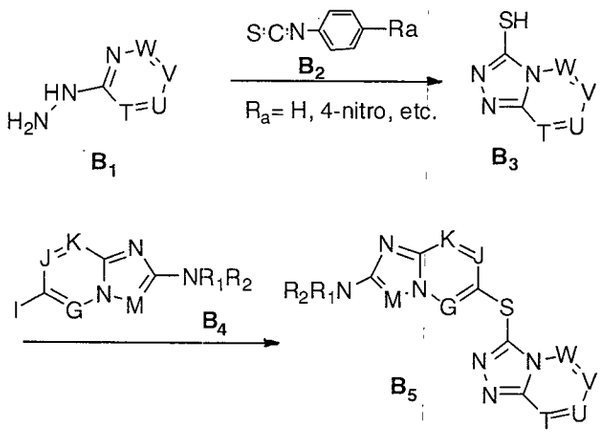
En las reacciones descritas de aquí en adelante puede ser necesario proteger grupos funcionales reactivos, por ejemplo grupos hidroxi, amino, imino, tio o carboxi, donde estos se desean en el producto final, para evitar su participación no deseada en las reacciones. Los grupos protectores convencionales se pueden usar 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.

Esquema de reacción A



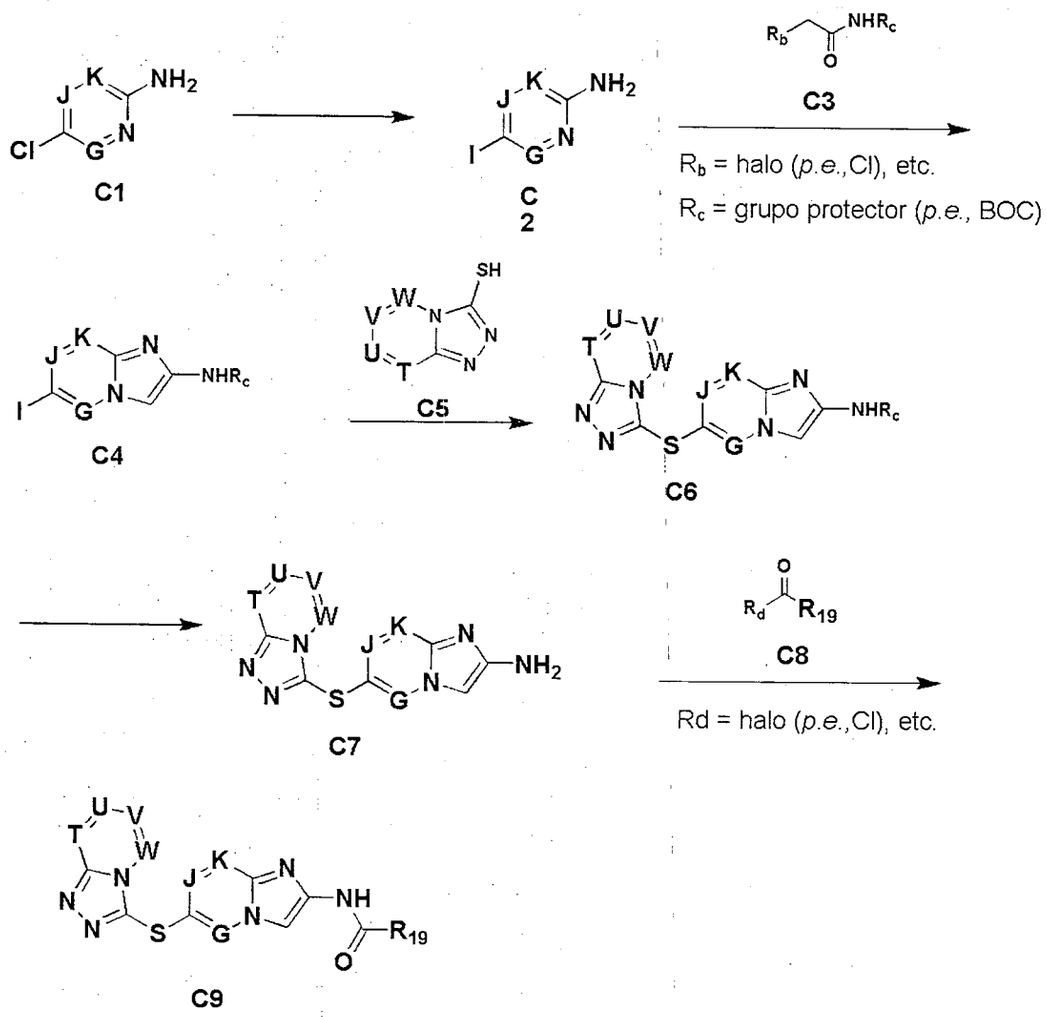
El compuesto **A2** se puede preparar a partir del compuesto **A1** en tres etapas siguiendo un método análogo al descrito en la Patente US No. 6.358.971, que se incorpora como referencia en la presente en su totalidad. La reducción del éster se puede lograr en presencia de un agente reductor tal como LAH o $NaBH_4$ en THF o dioxano a 0 – 80 °C durante 1 – 8 horas para proveer alcohol (A3). Se puede usar acoplamiento de Mitsunobu estándar de A3 y A4 en presencia de trifenilfosfina y un azodicarboxalato, tales como DEAD o DIAD, a 0 – 80 °C durante 1 – 24 horas para proveer los compuestos A5 y A6. Los compuestos **A5** y **A6** se pueden separar usando una variedad de técnicas conocidas en el arte que incluyen, por ejemplo, LCMS preparativa.

Esquema de reacción B



El compuesto **B1** se trata con el compuesto **B2** (*por ejemplo*, fenilisotiocianato o p–nitrofenilisotiocianato) en DME a 100 – 120 °C en un microondas durante 1 – 8 horas para proveer tiol (**B3**).Se puede usar acoplamiento mediado por paladio del compuesto **B3** y **B4** en DME con $Pd_2(dba)_3$ y 4,5–bis(fenilfosfino)–9,9–dimetilxanteno a 100 – 120 °C en un microondas durante 1 – 8 horas para proveer el compuesto **B5**.

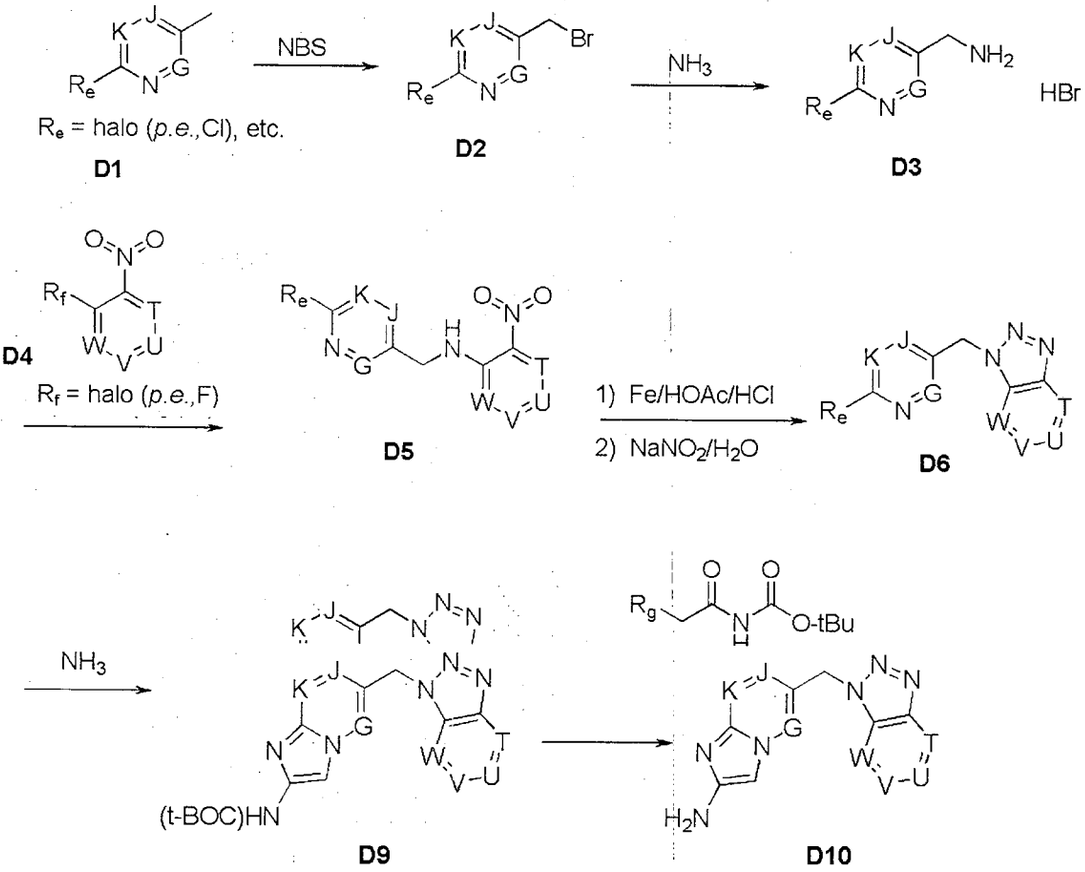
Esquema de reacción C



Se calienta anilina (**C1**) en HI a 100°C durante 18 horas para proveer el compuesto **C2**. La anilina (**C2**) se trata con acetamida (**C3**) y una base tal como fosfato hidrógeno de sodio en un solvente polar (por ejemplo, DMA, DMF o DMSO) y se calienta a 100 – 120 °C en un microondas durante 1 – 8 horas para proporcionar el producto ciclado **C4**. El acoplamiento mediado por paladio de **C4** y **C5** se puede lograr en DME con $Pd_2(dba)_3$ y 4,5–bis(fenilfosfino)–9,9–dimetilxanteno a 100 – 120 °C en un microondas durante 1 – 8 horas para proveer el compuesto **C6**. La eliminación del grupo R_c de **C6** se puede lograr en un solvente tal como THF o dioxano o un alcohol tal como MeOH, EtOH, o iPrOH en presencia de un ácido tal como HCl o TFA a 0 – 100 °C durante 1 – 24 horas para proveer el compuesto **C7**. El compuesto **C7** se trata con el cloruro de acilo

apropiado en un solvente (*por ejemplo*, DCM, THF, o $CHCl_3$) en presencia de una base (*por ejemplo*, TEA, DIEA, o piridina) a 0 – 80 °C durante 1 – 24 horas para proveer el compuesto **C9**.

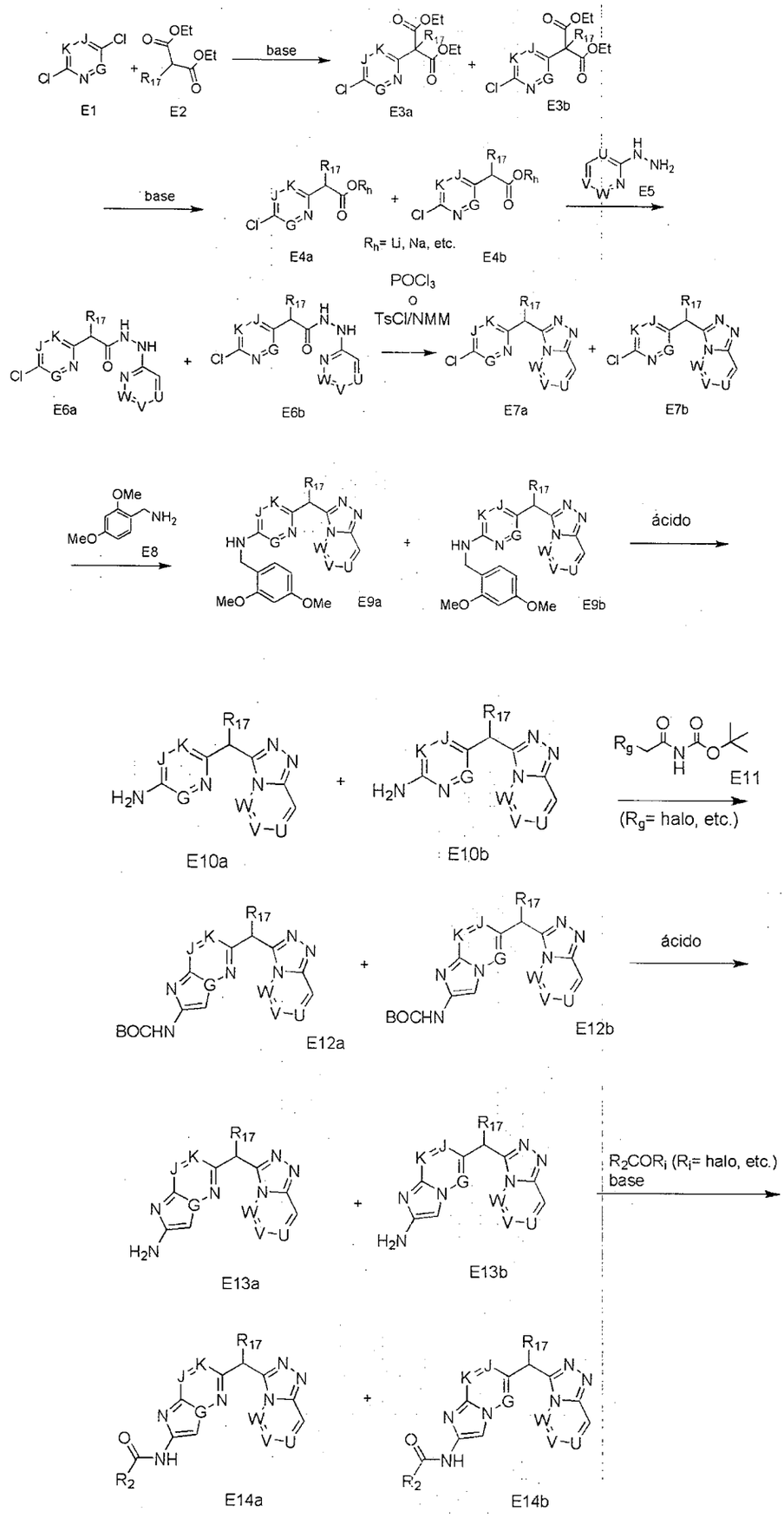
Esquema de reacción D



El compuesto **D1** se broma en condiciones estándares tales como NBS en presencia de un peróxido, AIBN, o 200 – 400 w de luz en CCl_4 a reflujo (*por ejemplo*, durante 1 – 8 horas). El desplazamiento del bromo (**D2**) con amoníaco en un solvente alcohólico (*por ejemplo*, MeOH, EtOH, o i–PrOH) a 0 – 80 °C durante 1 – 24 horas proporciona el compuesto **D3**. La reacción de sustitución con los compuestos **D3** y **D4** se logra en un solvente (*por ejemplo*, DMF, DMA, o EtOH) en presencia de una base (*por ejemplo*, TEA, DIEA, o piridina) a 0 – 80 °C durante 1 – 24 horas para proveer el arilnitro **D5**. La reducción del arilnitro (**D5**) se logra en condiciones estándares usando un catalizador de paladio tal como 10% Pd/C o metal (*por ejemplo*, Fe o Zn) en medio ácido. El cierre del anillo posterior de la anilina resultante al triazol se logra en presencia de $NaNO_2$ acuoso para proveer el

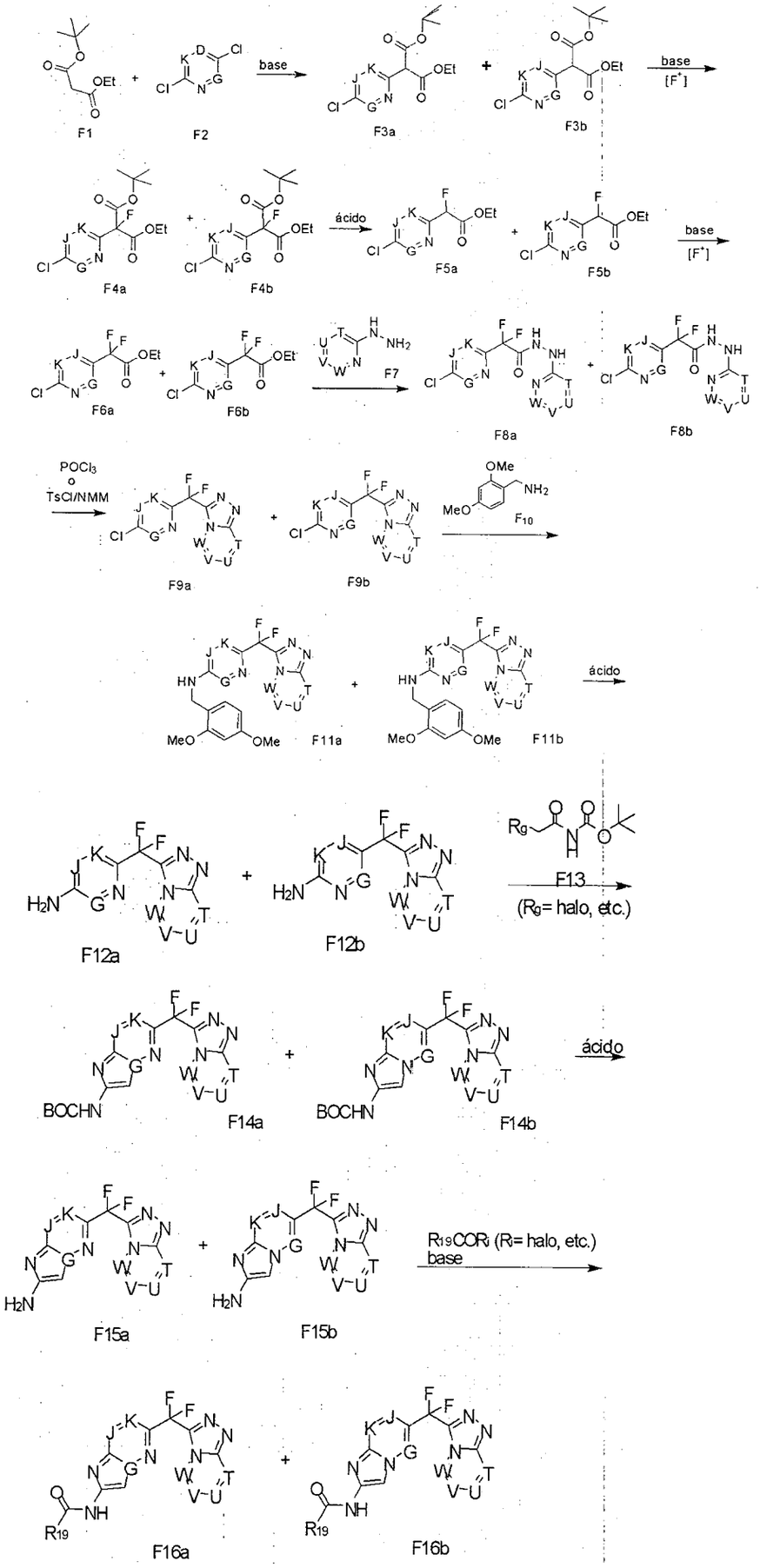
compuesto **D6**. El tratamiento del compuesto **D6** en solvente saturado con amoníaco (*por ejemplo*, EtOH o i–PrOH en un recipiente sellado) a 100 – 150 °C durante 1 – 4 días proporciona anilina **D7**. La anilina (**D7**) se trata con acetamida (**D8**) y una base tal como fosfato hidrógeno de sodio en un solvente polar (*por ejemplo*, DMA, DMF, o DMSO) y se calienta a 100 – 120 °C en un microondas durante 1 – 8 horas para proporcionar el producto ciclado **D9**. El tratamiento del compuesto **D9** con ácido (*por ejemplo*, HCl o TFA) proporciona el compuesto **D10**.

Esquema de reacción E



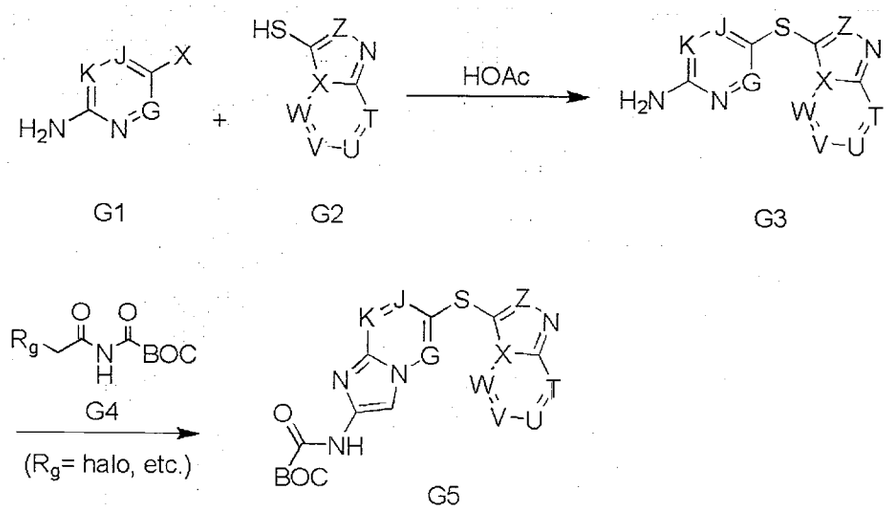
Los compuestos **E3a** y **E3b** se pueden preparar a partir de los compuestos **E1** y **E2** por el tratamiento del compuesto E2 con una base tal como NaH en un solvente tal como TF o dioxano a –78 – 0 °C y posterior tratamiento con el compuesto E1. Los compuestos **E3a** y **E3b** opcionalmente se separar antes del uso posterior. El tratamiento del compuesto E3a y/o E3b con una base tal como LiOH o NaOH a –20 – 75 °C durante 1 – 8 horas proporciona los compuestos E4a y/o E4b como sal de litio o sodio, respectivamente. El tratamiento de los compuestos E4a y/o E4b con el compuesto E5 en presencia de EDC o DCC durante 1 – 24 horas proporciona los compuestos E6a y/o E6b. El tratamiento de los compuestos E6a y/o E6b con $POCl_3$ a 80 – 160 °C proporciona los compuestos E7a y/o E7b. Alternativamente, los compuestos E7a y/o E7b se pueden preparar tratando los compuestos E6a y/o E6b con TsCl/N-metilmorfolina a temperatura ambiente a 100 °C por 30 min a 8 hrs. El acoplamiento del compuesto E8 y los compuestos E7a y/or E7b se logra en un solvente tal como TF, dioxano o DMF a 25 – 100 °C durante 2 – 24 horas en la presencia de una co–base tal como DIEA o Et_3N. La eliminación del grupo dimetoxi bencilo de los compuestos E9a y/o E9b se obtiene por el tratamiento de los compuestos E9a y/o E9b con un ácido tal como TFA a 25 – 75 °C durante 2 – 24 horas para proporcionar los compuestos E10a y/o E10b. El tratamiento de los compuestos E10a y/o E10b con el compuesto E11 en presencia de una base tal como Na_2HPO_4 en un solvente tal como DMA a 120 °C proporciona los compuestos E12a y/o E12b. El tratamiento de compuestos E12a y/o E12b con un ácido tal como TFA o HCl proporciona los compuestos E13a y/o E13b. El tratamiento de los compuestos E13a y/o E13b con un haluro ácido en presencia de una co–base tal como DIEA o Et_3N a 25 – 75 °C en un solvente tal como DCM, TF, dioxano o DMF proporciona los compuestos E14a y/o E14b.

Esquema de reacción F



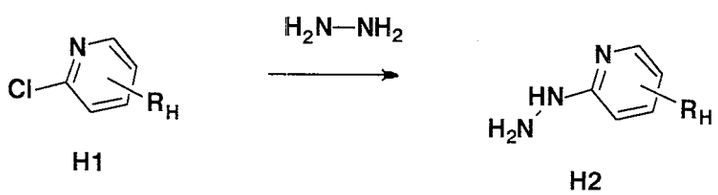
Los compuestos **F3a** y **F3b** se pueden preparar a partir de los compuestos **F1** y **F2** por el tratamiento del compuesto F1 con una base tal como NaH en un solvente tal como THF o dioxano a –78 – 0 °C y posterior tratamiento con el compuesto F2. . Los compuestos **F3a** y **F3b** se separan opcionalmente antes del uso posterior. El tratamiento de los compuestos F3a y/o F3b con una base tal como NaH y una fuente de ion fluoruro proporciona proporciona los compuestos F4a y/o F4b. El posterior tratamiento de los compuestos F4a y/o F4b con un ácido tal como TFA o HCl en un solvente tal como THF, DCM, o dioxano a 0 – 75 °C durante 1 – 8 horas proporciona los compuestos F5a y/o F5b. El tratamiento de los compuestos F5a y/o F5b con una base tal como NaH y una fuente de ion fluoruro proporcionan los compuestos F6a y/o F6b. El tratamiento de compuestos F6a y/o F6b con el compuesto F7. El tratamiento de compuestos F6a y/o F6b con el compuesto F7 en presencia de una base tal como TEA o DIEA en solventes tales como MeOH o EtOH durante 1 – 24 horas proporciona los compuestos F8a y/o F8b. El tratamiento de los compuestos F8a y/o F8b con $POCl_3$ a 80–160 °C proporciona los compuestos F9a y/o F9b. Alternativamente, los compuestos F9a y/o F9b se pueden preparar tratando los compuestos F8a y/o F8b con TsCl/N-metilmorfolina a temperatura ambiente a 100 °C por 30 min a 8 hrs. El acoplamiento de los compuestos F9a y/o F9b con el compuesto F10 se obtiene en un solvente tal como THF, dioxano o DMF a 25 – 100 °C durante 2 – 24 horas en presencia de una co–base tal como DIEA o Et_3N. La eliminación del grupo dimetoxi bencilo de los compuestos F11a y/o F11b se obtiene por el tratamiento de los compuestos F11a y/o F11b con un ácido tal como TFA a 25 – 75 °C durante 2 – 24 horas para proporcionar los compuestos F12a y/o F12b. El tratamiento de los compuestos F12a y/o F12b con el compuesto F13 en presencia de una base tal como Na_2HPO_4 en un solvente tal como DMA a 120 °C proporciona los compuestos F14a y/o F14b. El tratamiento de los compuestos F14a y/o F14b con un ácido tal como TFA o HCl proporciona los compuestos F15a y/o F15b. El tratamiento de los compuestos F15a y/o F15b con un haluro ácido en presencia de una co–base tal como DIEA o Et_3N a 25 – 75 °C en un solvente tal como DCM, TF, dioxano o DMF proporciona los compuestos F16a y/o F16b.

Esquema de reacción G



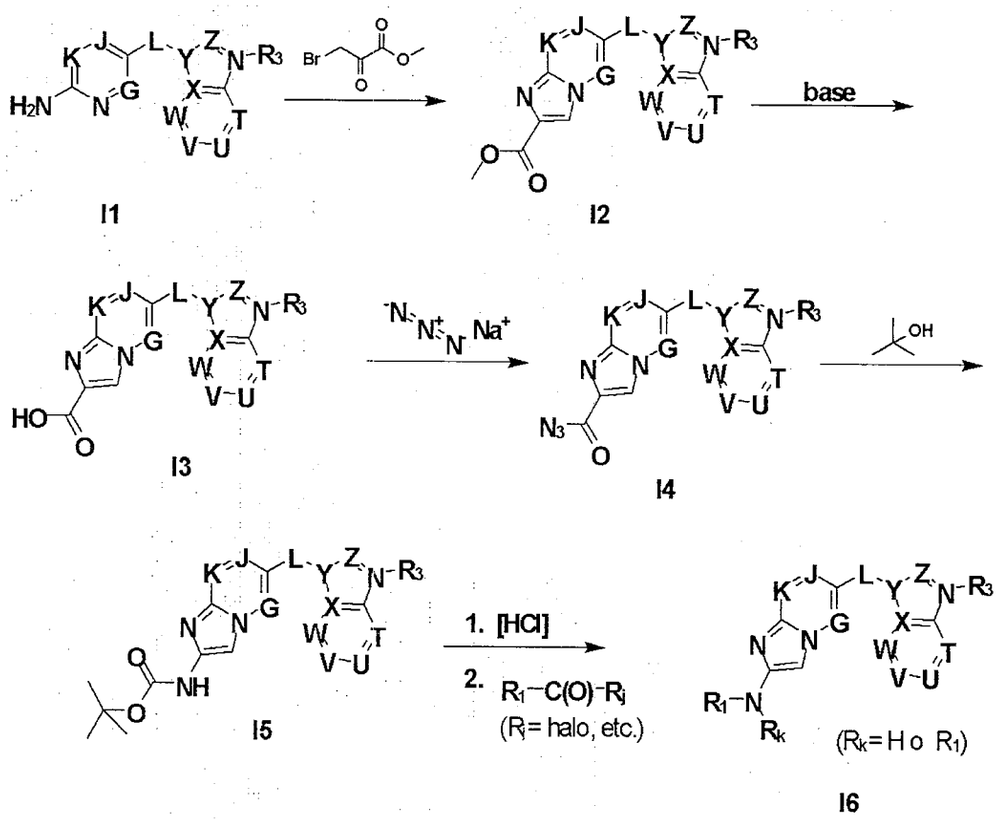
El calentamiento del compuesto G1 y G2 en HOAc a 50 – 100 °C durante 2 – 24 horas proporciona el compuesto G3. El tratamiento del compuesto G3 con el compuesto G4 en presencia de una base tal como Na_2HPO_4 en un solvente tal como DMA a 120 °C proporciona el compuesto G5.

Esquema de reacción H



Una solución de H1 (5 mmol; en donde R_H es R_8, R_9, R_{10} o R_{11}) e hidrazina (30 mmol) en isopropanol o EtOH (5ml) se calienta en condiciones de microonda a 60–160 °C durante 2–5 horas de acuerdo con los sustratos. El producto sólido se filtra, lava con agua y se seca al alto vacío. El exceso de hidracina opcionalmente se puede eliminar por la concentración de la mezcla y coevaporación de esta con MeOH y Et_3N. El producto se puede suspender en éter, filtrar y secar bajo alto vacío (*por ejemplo*, toda la noche).

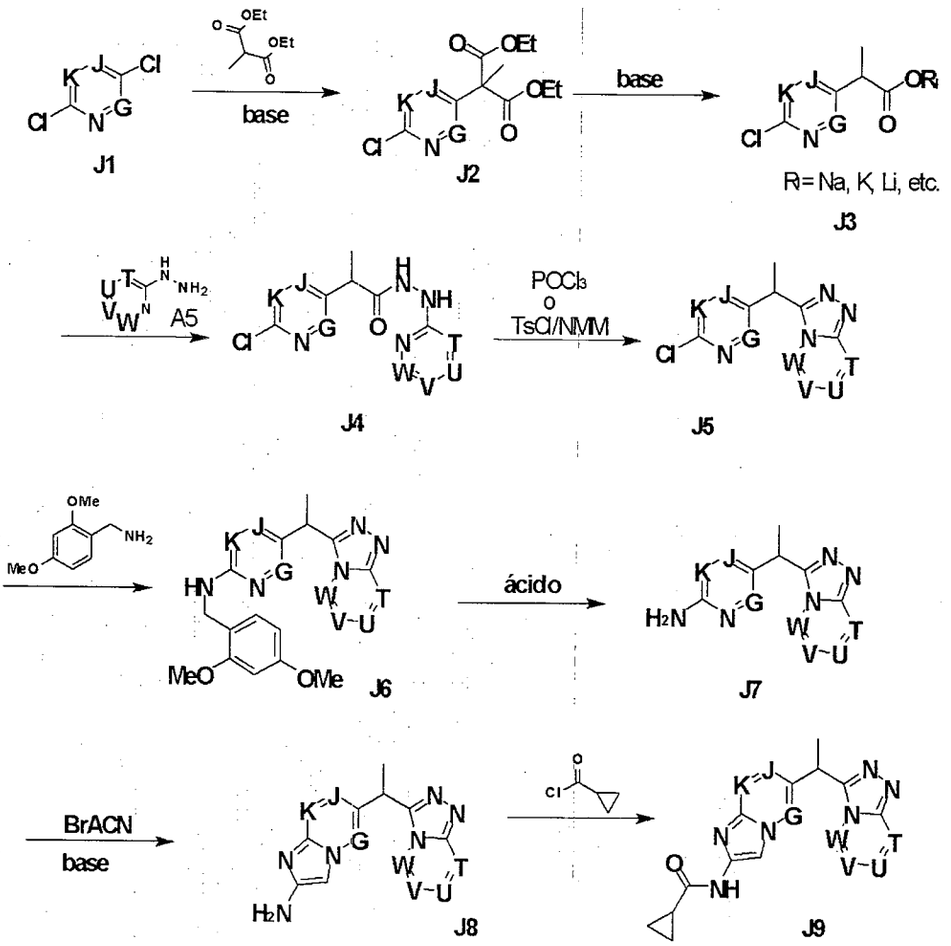
Esquema de reacción I



El compuesto I1 se trata con 3–bromo–2–oxopropanoato de metilo en presencia de una base tal como $NaHCO_3$, Na_2CO_3, fosfato de sodio (mono, di, o tri–básica), o K_2CO_3 en un solvente tal como dioxano o THF y se calienta a 50 – 100 °C durante 1 – 18 horas para proveer el compuesto de estructura I2. El compuesto I2 se saponifica con una base tal como NaOH, KOH, o LiOH en un solvente tal como MeOH, EtOH, o mezclas de alcohol agua con agitación durante 1 – 18 horas a 25 – 100 °C para proveer el compuesto de estructura I3. El compuesto I3 se puede tratar con azida sódica y PyBOB en presencia de una base tal como TEA, DIEA, o piridina en un solvente anhidro tal como DMA o DMF y se agita durante 1 – 18 horas a temperatura ambiente para proveer el compuesto I4. El compuesto I4 se agita en t–butanol durante 1 – 18 horas a 25 – 120 °C para proveer el compuesto I5. El compuesto I5 se trata con un ácido tal como TFA o HCl en un solvente tal como DCM o dioxano y se agita durante 1 – 18 horas a 25 – 100 °C. Este producto desprotegido luego se trata con un cloruro de acilo en presencia de una base tal como TEA, DIEA, o piridina (que da origen a un producto bisacilado) o sin una

base (que da origen a un producto monoacilado) en un solvente tal como DCM, THF, dioxano, o DMF y se agita durante 1 – 18 horas a 25 – 100°C para producir compuestos de estructura I6.

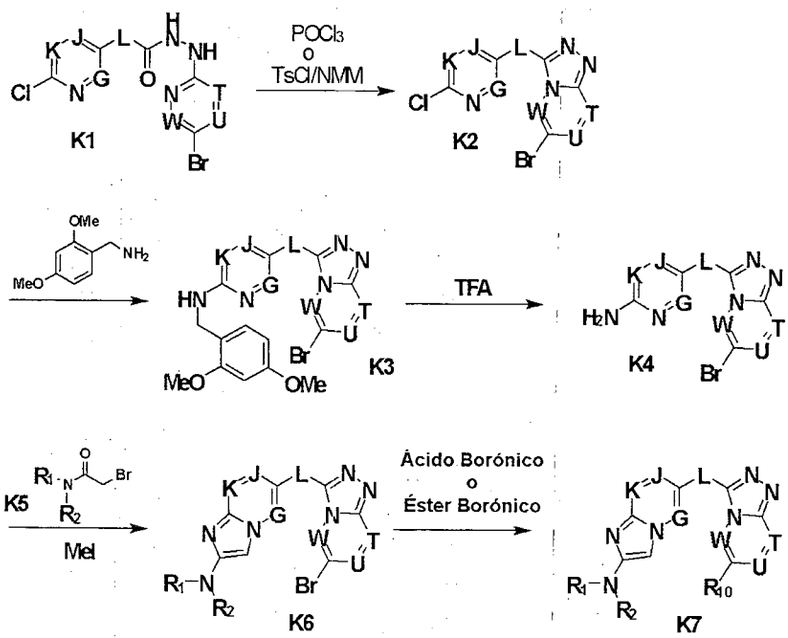
Esquema de reacción J



A una mezcla de una base tal como NaH o t–butóxido de potasio en un solvente tal como dioxano o THF se añade 2–metilmalonato de dietilo a –78 – 0°C. La mezcla se deja calentar a temperatura ambiente durante 1 – 4 horas. A esta se añade J1 en porciones y la reacción luego se agita durante 1 – 18 horas a 25 – 100°C para dar los compuestos de estructura J2. El compuesto J2 se saponifica con una base tal como NaOH, KOH, o LiOH en un solvente tal como MeOH, EtOH, o mezclas de alcohol-agua con agitación durante 1 – 18 horas a 25 – 100 °C para proveer el compuesto de estructura J3 como la sal apropiada. El compuesto J3 y A5 en presencia de reactivos de acoplamiento tales como EDCI y HoBT o PyBOB

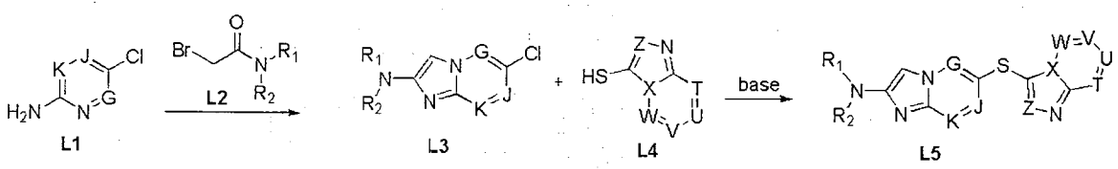
en un solvente tal como DMF o DMA are se agita durante 1 – 8 horas a 25 – 100 °C para proveer el compuesto de estructura J4. El compuesto J4 se calienta en oxicloruro de fósforo durante 1 – 18 horas a 80–160 °C para dar los compuestos de estructura J5. Alternativamente, el compuesto J5 se puede preparar tratando el compuesto J4 con TsCl/N-metilmorfolina a temperatura ambiente a 100 °C por 30 min a 8 hrs. El compuesto J5 se trata con 2,4–dimetoxibencilamina en presencia de una base tal como $NaHCO_3$, Na_2CO_3, fosfato de sodio (mono, di, o tri–básico), o K_2CO_3 y en un solvente tal como IPA y se calienta en un microondas durante 1–24 horas a 75 – 150°C para dar compuestos de estructura J6. El compuesto J6 se trata con un ácido tal como TFA o HCl en un solvente tal como DCM o dioxano durante 1 – 18 horas a 25 – 100 °C para dar compuestos de estructura J7. El compuesto J7 se trata con bromoacetonitrilo en presencia de una base tal como $NaHCO_3$, Na_2CO_3, fosfato de sodio (mono, di, o tribásica), o K_2CO_3 y en un solvente tal como IPA durante 1 – 18 horas a 100 °C en tubo sellado para proveer los compuestos de estructura J8. El compuesto J8 se trata con cloruro de ciclopropancarbonilo en presencia de una base tal como TEA, DIEA, o piridina o en ausencia de una base y en un solvente tal como DCM, THF, o dioxano durante 1 – 8 horas a temperatura ambiente para proveer los compuestos de estructura J9.

Esquema de reacción K



El compuesto K1 se calienta en oxicloruro de fósforo durante 1 – 18 horas a 80–160 °C para dar los compuestos de estructura K2. Alternativamente, el compuesto K2 se puede preparar tratando el compuesto K1 con TsCl/N-metilmorfolina a temperatura ambiente a 100 °C por 30 min a 8 hrs. El compuesto K2 se trata con 2,4–dimetoxibencilamina en presencia de una base tal como $NaHCO_3$, Na_2CO_3, fosfato de sodio (mono, di, o tri–básica), o K_2CO_3 y en un solvente tal como IPA y se calienta en un horno de microondas durante 1– 24 horas a 75 – 150 °C para dar to los compuestos de estructura K3. Compuesto K3 se trata con un ácido tal como TFA o HCl en un solvente tal como DCM o dioxano durante 1 – 18 horas a 25 – 100 °C para dar los compuestos de estructura K4. Los compuestos de estructura K4 se calentaron con los compuestos de estructura K5 en presencia de KI y una base tal como fosfato ácido de sodio y en un solvente tal como DMA o DME durante 1 – 24 horas a 50 – 120 °C para proporcionar los compuestos de estructura K6. El compuesto K6 se trató con el ácido borónico o éster borónico apropiado en presencia de un catalizador tal como tetrakis(trifenilfosfina)paladio(0) y una base tal como Cs_2CO_3 (ac) o K_2CO_3 (ac) en un solvente tal como dioxano, TF, o DME durante 15 min – 8 horas a 50 – 120 °C para dar los compuestos de estructura K7.

Esquema de reacción L



El compuesto L1 se trata con el compuesto L2 y una base (por ejemplo, K_2HPO_4) en un solvente polar (por ejemplo, DMA, DMF o DMSO) y se calienta a65 – 85°C para proporcionar el compeusto L3. El compuesto L3 se hace reaccionar con el compueto L4 y una base (por ejemplo, K_2CO_3) en un solvente polar (por ejemplo, DMA, DMF o DMSO) a 130 - 160°C y presión atmosférica a 125 psi de N_2 para proporcionar el compeusto L5.

Los componentes quirales se pueden separar y purificar usando cualquiera de una variedad de técnicas conocidas por los expertos en el arte. Por ejemplo, los componentes quirales se pueden purificar usando cromatografía de fluido

supercrítico (SFC). En una variación particular, se realizan análisis SFC/MS analíticos quirales usando un sistema analítico Berger SFC (AutoChem, Newark, DE) que consiste en un módulo de control de fluido de bomba dual Berger SFC dual con una bomba de fluido supercrítico Berger FCM 1100/1200 y una bomba de fluido modificador FCM 1200, un horno Berger TCM 2000 y un automuestreador Alcott 718. El sistema integrado se puede controlar con un programa de computación BI–SFC Chemstation versión 3.4. La detección se puede lograr con un 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 en una columna ChiralPak AD–H, ChiralPak AS–H, ChiralCel OD–H, o ChiralCel OJ–H (5 µ4.6 x 250 mm; Chiral Technologies, Inc. West Chester, PA) con 10 a 40% de metanol como modificador y con o sin acetato de amonio (10 mM). Se puede utilizar alguno de una variedad de velocidades de flujo que incluye, por ejemplo, 1.5 o 3.5 ml/min con una presión de entrada ajustada a 100 bar. En forma adicional, se puede usar una variedad de condiciones de inyección de muestra que incluyen, por ejemplo, inyecciones de muestra de 5 o 10 µL en metanol a 0.1 mg/ml de concentración.

En otra variación, se realizan separaciones quirales preparativas usando un sistema de purificación Berger MultiGram II SFC. Por ejemplo, las muestras se pueden cargar en una columna ChiralPak AD (21 x 250 mm, 10µ). En variaciones particulares, la velocidad de flujo para la separación puede ser 70 ml/min, el volumen de inyección hasta 2 ml, y la presión de entrada ajustada a 130 bar. Se pueden aplicar inyecciones apiladas para aumentar la eficiencia.

En cada uno de los anteriores procedimientos o esquemas de reacción, se pueden seleccionar diversos sustituyentes entre los diversos sustituyentes descritos en otra parte de la presente.

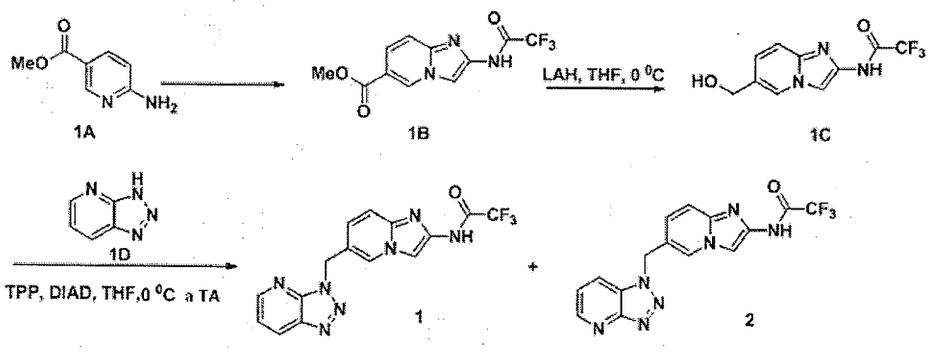
Las descripciones de la síntesis de los compuestos de acuerdo con la presente invención particulares sobre la base del esquema de reacción anterior se exponen en la presente.

Ejemplos de Inhibidores de cMET

La presente invención también se ejemplifica, pero sin limitación, con los siguientes ejemplos que describen la síntesis de compuestos particulares de

acuerdo con la invención.

Compuestos 1 y 2: N–(6–((3H–[1,2,3]triazolo[4,5–b]piridin–3–il)metil)imidazo[1,2–a]piridin–2–il)–2,2,2–trifluoroacetamida y N–(6–((1H–[1,2,3]triazolo[4,5–b]piridin–1–il)metil)imidazo–[1,2–a]piridin–2–il)–2,2,2–trifluoroacetamida



2–(2,2,2–trifluoroacetamido)imidazo[1,2–a]piridin-6–carboxilato de metilo (1B): El compuesto **1B** se preparó a partir del compuesto **1A** en tres etapas siguiendo un método análogo al que se describe en la Patente US No. 6,358,971, que se incorpora como referencia en la presente en su totalidad. En forma específica, una mezcla de 6–aminonicotinato de metilo (**1A**, 3 g, 19.7 mmol) y cloruro de tosilo (4.5 g, 23.6 mmol) en piridina (40 ml) se calentó a 80 °C durante 16 horas. La reacción se enfrió a temperatura ambiente y se eliminó piridina in vacuo. El residuo resultante se diluyó con agua y se dejó agitar durante 10 min. El sólido resultante se filtró y se secó al vacío para proveer 6–(4–metilfenilsulfonamido)nicotinato de metilo que se uso sin purificación posterior. A una suspensión de 6–(4–metilfenilsulfonamido)nicotinato de metilo (5.3 g, 17.3 mmol) en DMF anhidro se añadió sucesivamente DIEA (3.31 ml, 19.03 mmol) y luego 2–bromoacetamida (2.63 g, 19.03 mmol). La reacción se agitó a temperatura ambiente durante 24 horas y luego se vertió en agua. El sólido resultante se filtró y se secó al vacío para proveer 1–(2–amino–2–oxoetil)–6–(4–metilfenilsulfonamido)–1,6–dihidropiridin-3–carboxilato de metilo que se uso sin purificación posterior. A una suspensión de 1–(2–amino–2–oxoetil)–6–(4–metilfenilsulfonamido)–1,6–dihidropiridin-3–carboxilato de metilo (1.0 g, 2.8 mmol) en DCM (20 ml) se añadió TFAA (8.0 ml, 57.5 mmol) gota a gota a temperatura ambiente. La reacción se sometió a reflujo durante 2 horas, se enfrió a

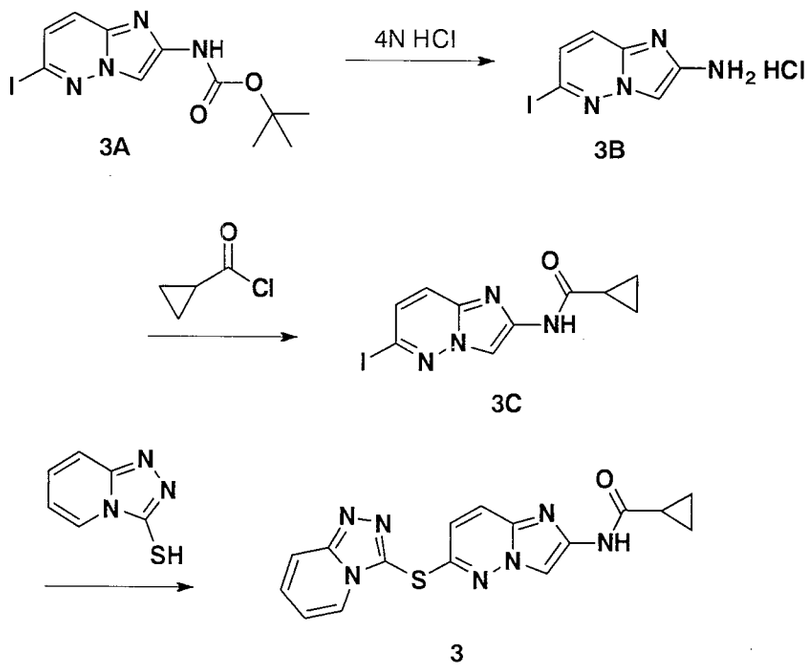
temperatura ambiente, y luego se concentró in vacuo. El residuo resultante se suspendió en bicarbonato de sodio saturado y se agitó durante 15 min. El sólido resultante se filtró y se secó al vacío para proveer 2–(2,2,2–trifluoroacetamido)imidazo[1,2–a]piridin-6–carboxilato de metilo (**1B**) que se uso sin purificación posterior.

2,2,2–Trifluoro–N–(6–(hidroximetil)imidazo[1,2–a]piridin–2–il)acetamida (1C): A una solución agitada del compuesto **1B** (470 mg, 1.64 mmol) en THF anhidro (20 ml) se añadieron en porciones hidruro de litio y aluminio (155 mg, 4.09 mmol) a 0 °C. Después de agitar durante 1 h a 0 °C, la reacción se inactivó con 0.16 ml de agua, seguido por 0.16 ml de 15% de NaOH y 0.48 ml de agua. La mezcla de reacción heterogénea se agitó durante 0.5 h a temperatura ambiente y luego se filtró a través de celite. El residuo se lavó con THF. El filtrado y los lavados se concentraron y el residuo bruto se purificó por cromatografía en columna para suministrar el compuesto **1C** (220 mg, 52%). ^{1}H NMR (400 MHz, DMSO–d_6) δppm 12.41 (s, 1H), 8.52 (s, 1H), 8.21 (s, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.25 (d, J = 9.6 Hz, 1H), 5.36 (t, *J*=5.6 Hz, 1 H) 4.48 (d, *J*=5.6 Hz, 2 H) ESI–MS:m/z 260.2 $(M+H)^+$.

N–(6–((3H–[1,2,3]triazolo[4,5–b]piridin–3–il)metil)imidazo[1,2–a]piridin–2–il)–2,2,2–trifluoroacetamida y N–(6–((1H–[1,2,3]triazolo[4,5–b]piridin–1–il)metil)imidazo–[1,2–a]piridin–2–il)–2,2,2–trifluoroacetamida (1 y 2): A una solución agitada de compuesto **1C** (30 mg, 0.12 mmol) en THF anhidro (3.0 ml) se añadieron sucesivamente el compuesto **1D** (28 mg, 0.23 mmol) y trifenilfosfina (61 mg, 0.23 mmol). La mezcla de reacción se enfrió a 0°C, y a esta se añadió diisopropil–azodicarboxilato (0.05 ml, 0.23 mmol) en forma de gota. Después de terminar la adición, la agitación continuó durante otra 0.5 h a 0°C y luego durante 12 h a temperatura ambiente. Los solventes se extrajeron al vacío y el residuo se purificó por HPLC preparativa para proveer los compuestos 1 y 2 en forma de sales de TFA. ESI–MS para ambos compuestos: m/z 362.1 $(M+H)^+$.

Compuesto 3: N–(6–([1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclo–propancarboxamida

Método A



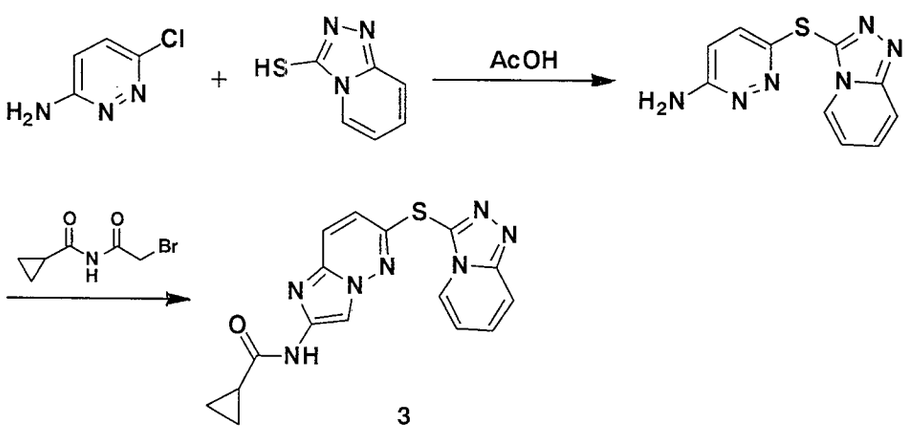
Clorhidrato de 6–yodoimidazo[1,2–*b*]piridazin–2–amina (3B): El compuesto **3B** se sintetizó de acuerdo con un procedimiento análogo al que se describe en la Publicación de patente internacional No. WO 2008/06192 (Takeda Pharmaceutical Company Limited), que se incorpora como referencia en la presente en su totalidad. En forma específica, 6–yodoimidazo[1,2–b]piridazin–2–ilcarbamato de ter–butilo (**3A**, 5.9 g, 16.38 mmol) se disolvió en HCl 4 N en dioxano (60 ml) y se agitó a temperatura ambiente durante 4 horas. Se añadió éter (140 ml) a la reacción y se formó un precipitado marrón. El precipitado se filtró y lavó con éter para dar clorhidrato de 6–yodoimidazo[1,2–b]piridazin–2–amina en rendimiento cuantitativo. Este material se uso sin purificación. ESI–MS:m/z 261.0 $(M+H)^+$.

N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (3C): El compuesto **3C** se sintetizó de acuerdo con un procedimiento análogo al que se describe en Publicación de patente internacional No. WO 2008/06192 (Takeda Pharmaceutical Company Limited), que se incorpora como referencia en la presente en su totalidad. Clorhidrato de 6–yodoimidazo[1,2–b]piridazin–2–amina (4.45 g, 17.11 mmol) y cloruro de ciclopropancarbonilo (1.35 ml, 18.82 mmol) se

disolvieron en DMA (85 ml) y se agita durante 3 horas a temperatura ambiente. La mezcla de reacción luego se vertió en agua (400 ml) dando como resultado la formación de un precipitado marrón. El sólido se filtró y se secó al vacío para dar N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (4.2 g, 77%). ^{1}H NMR (400MHz, DMSO–d_6) δ = 11.21 (s, 1 H), 8.26 – 8.17 (m, 1 H), 7.74 (d, *J* = 9.3 Hz, 1 H), 7.49 (d, *J* = 9.1 Hz, 1 H), 2.07 – 1.87 (m, 1 H), 0.97 – 0.77 (m, 4 H) ESI–MS:m/z 329.1 $(M+H)^+$.

***N*–(6–([1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–il)ciclopropancarboxamida (3):** N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (0.5 g, 1.52 mmol), [1,2,4]triazolo[4,3–*a*]piridin-3–tiol (0.23 g, 1.52 mmol), Tris(dibencilidenacetona)dipaladio(0) (84 mg, 0.09 mmol), 9,9–Dimetil–4,5–bis(difenilfosfino)xanteno (106 mg g, 0.18 mmol), y DIEA (0.531 ml, 3.05 mmol) se disolvieron en DME (15.2 ml) y se calentaron en un microondas a 120°C durante 30 min. La mezcla de reacción se concentró a sequedad, se reconstituyó en DMSO, y se purificó por LCMS preparativa para dar *N*–(6–([1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–il)ciclopropancarboxamida (1 g, 43 %) en forma de sal de TFA. ^{1}H NMR (400MHz, DMSO–d_6) δ = 11.17 (s, 1 H), 8.57 – 8.44 (m, 1 H), 8.03 – 7.94 (m, 1 H), 7.96 – 7.88 (m, 2 H), 7.59 (ddd, *J* = 1.0, 6.6, 9.3 Hz, 1 H), 7.22 – 7.11 (m, 1 H), 7.11 – 7.03 (m, 1 H), 1.97 – 1.84 (m, 1 H), 0.83 – 0.73 (m, 4 H) ESI–MS:m/z 352.3 $(M+H)^+$. MP 193–195°C.

Método B



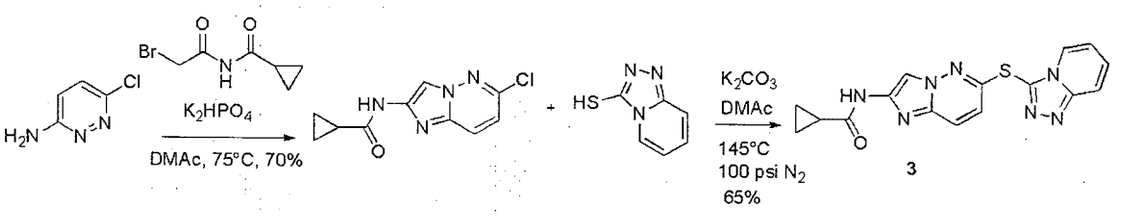
6–([1,2,4]Triazolo[4,3–a]piridin–3–ilsulfanil)–piridazin–3–ilamina: Una mezcla

de reacción de [1,2,4]triazolo[4,3–a]piridin-3–tiol (8.49 g, 55.0 mmol) y 6–cloropiridazin–3–amina (6.82 g, 50 mmol) en ácido acético (100 mL) se calentó a 80 °C durante 20 horas. La reacción se extrajo a sequedad por medio de evaporación rotatoria y el material resultante se suspendió en H_2O (100 ml). A esta suspensión, se añadió Na_2CO_3 en porciones hasta obtener pH 10 y luego la mezcla se sometió a sonicación. El sólido resultante se recolectó por filtración y se lavó por completo con agua seguido por éter etílico. El sólido se secó al vacío sobre P_2O_5 para proporcionar el compuesto del título, 6–([1,2,4]Triazolo[4,3–a]piridin–3–ilsulfanil)–piridazin–3–ilamine, en forma de polvo blanco (11.0 g). ^1H NMR (400 MHz, DMSO–d_6) δ ppm 7.15 – 7.25 (m, 1 H) 7.53 – 7.58 (m, 1 H) 7.61 (ddd, *J*=9.22, 6.69, 1.26 Hz, 1 H) 7.84 – 7.90 (m, 1 H) 7.99 (dt, *J*=9.09, 1.01 Hz, 1 H) 8.51 (dt, *J*=7.01, 1.04 Hz, 1 H) 8.79 (br. s., 2 H). ESI–MS:m/z 553.2 $(M+H)^+$.

N–(6–([1,2,4]Triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: Una mezcla de 6–([1,2,4]triazolo[4,3–a]piridin–3–iltio)piridazin–3–amina (2.443 g, 10 mmol), N–(2–bromoacetil)ciclopropancarboxamida (3.09 g, 15.00 mmol), fosfato ácido de potasio (5.23 g, 30.0 mmol) y yoduro de potasio (0.830 g, 5.00 mmol) en DMA (100 ml) se agitó a 120 °C durante 2 horas. Se añadieron cantidades adicionales de N–(2–bromoacetil)ciclopropancarboxamida (2.06 g, 10 mmol) e fosfato ácido de potasio (1.74g, 10 mmol) a la mezcla y la reacción se agitó a 120 °C durante otras 2 horas. La reacción luego se agitó a temperatura ambiente toda la noche. La reacción mixture nuevamente se agitó a 140 °C durante 3 horas y luego se enfrió a temperatura ambiente. El sólido resultante se filtró y se lavó con DMA. El filtrado se concentró a 100 ml y luego se vertió en agua (300 ml). El precipitado resultante se recolectó por filtración y se lavó por completo con agua. El material sólido se resuspendió en 10% de MeOH/CH2Cl2 (100 ml), se sometió a sonicación, se reflujó durante 30 min y se enfrió a temperatura ambiente. La solución de MeOH/CH2Cl2 se filtró a través de una bolsa de sílice, se lavó con 10% de MeOH/CH2Cl2 (200 ml). A la anterior solución orgánica, se añadió carbón activado (0.5g), la solución se sometió a reflujo durante 30 min, y luego se agitó a temperatura ambiente toda la noche. El carbón se filtró a través de celite, y el filtrado se concentró a sequedad para proporcionar un sólido blanco. Este sólido se sometió a reflujo en MeOH (10 ml) durante 30 min. y se enfrió a temperatura

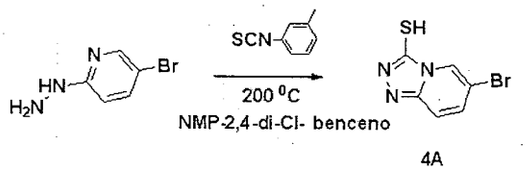
ambiente. El sólido blanco resultante se recolectó por filtración, se lavó con MeOH (2 ml) y se secó al vacío para proporcionar el compuesto del título, N–(6–([1,2,4]Triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (1.2 g). ^{1}H NMR (400MHz, DMSO–d_6) δ = 11.17 (s, 1 H), 8.57 – 8.44 (m, 1 H), 8.03 – 7.94 (m, 1 H), 7.96 – 7.88 (m, 2 H), 7.59 (ddd, *J* = 1.0, 6.6, 9.3 Hz, 1 H), 7.22 – 7.11 (m, 1 H), 7.11 – 7.03 (m, 1 H), 1.97 – 1.84 (m, 1 H), 0.83 – 0.73 (m, 4 H) ESI–MS:m/z 352.3 $(M+H)^+$. MP 193–195°C.

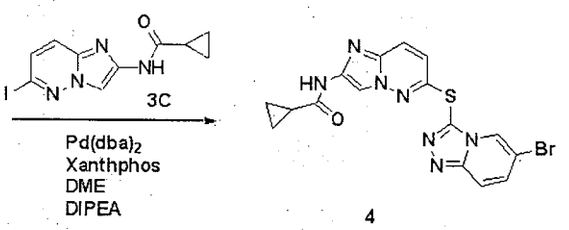
Método C



6-Cloropiridazin-3-amina, N-(2-bromoacetil)ciclopropancarboxamida, y fosfato ácido de potasio se mezclaron en DMA a 75°C para proporcionar la N-(6-cloroimidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida. La N-(6-cloroimidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida se hace reaccionar con [1,2,4]triazolo[4,3-a]piridini-3-tiol y K_2CO_3 en DMA a 145°C y 100 psi de N_2 para proporcionar la N-(6-([1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclo-propancarboxamida.

Compuesto 4: N–(6–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

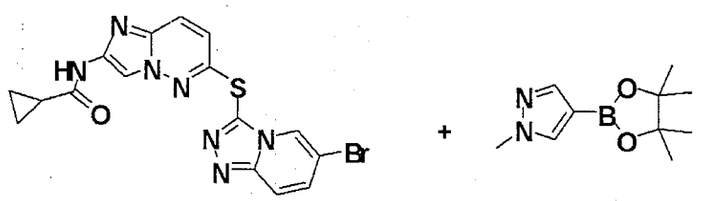




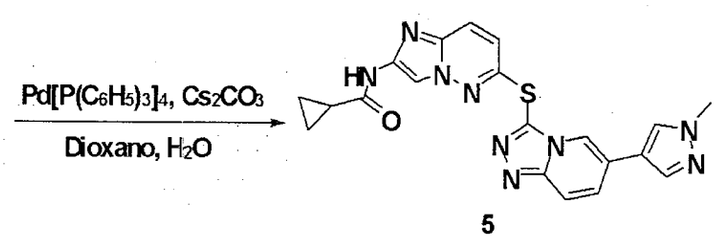
6–bromo–[1,2,4]triazolo[4,3–a]piridin-3–tiol (4A): A la solución suspendida de 5–Bromo–2–hidrazinilpiridina (1.85g, 10mmol) en una mezcla de 1,4–diclorobenceno y NMP (5:1, 10 ml) se añadió isotiocianato–3–metilbenceno (1.5g 10 mmol). La mezcla se agitó a ta durante 5 min, 70 °C durante 15 min, y luego se calentó en condiciones de microondas a 200 °C durante 1.5 h. La mezcla se vertió en éter (20 ml). El sólido se filtró y se lavó con éter para dar el producto del título.

N–(6–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (4): A un tubo sellado empacado con N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (100 mg, 0.3 mmol), compuesto **4A**, $Pd(dba)_2$ (3%/mol), xanthphos (5%/mol) y DIPEA (1.5 mmol) se añadió DME (2 ml). Después de desgasificar al vacío, la mezcla se calentó en condiciones de microondas a 125 °C durante 30 min. La mezcla se purificó por LCMS para dar el compuesto del título en forma de sal de TFA. ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD 10:1) δppm 8.5 (s, 1 H), 8.1 (s, 1 H), 7.8 (d, *J*=9.8 Hz, 1 H), 7.7 (d, *J*=9.2 Hz, 2 H), 7.60 (d, *J*=9.6 Hz, 1 H), 7.1 (d, *J*=9.36 Hz, 1 H), 1.7 (m, 1 H), 1.05 (m, 2 H), 0.90 (m, 2H) ESI–MS:m/z 430.2 $(M+H)^+$.

Compuesto 5: N–(6–(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)–imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



4

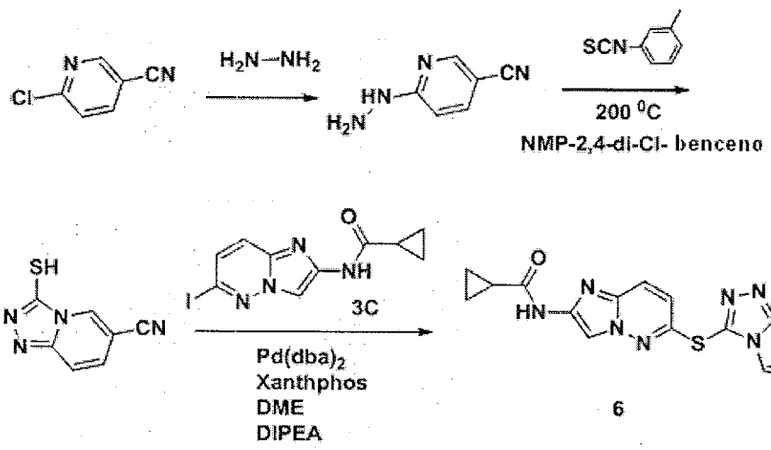


5

A una mezcla del compuesto **4** (15mg, 0.35 mmol), 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (11 mg, 0.52 mmol), Cs_2CO_3 (350 mg), y tetrakis(trifenilfosfina)paladio(0) (*es decir*, $Pd[P(C_6H_5)_3]_4$) (1%/mol) en dioxano–

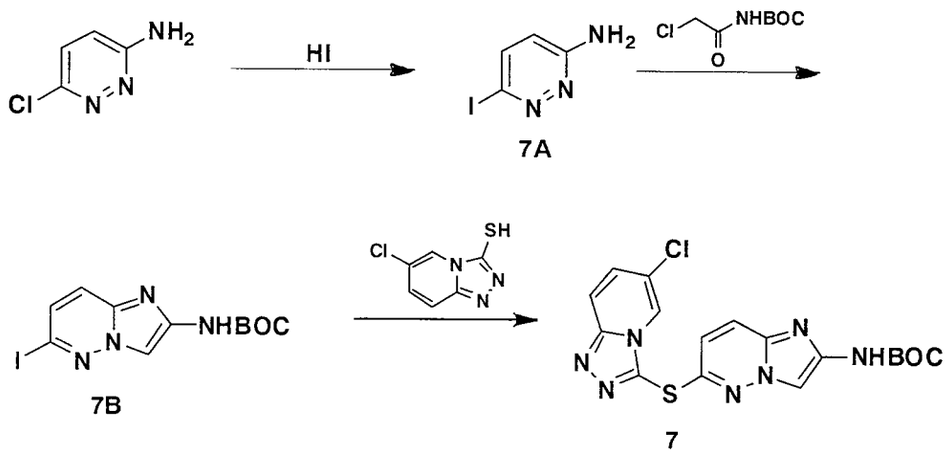
H_2O (20:1, 1.5 ml) se calentó en condiciones de microondas a 140 °C durante 30 min. La mezcla se purificó por LCMS para dar el compuesto del título en forma de sal de TFA. ^1H NMR (400 MHz, $CDCl_3$–CD_3OD 10:1) δ ppm 8.33 (s, 1 H), 8.14(s, 1 H), 7.75 (s, 1H), 7.70 (s, 1H), 7.67 (d, *J*=9.5 Hz, 1 H), 7.56 (dd, *J*=9.4 y 1.6 Hz, 1 H), 7.06 (d, *J*=9.4 Hz, 1 H), 3.96 (s, 3 H), 1.67 (m, 1 H), 1.06 (m, 2 H), 0.90 (m, 2H) ESI–MS:m/z 432.2 $(M+H)^+$.

Compuesto 6: N–(6–(6–ciano–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



A una mezcla suspendida de 6–cloronicotinonitrilo (7g, 50.8 mmol) en EtOH (50 ml), se añadió NH_2NH_2 (10g, 310.2 mmol). La mezcla se agitó a temperatura ambiente durante 10 min, y luego 60 °C durante 5h. La mezcla se enfrió a temperatura ambiente. Los sólidos se filtraron, lavaron con agua y se secaron bajo alto vacío para dar 6–hidrazinilnicotinonitrilo (3.5 g). El compuesto **6** se preparó a partir de 6–hidrazinilnicotinonitrilo siguiendo el procedimiento de la síntesis del compuesto **4**. ^1H NMR (400 MHz, CDCl3–CD3OD 10:1) δ ppm 11.37 (s, 1H), 8.70 (t, *J*= 1.2 Hz, 1 H), 8.14 (s, 1H), 8.11(dd, *J*= 1.04 y 9.52 Hz, 1 H), 7.96 (dd, *J*= 1.12 y 9.52 Hz, 1 H), 7.61 (dd, *J*= 1.52 y 9.48 Hz, 1 H), 7.38 (d, *J*=9.0 Hz, 1 H), 1.77 (m, 1 H), 1.06 (m, 2 H), 0.90 (m, 2H) ESI–MS:m/z 377.2 $(M+H)^+$.

Compuesto 7: 6–(6–cloro–[1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–ilcarbamato de *ter*–butilo



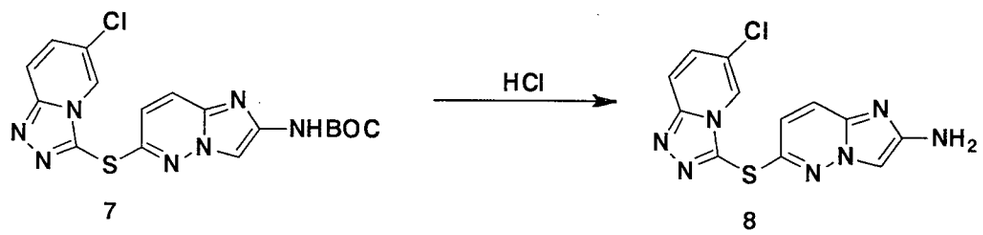
6–yodopiridazin–3–amina (7A): El compuesto **7A** se sintetizó de acuerdo con un procedimiento análogo al que se describe en Publicación de patente internacional No. WO 2007/30366 (Smithkline Beecham Corporación), que se incorpora como referencia en la presente en su totalidad. En forma específica, 6–cloropiridazin–3–amina (10.0 g, 77.2 mmol) se mezcló con ácido yodhídrico (78 ml, acuoso 57%) y se calentó a 100 °C toda la noche. Se añadió acetato de etilo (50 ml) después la reacción se enfrió a temperatura ambiente. La mezcla resultante se sometió a sonicación y filtró. La torta de filtrado se lavó con cantidades abundantes de acetato de etilo. El material bruto luego se secó bajo alto vacío para dar 6–yodopiridazin–3–amina (**7A**; 24 g, 89 %) en forma de un sólido amarillo brillante, que se uso sin purificación posterior. ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 8.36 – 8.08 (m, 1 H), 7.95 (d, *J* = 9.6 Hz, 1 H), 7.12 – 7.03 (m, 1 H). ESI–MS:m/z 221.9 $(M+H)^+$.

6–yodoimidazo[1,2–*b*]piridazin–2–ilcarbamato de *ter*–butilo (7B): Una mezcla que contiene compuesto **7A** (2.5 g, 11.3 mmol), 2–cloroacetilcarbamato de *ter*–butilo (2.4 g, 12.4 mmol), fosfato hidrógeno de sodio (3.2 g, 22.6 mmol) y DMA (23 ml) se calentó a 120°C durante dos horas. La mezcla se enfrió a temperatura ambiente, se vertió en un matraz que contiene 400 ml de agua y se sometió a sonicación. Los sólidos se filtraron, lavaron con agua luego se secaron al vacío. Los sólidos luego se tomaron en 600 ml de acetato de etilo y se filtraron en bolsa corta de gel de sílice. El filtrado se concentró para dar el compuesto **7B** (1.6 g, 39 %), en forma de sólido verde oscuro, que se uso sin purificación posterior. ^{1}H

NMR (400MHz, DMSO–d_6) δ ppm 10.21 (br. s., 1 H), 8.06 – 8.00 (m, 1 H), 7.69 (d, *J* = 9.9 Hz, 1 H), 7.46 (d, *J* = 9.3 Hz, 1 H), 1.48 (s, 9 H) ESI–MS:m/z 361.1 $(M+H)^+$.

6–(6–cloro–[1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–ilcarbamato de *ter*–butilo (7): El compuesto combinado **7B** (50 mg, 0.14 mmol), 6–cloro–[1,2,4]triazolo[4,3–a]piridin-3–tiol (28 mg, 0.15 mmol), Tris(dibencilidenacetona)dipaladio(0) (11 mg, 0.01 mmol), 9,9–Dimetil–4,5–bis(difenilfosfino)xanteno (14 mg, 0.025 mmol), DIEA (48 uL, 0.28 mmol) y DME (1.4 ml) se calentaron en una unidad de microondas de alta absorbancia, 120°C durante 30 min. El material bruto resultante se purificó por gel de sílice usando 5% de MeOH en DCM. Las fracciones más limpias se concentraron para dar el compuesto **7** (0.06 g; rendimiento cuantitativo). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 10.18 (br. s., 1 H), 8.86 – 8.82 (m, 1 H), 8.11 – 8.05 (m, 1 H), 7.89 (d, *J* = 9.3 Hz, 1 H), 7.73 (s, 1 H), 7.66 (dd, *J* = 1.9, 9.7 Hz, 1 H), 7.09 (d, *J* = 9.6 Hz, 1 H), 1.48 – 1.41 (m, 9 H) ESI–MS:m/z 418.2.0 $(M+H)^+$.

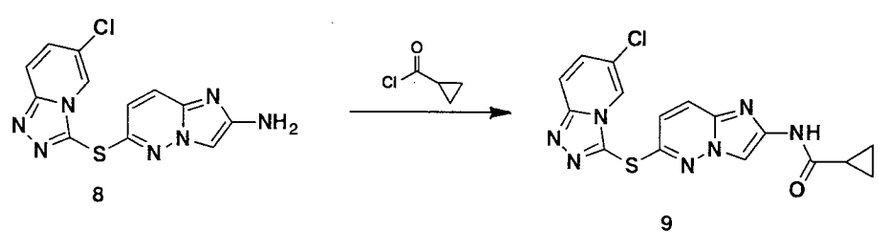
Compuesto 8: 6–(6–cloro–[1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–amina



7 8

El compuesto **7** (0.15 g, 0.42 mmol) y HCl 4 N en dioxano (2 ml) se combinaron y se agitaron a TA durante 2 horas para producir el compuesto **8**. La mezcla de reacción bruta se concentró y se uso sin purificación. ESI–MS:m/z 318.2 $(M+H)^+$.

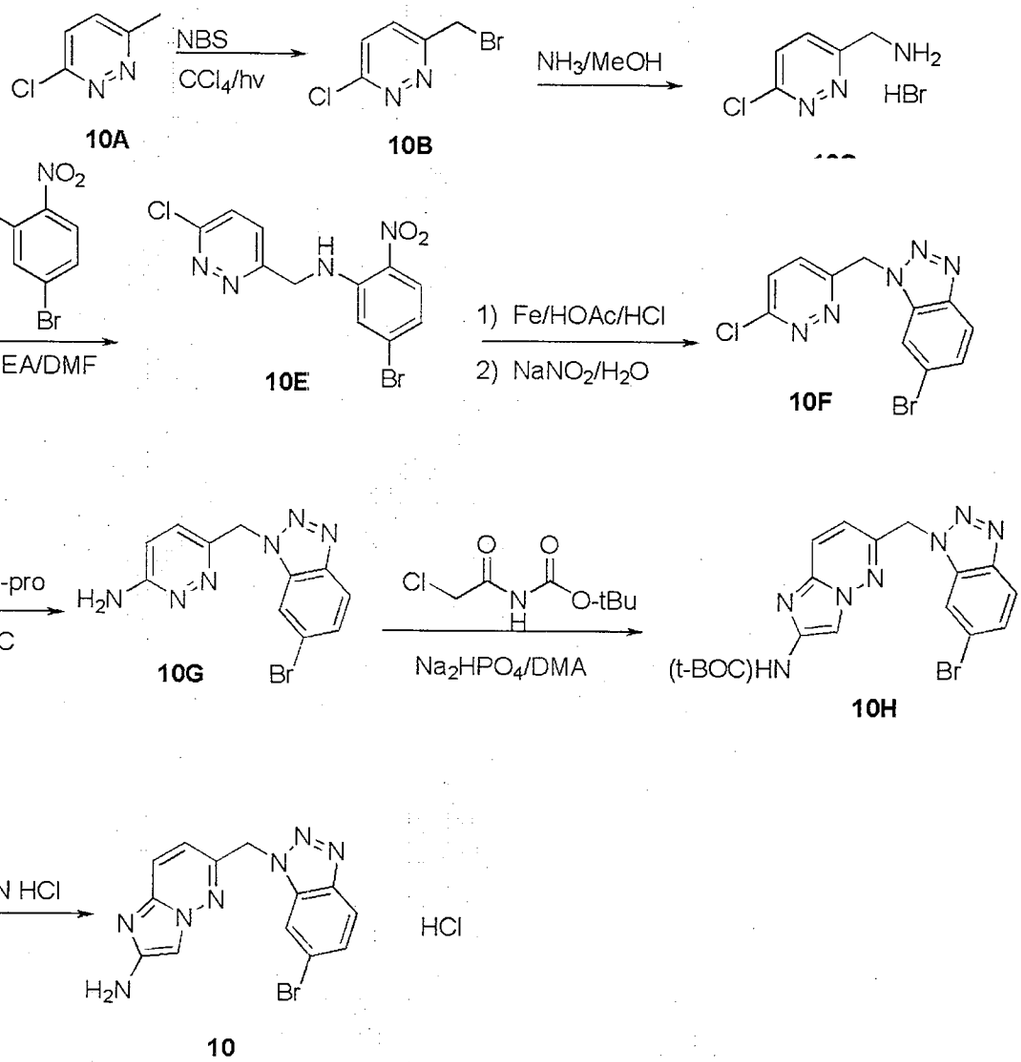
Compuesto 9: *N*–(6–(6–cloro–[1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–il)ciclopropancarboxamida



8 9

El compuesto **8** (0.13 g, 0.41 mmol), cloruro de ciclopropancarbonilo (112 uL, 1.23 mmol), trietilamina (690 ml, 4.9 mmol) y DCE (2 ml) se combinaron y se agitaron durante 2 horas para producir el compuesto **9**. La mezcla de reacción se concentró y se purificó por LC preparativa. ESI–MS:m/z 386.3 $(M+H)^+$.

Compuesto 10: Clorhidrato de 6–(6–Bromo–benzotriazol–1–ilmetil)–imidazo[1,2–b]piridazin–2–ilamina



3–Bromometil–6–cloro–piridazina (10B): Una solución de 3–Cloro–6–metil–piridazina **10A** (5.12 g, 40 mmol) y NBS (8.90 g, 50 mmol) en CCl_4 (300 ml) se sometió a reflujo bajo la luz (200 w) durante 4 horas. La mezcla de reacción se enfrió a temperatura ambiente y se filtró. El residuo sólido se lavó por completo con Cl_4C y se filtró. Los filtrados se combinaron, concentraron a un volumen

pequeño y se cargaron en columna de gel de sílice. La columna se eluyó con 50% hexano/ acetato de etilo para dar 2.2 g del producto deseado (**10B)** que se secó al vacío y se uso inmediatamente en la próxima etapa. ESI–MS:m/z 206.9 $(M+H)^+$.

Bromhidrato de C–(6–Cloro–piridazin–3–il)–metilamina (10C): Una solución del compuesto **10B** (2.08g, 10 mmol) en metanol (50 ml) se añadió en una solución presaturada de amoníaco/metanol (200 ml) a 0 °C. La solución de reacción se selló y se agitó a temperatura ambiente toda la noche. La solución de metanol se concentró y secó al vacío para dar 2.2 g del producto bruto (**10C**) en forma de sal de bromhidrato, se uso en la próxima etapa sin purificación adicional. ESI–MS:m/z 144.1 $(M+H)^+$.

(5–Bromo–2–nitro–fenil)–(6–cloro–piridazin–3–ilmetil)–amina (10E): Una solución del compuesto **10C** (1.00 g, 4.46 mmol) y 4–bromo–2–fluoro–1–nitro–benceno (**10D**) (0.97g, 4.40 mmol) en DMF (50 ml) con DIEA (1.30 g, 10 mmol) se agitó a 65 °C durante dos horas. La reacción se vertió en ice/agua y el precipitado sólido se recolectó por filtración, se lavó con agua y se secó al vacío sobre P_2O_5 toda la noche para dar 1.5 g del producto deseado (**10E**). ESI–MS:m/z 342.9 $(M+H)^+$.

6–Bromo–1–(6–cloro–piridazin–3–ilmetil)–1H–benzotriazol (10F): A una solución del compuesto **10E** (1.40 g, 4.08 mmol) en HOAc/HCl (50/5 ml) se añadió polvo de hierro (2.2 g, 40 mmol). La mezcla de reacción se agitó a 50 °C durante 30 minutos, luego se enfrió a temperatura ambiente y se filtró. Una solución de $NaNO_2$ (0.35 g, 5 mmol) en agua (2 ml) luego se añadió gota a gota en la anterior solución ácida a 0 °C. La solución de reacción se agito durante una hora y se concentró a sequedad a presión reducida. El residuo resultante se sometió a sonicación en solución de acetato de etilo/$NaHCO_3$ y el precipitado se filtró y lavó por completo con acetato de etilo. La solución orgánica se separó y secó con $MgSO_4$, se filtró y concentró para dar 1.2 g del producto deseado (**10F**). ESI–MS:m/z 323.9 $(M+H)^+$.

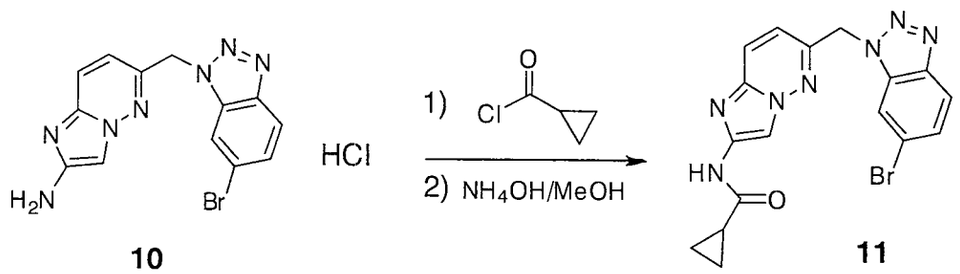
6–(6–Bromo–benzotriazol–1–ilmetil)–piridazin–3–ilamina (10G): A una suspensión del compuesto **10F** (1.2g, 3.7 mmol) en isopropanol (15 ml) en un tubo de presión se acero inoxidable, un gas amoníaco se burbujeó a –78 °C durante 5 minutos. El tubo de presión se selló y calentó en un baño de aceite a 140 °C durante tres días. La solución de reacción luego se volvió a enfriar, se transfirió a

un frasco redondo, se concentró y se secó al vacío para dar 1.3 g del producto bruto (**10G**), se uso en la próxima etapa sin purificación adicional. ESI–MS:m/z 305.1 $(M+H)^+$.

ter–butil éster del ácido [6–(6–Bromo–benzotriazol–1–ilmetil)–imidazo[1,2–b]piridazin–2–il]–carbámico (10H): Una mezcla del compuesto **10G** (1.0 g, 3.28 mmol), *ter*–butil éster del ácido (2–cloro–acetil)–carbámico (1.0 g, 5.0 mmol) y Na_2HPO_4 (1.4 g, 10 mmol) en DMA (50 ml) se agitó a 135 °C durante cuatro horas. Se eliminó el solvente a presión reducida. El residuo se sometió a sonicación en acetato de etilo/agua, y el precipitado se filtró. La solución de acetato de etilo se separó y concentró y se cargó en gel de sílice. La columna de sílice se eluyó con hexano/acetato de etilo (1/2) para dar 0.45 g del producto deseado (**10H**). ESI–MS:m/z 444.1 $(M+H)^+$.

Clorhidrato de 6–(6–Bromo–benzotriazol–1–ilmetil)–imidazo[1,2–b]piridazin–2–ilamina (10): Una solución de compuesto **10H** (0.44 g, 1.0 mmol) en HCl 4 N/dioxano (10 ml) se agitó a temperatura ambiente durante 60 minutos, se concentró y se secó al vacío para dar 0.3 g de producto (**10**) en forma de sal clorhidrato. ESI–MS:m/z 344.1 $(M+H)^+$.

Compuesto 11: [6–(6–bromo–benzotriazol–1–ilmetil)–imidazo[1,2–b]piridazin–2–il]–amida del ácido ciclopropancarboxílico

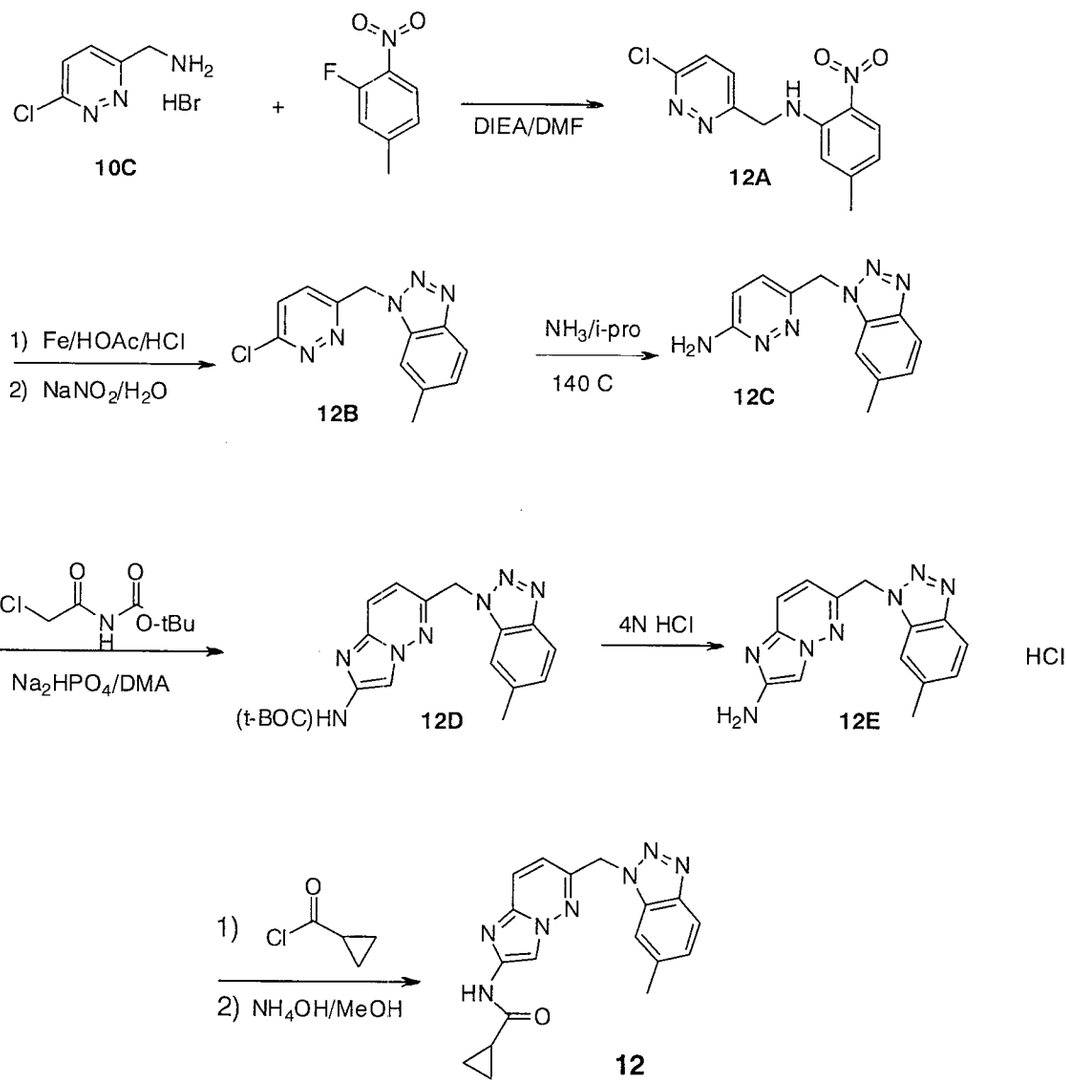


10 **11**

A una solución del compuesto **10** (0.34 g, 1 mmol) en CH_2Cl_2 (25 ml) se añadió DIEA (0.31g, 3 mmol), seguido por cloruro de ciclopropancarbonilo (0.23g, 2.2 mmol). La solución de reacción se agitó a temperatura ambiente durante 60 minutos y se concentró. El residuo se volvió a disolver en metanol (10 ml) y se añadió hidróxido de amonio (0.5 ml). La solución de reacción se agita durante 30 minutos y se concentró. El residuo se disolvió en acetato de etilo y se lavó con 5% de ácido cítrico y luego $NaHCO_3$ saturado. La fase orgánica se secó con $MgSO_4$ y

concentró para dar 0.25 g del producto deseado (**11**). ESI–MS:m/z 412.1 $(M+H)^+$.

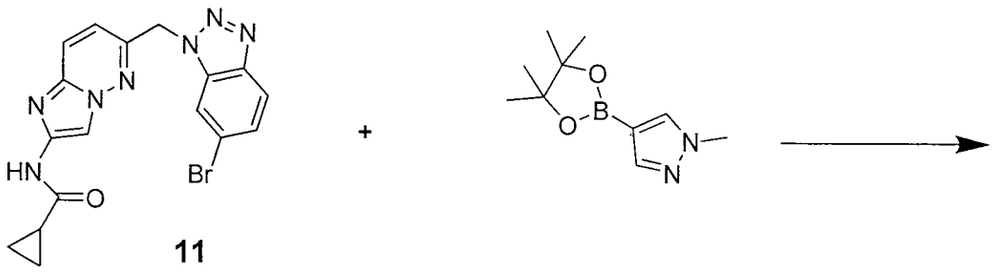
Compuesto 12: N–(6–((6–metil–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



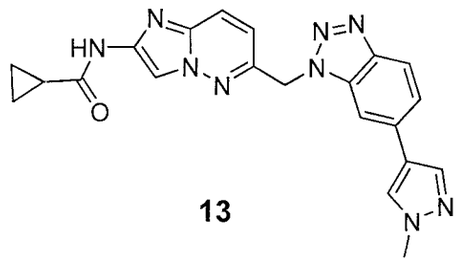
El compuesto **12E** se preparó usando a un procedimiento similar al descrito en relación con el compuesto **10**, excepto que se uso 2–fluoro–4–metil–1–nitro–benceno en lugar del compuesto **10D**. El compuesto **12** luego se preparó a partir del compuesto **12E** usando el método descrito en relación con el compuesto **11**. ^{1}H NMR (DMSO–d_6): δ ppm 11.20 (s, 1H), 8.20 (s, 1H), 7.96 (m, 2H), 7.68 (s, 1H), 7.28 (d, 1H), 7.10 (d, 1H), 6.14 (s, 2H), 2.46 (s, 3H), 1.94 (m, 1H), 0.80 (m, 4H).

Compuesto 13: {6–[6–(1–metil–1H–pirazol–4–il)–benzotriazol–1–ilmetil]–

imidazo[1,2–b]piridazin–2–il}–amida del ácido ciclopropancarboxílico



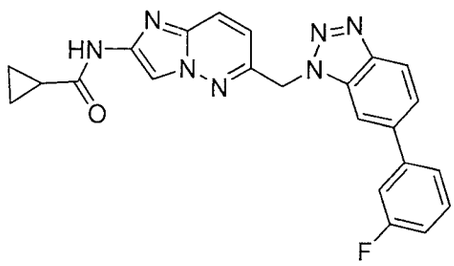
11



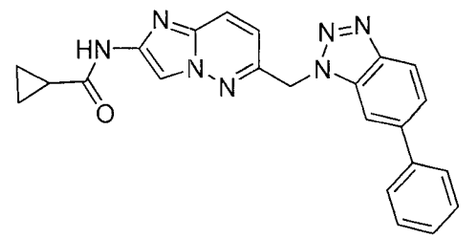
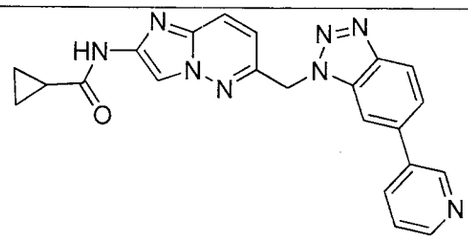
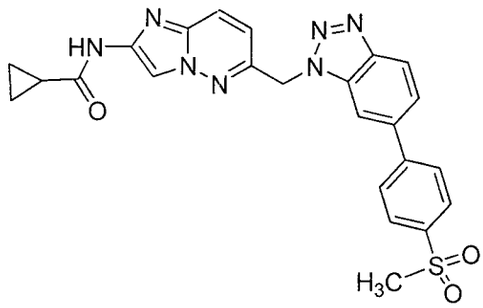
13

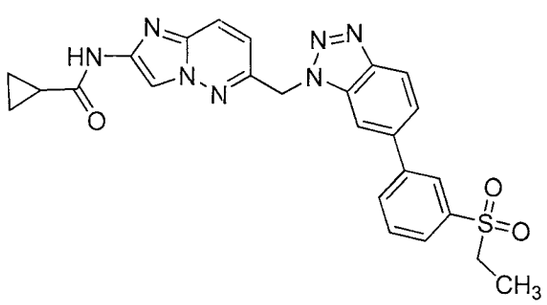
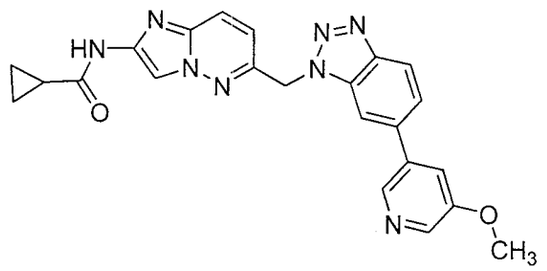
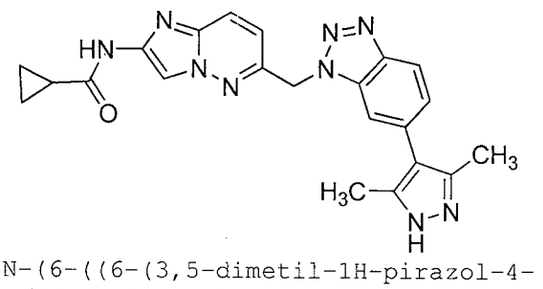
Una mezcla del compuesto **11** (20 mg, 0.05 mmol), pinacol éster del ácido 1–metilpirazol–4–borónico (20 mg, 0.1 mmol) y cantidad catalítica de $Pd(dppf)Cl_2$ en una solución de $NaHCO_3$ saturado en dioxano/H2O (2/1) solución (0.5 ml) se calentó usando un horno a microondas a 120 °C durante 30 minutos. Después de la purificación por LCMS preparativa, se obtuvieron 11 mg del producto deseado como sal de TFA. ^1H NMR (DMSO–d_6): δ ppm 11.40 (s, 1H), 8.32 (s, 1H), 8.16 (s, 1H), 8.08 (s, 1H), 8.04 (d, 1H), 7.96 (m, 2H), 7.64 (m, 1H), 7.14 (d, 1H), 6.16 (s, 2H), 3.90 (s, 3H), 1.94 (m, 1H), 0.80 (m, 4H) ESI–MS:m/z 414.2 $(M+H)^+$.

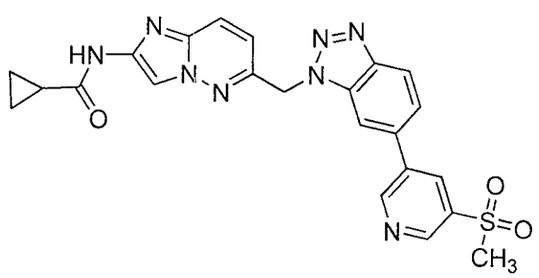
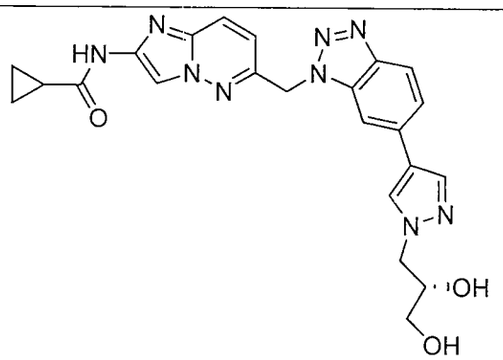
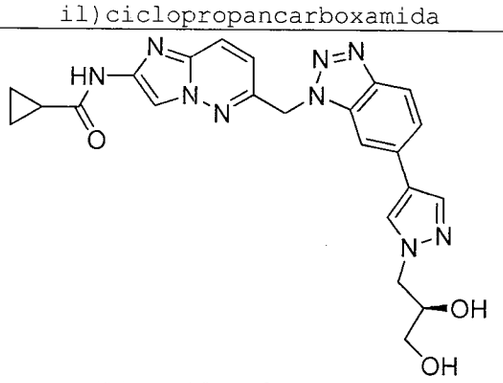
De una manera similar al compuesto **13**, se sintetizaron y purificaron los compuestos **14–24** a partir del compuesto **11** y el correspondiente ácido o éster borónico.

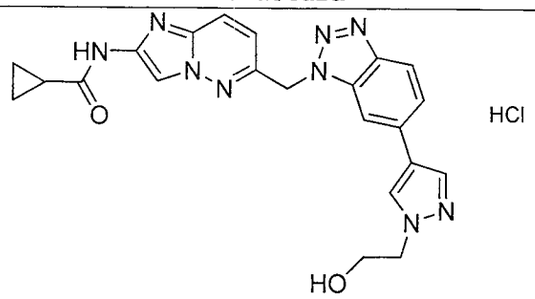
Compuesto	Estructura	LC/MS	NMR
14	 N-(6-((6-(3-fluorofenil)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	427	^{1}H NMR (400MHz, DMSO-d_6) δ ppm 11.17 (s, 1 H), 8.40 - 8.28 (m, 1 H), 8.21 - 8.11 (m, 1 H), 7,97 (d, *J* = 9.3 Hz, 1 H), 7.86 - 7.78 (m, 1 H), 7.69 - 7.45 (m, 4 H), 7.31 - 7.21 (m, 1 H), 7.16 (d, *J* = 9.3 Hz, 1 H), 6.30 - 6.17 (m, 2 H), 1.92 (quin, *J* = 6.1 Hz, 1 H), 0.86 - 0.75 (m, 4 H)

000430

Compuesto	Estructura	LC/MS	NMR
15	 N-(6-((6-fenil-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	409	1H NMR (400MHz, DMSO-d6) δ ppm 11.18 (s, 1 H), 8.24 (s, 1 H), 8.19 - 8.13 (m, 2 H), 7.97 (d, J = 9.3 Hz, 1 H), 7.81 - 7.73 (m, 3 H), 7.52 (t, J = 7.6 Hz, 2 H), 7.45 - 7.38 (m, 1 H), 7.16 (d, J = 9.1 Hz, 1 H), 6.28 - 6.19 (m, 2 H), 1,92 (quin, J = 6.1 Hz, 1 H), 0.85 - 0.78 (m, 4 H)
16	 N-(6-((6-(piridin-3-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	410	---
17	 N-(6-((6-(4-(metilsulfonil)fenil)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	487	1H NMR (400MHz, DMSO-d6) δ ppm 11.18 (s, 1 H), 8.39 (s, 1 H), 8.25-8.20 (m, 1 H), 8.14 (s, 1 H), 8.09-8.03 (m, 4 H), 7.98 (d, J = 9.9 Hz, 1 H), 7.86-7.80 (m, 1 H), 7.17 (d, J = 9.3 Hz, 1 H), 6.27 (s, 2 H), 3.28 (s, 3 H), 1.98 - 1.85 (m, 1H), 0.85 - 0.77 (m, 4H)

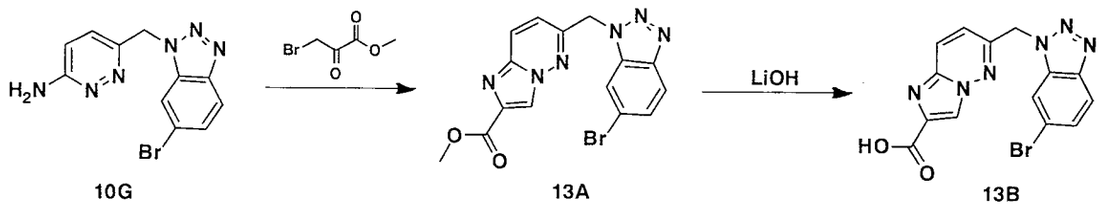
Compuesto	Estructura	LC/MS	NMR
18	 N-(6-((6-(3-(etilsulfonil)fenil)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	501	1H NMR (400MHz,DMSO-d6) δ ppm 11.17 (s, 1H), 8.39 (s, 1H), 8.28-8.20 (m, 2H), 8.13 (s, 2H), 7.95 (dd, J=8.7, 14.8 Hz, 3H), 7.90 - 7.79 (m, 2H), 7.15 (d, J=9.3 Hz, 1H), 6.28 (s, 2H), 1.92 (d, J=5.3 Hz, 1H), 1.14 (t, J=7.2 Hz, 4H), 0.88-0.76 (m, 4H)
19	 N-(6-((6-(5-metoxipiridin-3-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	440	1H NMR (400MHz, DMSO-d6) δ ppm 11.18 (s, 1H), 8.64 (d, J=1.8 Hz, 1H), 8.47 - 8.36 (m, 2H), 8.21 (d, J=8.8 Hz, 1H), 8.14 (s, 1H), 7.98 (d, J=9.3 Hz, 1H), 7.91 - 7.79 (m, 2H), 7.17 (d, J=9.3 Hz, 1H), 6.26 (s, 2H), 3.97 - 3.93 (m, 3H), 2.02-1.86 (m, 1H), 0.83 - 0.78 (m, 4H)
20	 N-(6-((6-(3,5-dimetil-1H-pirazol-4-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	427	1H NMR (400MHz, DMSO-d6) δ ppm 11.20 (s, 1H), 8.17 (s, 1H), 8.08 (d, J= 8.6 Hz, 1H), 7.99 (d, J=9.3 Hz, 1H), 7.71 (s, 1H), 7.44 - 7.35 (m, 1H), 7.17 (d, J=9.3 Hz, 1H), 6.20 (s, 2H), 2.26 - 2.16 (m, 6H), 2.02 - 1.88 (m, 1H), 0.90 - 0.77 (m, 4 H)

Compuesto	Estructura	LC/MS	NMR
21	 N-(6-((6-(5-(metilsulfonil)piridin-3-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	488	1H NMR (400MHz, DMSO-d6) δ ppm 11.17 (s, 1H), 9.35 (d, J=2.0 Hz, 1 H), 9.19 - 9.04 (m, 1H), 8.70 - 8.65 (m, 1H), 8.54 (s, 1H), 8.30-8.25 (m, 1 H), 8.18-8.10 (m, 1H), 8.00-7.91 (m, 2 H), 7.17 (d, J=9.3 Hz, 1 H), 6.29 (s, 2 H), 3.42 (s, 3 H), 1.96-1.86 (m, 1 H), 0.85 - 0.77 (m, 4H)
22	 (S)-N-(6-((6-(1-(2,3-dihidroxipropil)-1H-pirazol-4-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	474	1H NMR (400MHz, DMSO-d6) δ ppm 11.18 (s, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 8.14 (d, 2H), 8.00 (m, 3H), 7.70 (d, 1H), 7.20 (d, 1H), 6.16 (s, 2H), 4.26 (m, 1H), 4.10 (m, 1H), 3.34 (m, 1H), 1.94 (m, 1H), 0.83 (m, 4H).
23	 (R)-N-(6-((6-(1-(2,3-dihidroxipropil)-1H-pirazol-4-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	474	1H NMR (400MHz, DMSO-d6) δ ppm 11.18 (s, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 8.14 (d, 2H), 8.00 (m, 3H), 7.70 (d, 1H), 7.20 (d, 1H), 6.16 (s, 2H), 4.26 (m, 1H), 4.10 (m, 1H), 3.34 (m, 1H), 1.94 (m, 1H), 0.83 (m, 4H)

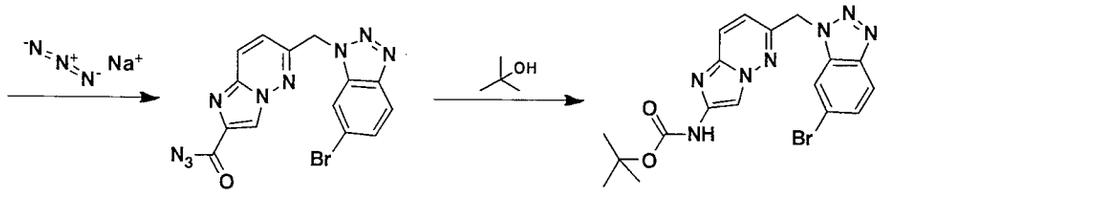
Compuesto	Estructura	LC/MS	NMR
24 a	 HCl Clorhidrato de N-(6-((6-(1-(2-hidroxietil)-1H-pirazol-4-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	444	1H NMR (DMSO-d6): δ 11.21 (s, 1H), 8.30 (s, 1H), 8.20 (s, 1H), 8.12 (s, 1H), 8.02 (m, 3H), 7.70 (d, 1H), 7.14 (d, 1H), 6.16 (s, 2H), 4.17 (t, 2H), 3.77 (m, 2H), 1.94 (m, 1H), 0.83 (m, 4H)

a Punto de fusión: > 200 °C.

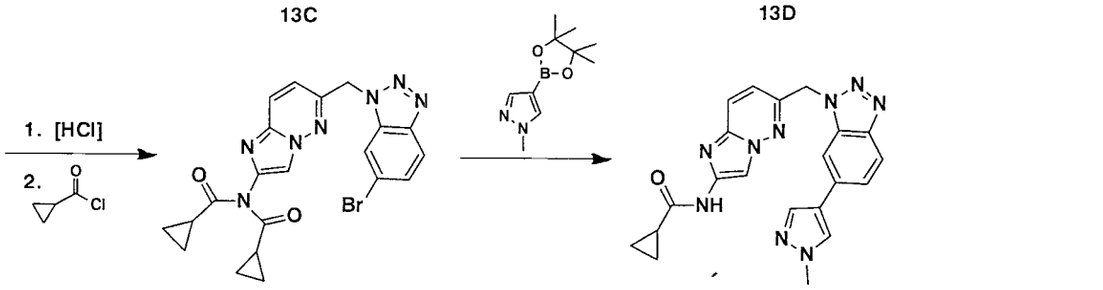
Compuesto 13: N–(6–((6–(1–metil–1H–pirazol–4–il)–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



10G 13A 13B



13C 13D



13E 13

6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin-2–carboxilato de etilo: Una mezcla de 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)piridazin–3–amina **10G** (4.8 g, 15.73 mmol), 3–bromo–2–oxopropanoato de etilo (4.60 g, 23.60 mmol) y $NaHCO_3$ (4.0 g) en dioxano se calentó a 60°C durante

1 hr. Se añadió 3–bromo–2–oxopropanoato de etilo adicional (1.5 g, 7.87 mmol, 0.5 eq) y se agitó a 60°C durante una hora adicional. La mezcla de reacción se filtró y se lavó con dioxano. Se añadió ácido 4–metilbencensulfónico (2.71 g, 15.73 mmol) al filtrado, y la reacción se calentó a 75°C durante 2 horas. La reacción se evaporó a sequedad por medio de evaporación giratoria y el residuo resultante se disolvió en EtOAc. La fase orgánica se lavó con NaHCO3 saturado seguido por NaOH 0.1 N (3x 150 ml). La solución se secó con $MgSO_4$, se filtró, se concentró a sequedad y se purificó por MPLC (10% MeOH/CH_2Cl_2) para proveer el compuesto del título, 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–carboxilato de etilo **13A** (4.7g, 11.6 mmol, 50%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 1.30 (t, *J*=7.07 Hz, 3 H) 4.30 (q, *J*=7.07 Hz, 2 H) 6.26 (s, 2 H) 7.33 (d, *J*=9.60 Hz, 1 H) 7.59 (dd, *J*=8.72, 1.64 Hz, 1 H) 8.08 (d, *J*=8.84 Hz, 1 H) 8.23 (d, *J*=9.60 Hz, 1 H) 8.31 (d, *J*=1.26 Hz, 1 H) 8.77 (s, 1 H). MS:m/z 401.2 $(M+H)^+$.

Ácido 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin-2–carboxílico: A una solución de 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin-2–carboxilato de etilo **13A** (5 g, 12.46 mmol) en 10% de H_2O/MeOH (200 ml), se añadió LiOH (0.597 g, 24.92 mmol). La reacción se agitó a temperatura ambiente durante 18 horas y luego se concentró para eliminar el MeOH. Se añadió H_2O (100 ml) y el pH se ajustó a 4 con HCl concentrado. El sólido resultante se recolectó por filtración, se lavó con agua seguido por EtOAc, y se secó al vacío sobre P_2O_5 para proveer el compuesto del título, ácido 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin-2–carboxílico **13B** (3.6 g 9.65 mmol, 77%). El filtrado se extrajo con EtOAc (3 x 150 ml) y las fases orgánicas se combinaron, secaron con $MgSO_4$, se filtraron y se concentraron a sequedad para dar 0.6 g adicionales del producto. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 6.24 (s, 2 H) 7.24 (d, *J*=9.35 Hz, 1 H) 7.58 (dd, *J*=8.84, 1.77 Hz, 1 H) 8.04 – 8.14 (m, 2 H) 8.32 (d, *J*=1.01 Hz, 1 H) 8.47 (s, 1 H). MS:m/z 373.2 $(M+H)^+$.

6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin-2–carbonilazida: A una solución agitada de ácido 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin-2–carboxílico **13B** (3.6 g, 9.65 mmol), N–etil–N–isopropilpropan–2–amina (7.48 g, 57.9 mmol) y azida sódica

(6.27 g, 96 mmol) en DMF anhidro (60 ml), se añadió en porciones PyBOP (6.02 g, 11.58 mmol) a temperatura ambiente durante 5 min. La reacción se agita durante otros 30 min y luego se vertió en una mezcla de EtOAc/H_2O (100/300 ml) y se agitó bien. El precipitado resultante se filtró, se lavó con H_2O seguido por EtOAc, y se secó al vacío sobre P_2O_5 durante 18 horas para proveer el compuesto del título, 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–carbonilazida **13C** (2.1g, 5.28 mmol, 55%). La solución en EtOAc se lavó con 5% de ácido cítrico (2 x100 ml), $NaHCO_3$, se secó con $MgSO_4$, se filtró y se concentró a sequedad para dar producto bruto adicional (1.6 g de 80% de material puro). ^1H NMR (400 MHz, DMSO–d_6) δ ppm 6.28 (s, 2 H) 7.37 (d, *J*=9.60 Hz, 1 H) 7.59 (dd, *J*=8.84, 1.77 Hz, 1 H) 8.09 (d, *J*=8.84 Hz, 1 H) 8.26 (d, *J*=10.10 Hz, 1 H) 8.32 (d, *J*=1.26 Hz, 1 H) 8.92 (s, 1 H). MS:m/z 398.2 $(M+H)^+$.

6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–ilcarbamato de ter–Butilo: Una suspensión de 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin-2–carbonil azida **13C** (1 g, 2.51 mmol) en 2–metilpropan–2–ol (50 ml, 753 mmol) se calentó a 100 °C en un microondas durante 3 horas. La reacción se repitió una vez. Las reacciones se combinaron y el solvente se eliminó por medio de evaporación giratoria. El residuo resultante se suspendió en EtOAc/H_2O y se sometió a sonicación. El sólido resultante se recolectó por filtración, se lavó con H_2O seguido por EtOAc, y se secó al vacío sobre P_2O_5 para proveer el compuesto del título, 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–ilcarbamato de ter–butilo **13D** (1.7g, 3.83 mmol, 77%). ^1H NMR (400 MHz, DMSO–d_6) δ ppm 1.47 (s, 9 H) 6.18 (s, 2 H) 7.13 (d, *J*=9.35 Hz, 1 H) 7.58 (dd, *J*=8.72, 1.64 Hz, 1 H) 7.94 (d, *J*=9.85 Hz, 2 H) 8.07 (d, *J*=8.84 Hz, 1 H) 8.31 (d, *J*=1.77 Hz, 1 H) 10.24 (br, 1 H). MS:m/z 444.2 $(M+H)^+$.

N–(6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–il)–N–(ciclopropancarbonil)ciclopropancarboxamida: Una mezcla de 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–ilcarbamato de ter–butilo **13D** (1.7 g, 3.83 mmol) en HCl 4 N/dioxano (30 ml) se agitó a temperatura ambiente durante 2 horas. El solvente se eliminó por medio de evaporación giratoria, y el residuo resultante se secó al vacío durante 18 horas para producir el 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–

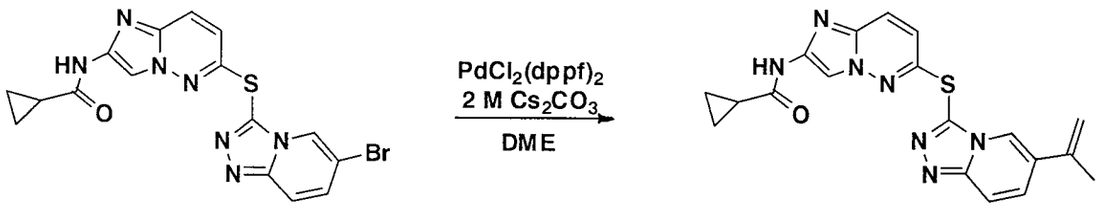
000436

il)metil)imidazo[1,2–b]piridazin–2–amina en forma de una sal HCl. Este material se uso sin purificación adicional. A una solución de 6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–amina HCl (1.8 g, 5.23 mmol) en CH_2Cl_2 se añadió N–etil–N–isopropilpropan–2–amina (2.70 g, 20.92 mmol) seguido por cloruro de ciclopropancarbonilo (1.640 g, 15.69 mmol) a 0°C. La reacción se agitó a temperatura ambiente durante 2 horas. La reacción luego se lavó con 5% de solución de ácido cítrico seguido por $NaHCO_3$ saturado, se secó con $MgSO_4$, se filtró y se concentró a sequedad. El residuo resultante se purificó por MPLC (5% MeOH/CH_2Cl_2) para proveer el compuesto del título, N–(6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–il)–N–(ciclopropancarbonil)-ciclopropancarboxamida **13E** (2.0 g, 4.1 mmol, 80%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.75 – 0.86 (m, 8 H) 1.93 (m, 2 H) 6.19 (s, 2 H) 7.16 (d, *J*=9.35 Hz, 1 H) 7.51 – 7.64 (m, 1 H) 7.99 (d, *J*=9.35 Hz, 1 H) 8.01 – 8.10 (m, 1 H) 8.13 (s, 1 H) 8.31 (d, *J*=1.77 Hz, 1 H). MS:m/z 480.2 $(M+H)^+$.

N–(6–((6–(1–metil–1H–pirazol–4–il)–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: Una mezcla de N–(6–((6–bromo–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–il)–N–(ciclopropancarbonil)ciclopropancarboxamida **13E** (0.7 g, 1.457 mmol), 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (0.303 g, 1.457 mmol) y $PdCl_2$(dppf)–CH_2Cl_2 (0.06 g, 0.075 mmol) en Na_2CO_3 (2N, 6 ml)/dioxano (12 ml) se calentó en un microondas a 110°C durante 45 min. La reacción se filtró y se lavó con EtOAc. Esta reacción se repitió dos veces. Las soluciones orgánicas se combinaron y se lavaron con 5% de ácido cítrico seguido por $NaHCO_3$, se secaron con $MgSO_4$, y se filtraron. Se añadió MeOH a la solución en EtOAc para dar 5% de MeOH (v/v), y la solución resultante se filtró a través de una columna de sílice corta y lavó por completo con 5% de MeOH/EtOAc. Se añadió carbón activado (1 g) al eluyente y se agitó a temperatura ambiente durante 1 hora. La solución se filtró a través de celite y se concentró a sequedad por medio de evaporación giratoria. El material resultante se suspendió en EtOAc (50 ml) y se sometió a sonicación. El sólido resultante se recolectó por filtración y se lavó con EtOAc para proveer el compuesto del título, N–(6–((6–(1–metil–1H–pirazol–4–il)–1H–benzo[d][1,2,3]triazol–1–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida **13** (820 mg, 1.98 mmol, 45%). El filtrado se concentró y

se reconstituyó en 10% MeOH/EtOAc, se cargó en una columna de sílice corta y se eluyó con 10% de MeOH/EA para proporcionar producto adicional (190 mg). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.76 – 0.86 (m, 4 H) 1.88 – 1.97 (m, 1 H) 3.88 (s, 3 H) 6.15 (s, 2 H) 7.12 (d, *J*=9.35 Hz, 1 H) 7.66 (dd, *J*=8.72, 1.39 Hz, 1 H) 7.93 – 8.01 (m, 2 H) 8.04 (d, *J*=8.84 Hz, 1 H) 8.10 (s, 1 H) 8.17 (s, 1 H) 8.26 (s, 1 H) 11.18 (s, 1 H). MS:m/z 414.2 $(M+H)^+$. MP 250.2 – 251.6°C.

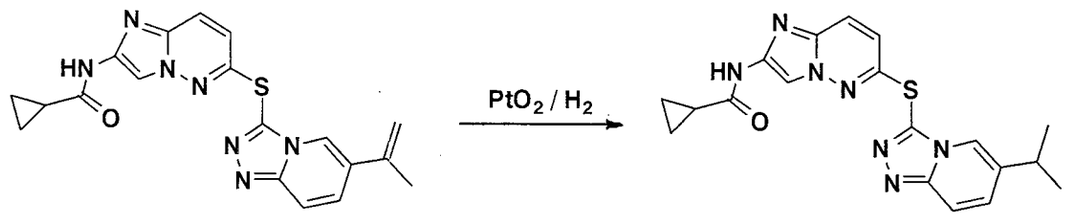
Compuesto 25: N–(6–(6–(prop–1–en–2–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



4 **25**

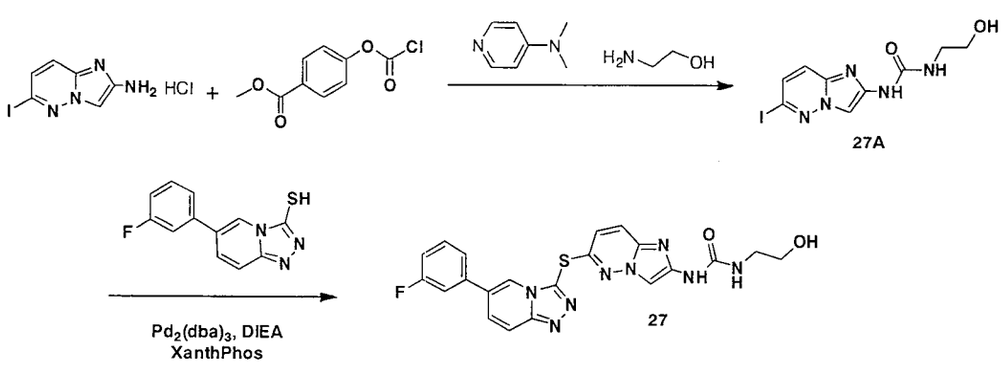
Una mezcla del compuesto **4** (50 mg, 0.10 mmol), 4,4,5,5–tetrametil–2–(prop–1–en–2–il)–1,3,2–dioxaborolano (71 mg, 0.43 mmol), Cs_2CO_3 (3 M; 0.11 ml, 0.30 mmol), y $PdCl_2(dppf)_2$ (4.0 mg, 0.0005 mmol) en DME (1.0 ml) se calentó en un microondas a 100 °C durante 1 hora. La mezcla de reacción luego se concentró a sequedad por medio de evaporación giratoria. El material bruto resultante se reconstituyó en DMSO (1.0 ml) y se purificó por medio LCMS disparada por masa preparativa usando un gradiente de elución de 25–50% ACN:0.05% TFA (ac). Las fracciones recolectadas se combinaron y el ACN se eliminó por medio de evaporación giratoria. La mezcla resultante se liofilizó para proveer la sal de TFA del compuesto del título. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 11.17 (s, 1 H) 8.31 (s, 1 H) 8.14(s, 1 H) 7.95 (s, 1H) 7.91 (d, *J*=9.5 Hz, 1 H) 7.64 (dd, *J*=9.4 y 1.6 Hz, 1 H) 7.05 (d, *J*=9.4 Hz, 1 H) 5.67 (s, 1 H) 5.29 (s, 1 H) 2.08 (m, 3 H) 1.89 (m, 1 H) 1.06 (m, 2 H) 0.90 (m, 2H) ESI–MS:m/z 391.1 $(M+H)^+$.

Compuesto 26: N–(6–(6–isopropil–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



A una solución de N–(6–(6–(prop–1–en–2–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (150 mg, 0.383 mmol) en etanol (20 ml) se añadió óxido de platino (IV) (4.35 mg, 0.019 mmol). La reacción se agita durante 24 horas a 25° bajo 10 psi de H_2. La mezcla de reacción luego se filtró a través de celite y el filtrado se concentró a sequedad por medio de evaporación giratoria. El material bruto resultante se reconstituyó en DMSO (1.0 ml) y se purificó por medio LCMS disparada por masa preparativa usando un gradiente de elución de 25–50% ACN:0.05% TFA (ac). Las fracciones recolectadas se combinaron y el ACN se eliminó por medio de evaporación giratoria. La mezcla resultante se liofilizó para proveer la sal de TFA del compuesto del título (6.0 mg, 0.015 mmol, 3.98% de rendimiento) en forma de sólido amarillo. ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 0.71 – 0.87 (m, 4 H) 1.19 (d, J=6.82 Hz, 6 H) 1.79 – 1.98 (m, 1 H) 3.02 (dt, J=13.71, 6.92 Hz, 1 H) 7.03 (d, J=9.35 Hz, 1 H) 7.62 (dd, J=9.47, 1.64 Hz, 1 H) 7.90 – 7.97 (m, 3 H) 8.26 (s, 1 H) 11.17 (s, 1 H). ESI–MS:m/z 394.3 $(M+H)^+$.

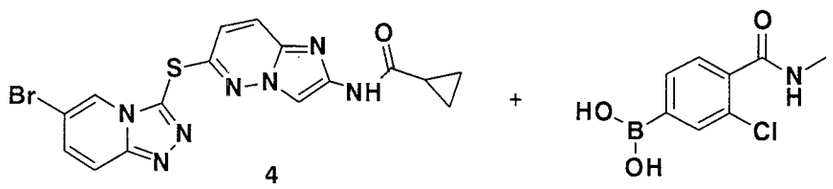
Compuesto 27: 1–(6–(6–(3–fluorofenil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)–3–(2–hidroxietil)urea



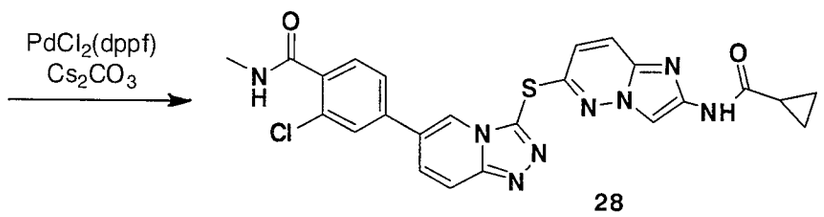
1–(2–Hidroxietil)–3–(6–yodoimidazo[1,2–b]piridazin–2–il)urea: A una solución de clorhidrato de 6–yodoimidazo[1,2–b]piridazin–2–amina (250 mg, 0.843 mmol) y DMAP (227 mg, 1.855 mmol) en DCM (Volumen: 5.0 ml) se añadió 4–(clorocarboniloxi)benzoato de metilo (199 mg, 0.927 mmol) a 25°C. La reacción se agitó a 25°C durante 1 hora para proveer una mezcla heterogénea verde oscura que se filtró. El sólido se resuspendió en DCM (Volumen: 5.0 ml), se trató con etanolamina (2 M en MeOH, 0.843 ml, 1.686 mmol) a temperatura ambiente, y luego se agita durante 1 hora adicional. La reacción luego se evaporó a sequedad por medio de evaporación giratoria, y el residuo resultante se suspendió en EtOAc (Volumen: 10.0 ml). La mezcla se filtró, y el sólido negro resultante se secó bajo alto vacío y se uso sin purificación adicional.

1–(6–(6–(3–Fluorofenil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)–3–(2–hidroxietil)urea: Una mezcla de 1–(2–hidroxietil)–3–(6–yodoimidazo[1,2–b]piridazin–2–il)urea (125 mg, 0.360 mmol), 6–(3–fluorofenil)–[1,2,4]triazolo[4,3–a]piridin-3–tiol (88 mg, 0.360 mmol), $Pd_2(dba)_3$ (19.79 mg, 0.022 mmol), XANTPHOS (25.00 mg, 0.043 mmol), y DIEA (0.126 ml, 0.720 mmol) en DME (Volumen: 2.0 ml) se calentó en el microondas al absorbancia alta durante 30 min a 120°C. La mezcla de reacción luego se concentró a sequedad por medio de evaporación giratoria. El material bruto resultante se reconstituyó en DMSO (Volumen: 1.0 ml) y se purificó por medio LCMS disparada por masa preparativa usando un gradiente de elución de 20–45% ACN:0.05% TFA (ac). Las fracciones recolectadas se combinaron y el ACN se eliminó por medio de evaporación giratoria. La mezcla resultante se liofilizó y se reconstituyó en agua:ACN (1:10, 5.0 ml) Se añadieron dos gotas de [HCl] y la solución resultante se liofilizó para proveer la sal de HCl del compuesto del título (20 mg, 0.043 mmol, 11.96% de rendimiento) en forma de sólido marrón. ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 3.14 (q, J=5.47 Hz, 2 H), 341 (m, 2 H), 6.61 (br. s., 1 H) 6.97 – 7.07 (m, 2 H) 7.21 – 7.32 (m, 1 H) 7.53 (td, J=7.96, 6.06 Hz, 1 H) 7.62 (d, J=8.34 Hz, 1 H) 7.65 – 7.72 (m, 1 H) 7.83 (d, J=9.35 Hz, 1 H) 7.99 (dd, J=9.60, 1.77 Hz, 1 H) 8.11 (dd, J=9.60, 1.01 Hz, 1 H) 8.69 – 8.93 (m, 1 H) 9.17 (s, 1 H). ESI–MS:m/z 465.3 $(M+H)^+$.

Compuesto 28: 2–cloro–4–(3–(2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–iltio)–[1,2,4]triazolo[4,3–a]piridin–6–il)–N–metilbenzamida



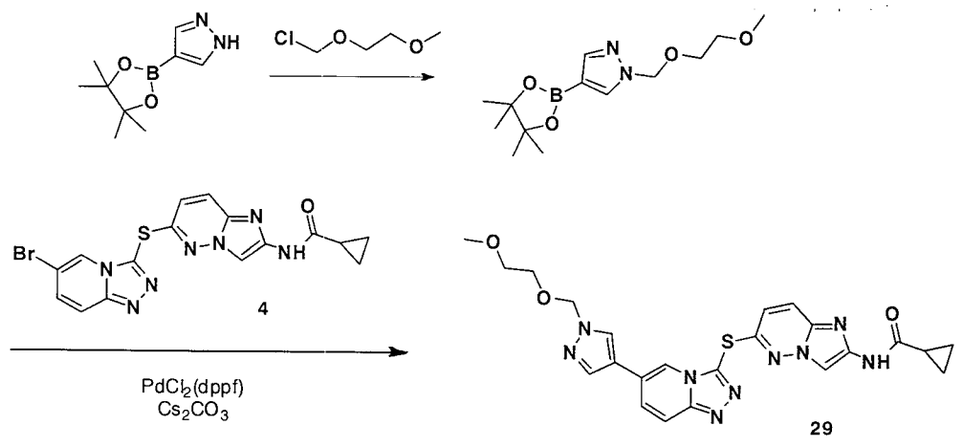
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28

Una mezcla de N–(6–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (150 mg, 0.349 mmol), ácido 3–cloro–4–(metilcarbamoil)fenilborónico (112 mg, 0.523 mmol), $PdCl_2$(dppf) (12.75 mg, 0.017 mmol), y carbonato de cesio (0.349 ml, 1.046 mmol) en DME (Volumen: 1.0 ml) se calentó en un microondas a alta absorbancia durante 1 hora a 100 °C. La mezcla de reacción luego se concentró a sequedad por medio de evaporación giratoria. El material bruto resultante se reconstituyó en DMSO (Volumen: 1.0 ml) y se purificó por medio LCMS disparada por masa preparativa usando un gradiente de elución de 20–45% ACN:0.05% TFA (ac). Las fracciones recolectadas se combinaron y el ACN se eliminó por medio de evaporación giratoria. La mezcla resultante se liofilizó para proveer la sal de TFA del compuesto del título (6.0 mg, 0.012 mmol, 3.32% de rendimiento) en forma de sólido amarillo pálido. ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 0.69 – 0.85 (m, 4 H) 1.81 – 1.96 (m, 1 H) 2.75 (d, J=4.55 Hz, 3 H) 7.07 (d, J=9.60 Hz, 1 H) 7.51 (d, J=8.08 Hz, 1 H) 7.79 (dd, J=7.83, 1.77 Hz, 1 H) 7.87 – 7.97 (m, 3 H) 8.00 (dd, J=9.60, 1.77 Hz, 1 H) 8.11 (dd, J=9.60, 1.01 Hz, 1 H) 8.39 (d, J=4.80 Hz, 1 H) 8.86 (d, J=1.52 Hz, 1 H) 11.15 (s, 1 H). ESI–MS:m/z 419.2 $(M+H)^+$.

Compuesto 29: N–(6–(6–(1–((2–metoxietoxi)metil)–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

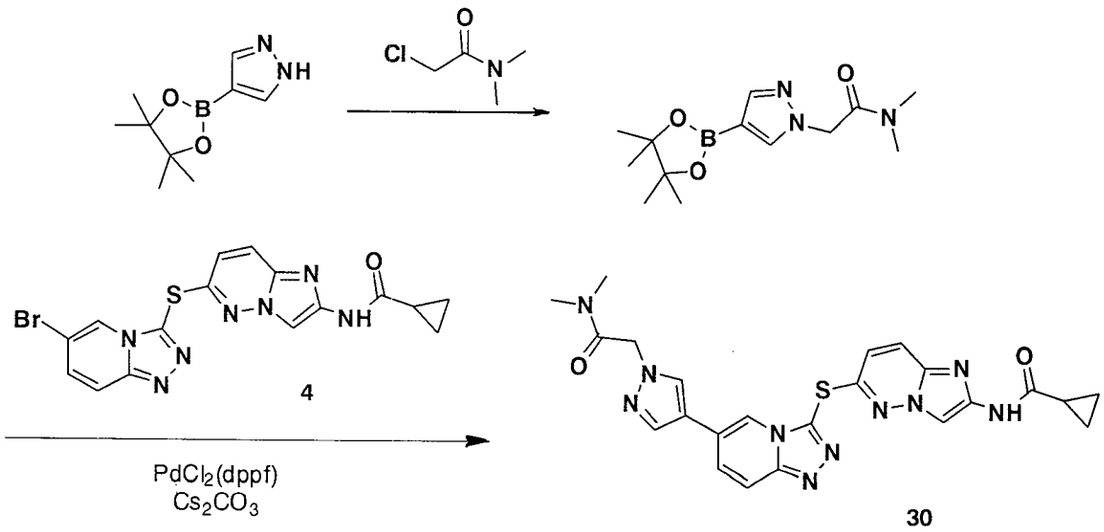


Una solución de 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (0.8 g, 4.1 mmol), carbonato de cesio (2.0 g, 6.2 mmol), y 1–(clorometoxi)–2–metoxietano (0.59 ml, 5.2 mmol) en DMF (14 ml) se calentó en un microondas a 90°C durante 1 hora. Después del calentamiento inicial, se añadieron 1–(clorometoxi)–2–metoxietano (0.59 ml) y carbonato de cesio (2 g) adicionales. El calentamiento se repitió durante 1 hora adicional. Las mezclas de reacción bruta luego se diluyeron con agua (250 ml) y extrajeron con acetato de etilo (3 x 50 ml). El compuesto del título se purificó por columna de gel de sílice usando DCM/EtOAc/MeOH (8/1.5/0.5) como eluyente para dar 1–(2–metoxietil)–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazole (1.6 g) en forma de aceite amarillo claro. ESI–MS:m/z 283.2 $(M+H)^+$.

Una mezcla de N–(6–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (100 mg, 0.232 mmol), 1–((2–metoxietoxi)metil)–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (328 mg, 1.162 mmol), pdcl2(dppf) (8.50 mg, 0.012 mmol), y carbonato de cesio (0.232 ml, 0.697 mmol) en dioxano (Volumen: 1.0 ml) se calentó en un microondas a alta absorbancia durante 1 hora a 100°C. La mezcla de reacción luego se concentró a sequedad por medio de evaporación giratoria. El material bruto resultante se reconstituyó en DMSO (Volumen: 1.0 ml) y se purificó por medio LCMS disparada por masa preparativa usando un gradiente de elución de 15–40% ACN:0.05% TFA (ac). Las fracciones recolectadas se combinaron y el ACN se eliminó por medio de

evaporación giratoria. La mezcla resultante se liofilizó para proveer la sal de TFA del compuesto del título (8.0 mg, 0.016 mmol, 6.81% de rendimiento) en forma de sólido amarillo pálido. ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 0.72 – 0.78 (m, 4 H) 1.90 (m, 1 H) 3.20 (m, 3 H) 3.38 – 3.42 (m, 2 H) 3.54 – 3.58 (m, 2 H) 5.45 (m, 2 H) 7.00 (m, 1 H) 7.67 (m, 1 H) 7.91 – 7.96 (m, 3 H) 8.04 (m, 1 H) 8.59 (m, 1 H), 8.76 (m, 1 H) 11.16 (s, 1 H). ESI–MS:m/z 506.3 $(M+H)^+$.

Compuesto 30: N–(6–(6–(1–(2–(dimetilamino)–2–oxoetil)–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

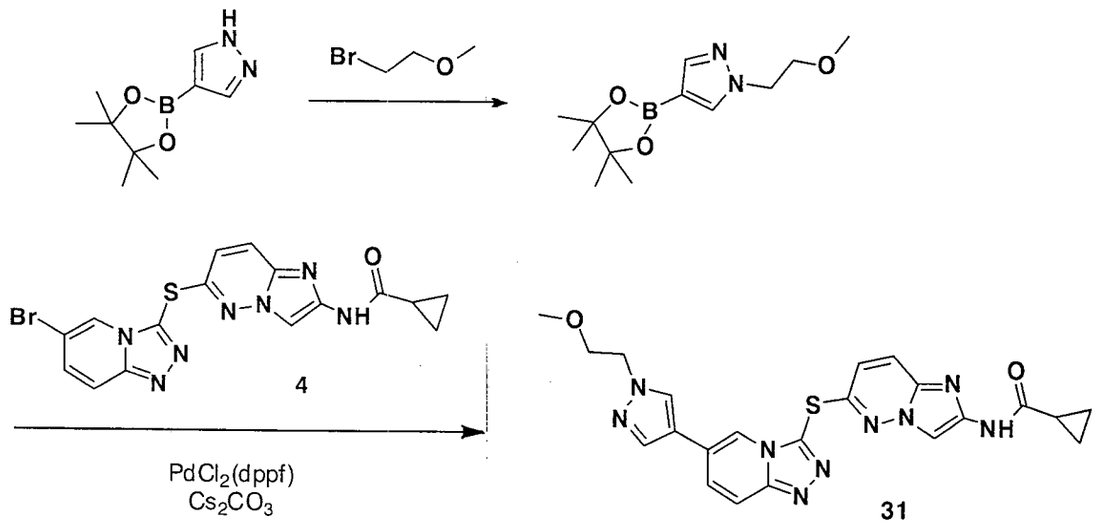


Una solución de 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (0.8 g, 4.1 mmol), carbonato de cesio (2.0 g, 6.2 mmol), y 2–cloro–N,N–dimetilacetamida (0.47 ml, 4.5 mmol) en DMF (14 ml) se calentó en un microondas a 90°C durante 1 hora. Las mezclas de reacción brutas luego se diluyeron con agua (300 ml) y extrajeron con acetato de etilo (3 x 50 ml). El producto se purificó por columna de gel de sílice usando DCM/EtOAc/MeOH (8/1.5/0.5) como eluyente para proveer N,N–dimetil–2–(4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol–1–il)acetamida (1.3 g) en forma de aceite amarillo claro. ESI–MS:m/z 280.3 $(M+H)^+$.

Una mezcla de N–(6–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (100 mg, 0.232 mmol), N,N–dimetil–2–(4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol–1–il)acetamida (324 mg, 1.162 mmol), pdcl2(dppf) (8.50 mg, 0.012 mmol), y carbonato de cesio (0.232 ml,

0.697 mmol) en dioxano (Volumen: 1.0 ml) se calentó en un microondas a alta absorbancia durante 1 hora a 100 °C. La mezcla de reacción luego se concentró a sequedad por medio de evaporación giratoria. El material bruto resultante se reconstituyó en DMSO (Volumen: 1.0 ml) y se purificó por medio LCMS disparada por masa preparativa usando un gradiente de elución de 15–40% ACN:0.05% TFA (ac). Las fracciones recolectadas se combinaron y el ACN se eliminó por medio de evaporación giratoria. La mezcla resultante se liofilizó para proveer la sal de TFA del compuesto del título (4.8 mg, 9.55 µmol, 4.11% de rendimiento) en forma de sólido amarillo. ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 0.79 (d, J=6.06 Hz, 4 H) 1.90 (d, J=6.57 Hz, 1 H) 2.84 (s, 3 H) 3.03 (s, 3 H) 5.12 (s, 2 H) 7.00 (d, J=9.35 Hz, 1 H) 7.87 – 7.97 (m, 3 H) 8.01 – 8.08 (m, 2 H) 8.31 (s, 1 H) 8.71 (s, 1 H) 11.16 (s, 1 H). ESI–MS:m/z 503.3 $(M+H)^+$.

Compuesto 31: **N**–(6–(6–(1–(2–metoxietil)–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

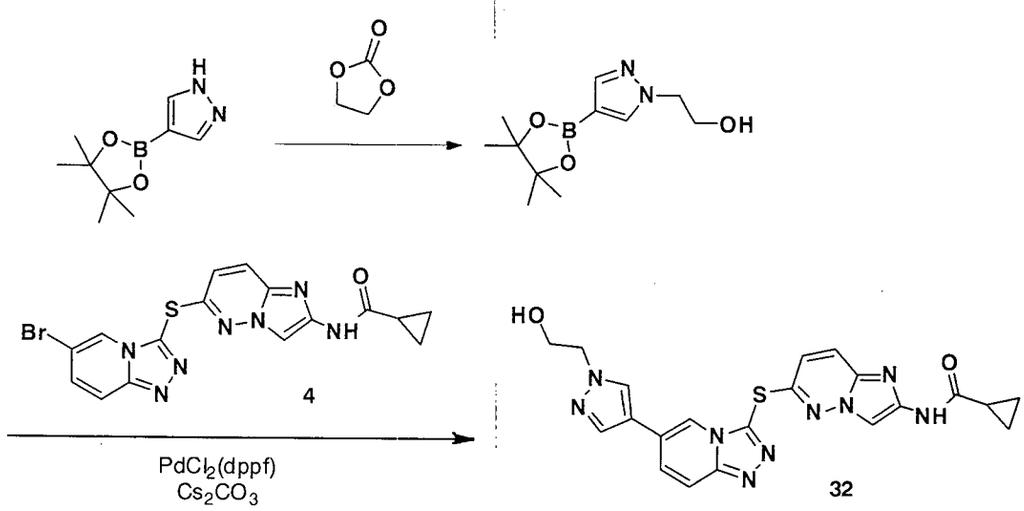


Una solución de 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (0.8 g, 4.1 mmol), carbonato de cesio (2.0 g, 6.2 mmol), y 1–bromo–2–metoxietano (0.41 ml, 4.3 mmol) en DMF (14 ml) se calentó en un microondas a 90°C durante 1 hora. Después del calentamiento inicial, se añadió 1–bromo–2–metoxietan (0.41 ml) se añadió a la reacción. El calentamiento se repitió durante 1 hora adicional. Las mezclas de reacción brutas luego se diluyeron con agua (250 ml) y se extrajeron con acetato de etilo (3 x 50 ml). El producto se purificó por columna de gel de

sílice usando DCM/EtOAc/MeOH (8/1.5/0.5) como eluyente para dar 1–(2–metoxietil)–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (1.2 g) en forma de aceite amarillo claro. ESI–MS:m/z 253.2 $(M+H)^+$.

Una mezcla de N–(6–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (100 mg, 0.232 mmol), 1–(2–metoxietil)–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (410 mg, 1.627 mmol), pdcl2(dppf) (8.50 mg, 0.012 mmol), y carbonato de cesio (0.232 ml, 0.697 mmol) en dioxano (Volumen: 1.0 ml) se calentó en un microondas a alta absorbancia durante 1 hora a 100 °C. La mezcla de reacción luego se concentró a sequedad por medio de evaporación giratoria. El material bruto resultante se reconstituyó en DMSO (Volumen: 1.0 ml) y se purificó por medio LCMS disparada por masa preparativa usando un gradiente de elución de 15–40% ACN:0.05% de TFA (ac). Las fracciones recolectadas se combinaron y el ACN se eliminó por medio de evaporación giratoria. La mezcla resultante se liofilizó para proveer la sal de TFA del compuesto del título (6.0 mg, 0.013 mmol, 5.43% de rendimiento) en forma de sólido amarillo. ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 0.69 – 0.86 (m, 4 H) 1.90 (m, 1 H) 3.20 (m, 3 H) 3.63 – 3.70 (m, 2 H) 4.22 – 4.27 (m, 2 H) 7.00 (m, 1 H) 7.57 (m, 1 H) 7.86 – 7.95 (m, 3 H) 8.04 (m, 1 H) 8.08 (m, 1 H) 8.37 (m, 1 H), 11.16 (s, 1 H). ESI–MS:m/z 476.3 $(M+H)^+$.

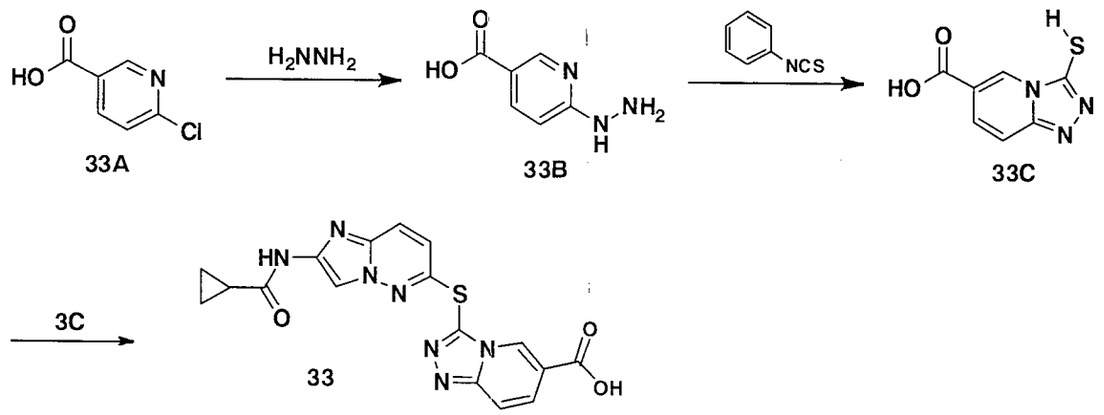
Compuesto 32: N–(6–(6–(1–(2–hidroxioxietil)–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



2–(4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol–1–il)etanol se sintetizó de acuerdo con el procedimiento de la publicación PCT No. WO 2008/44022, que se incorpora en la presente en su totalidad. En forma específica, 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1*H*–pirazol (5.0 g, 25.8 mmol), 1,3–dioxolan–2–ona (2.5 g, 28.3 mmol), e hidróxido de sodio (pellet, 1.0 g, 25.8 mmol) se disolvieron en DMF (206 ml). La mezcla de reacción se calentó a reflujo durante 2 horas. Se añadió carbón activado después de la reacción se enfrió a temperatura ambiente y la reacción se agita durante 1 hora y luego se filtró a través de celite. La torta de filtrado luego se lavó con DMF (120 ml), y el filtrado se concentró para proveer 2–(4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol–1–il)etanol en forma de un aceite amarillo (6 g). El material resultante se uso sin purificación adicional. ESI–MS:m/z 239.3 $(M+H)^+$.

Una mezcla de *N*–(6–(6–bromo–[1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–il)ciclopropancarboxamida (500 mg, 1.2 mmol), 2–(4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1*H*–pirazol–1–il)etanol (1.4 g, 5.8 mmol), carbonato de cesio (1.14 ml, 3 M solución), y [1,1'–bis(difenilfosfino)ferroceno]–dicloropaladio(II) (85 mg, 0.12 mmol) en DME (5 ml) se calentó en un microondas durante 30 min a 100°C. La mezcla de reacción luego se concentró a sequedad por medio de evaporación giratoria. El material bruto resultante se reconstituyó en DMSO (Volumen: 1.0 ml) y se purificó por medio LCMS disparada por masa preparativa usando un gradiente de elución de 10–35% ACN:0.05% TFA (ac). Las fracciones recolectadas se combinaron y el ACN se eliminó por medio de evaporación giratoria. La mezcla resultante se liofilizó y se reconstituyó en agua:ACN (1:10, 5.0 ml) Se añadieron dos gotas de HCl concentrado y la solución resultante se liofilizó para proveer la sal de HCl del compuesto del título ^{1}H NMR (400MHz, DMSO–d_6)δ ppm 11.16 (s, 1 H) 8.69 (s, 1 H) 8.38 (s, 1 H) 8.04 – 8.08 (m, 1 H) 8.02 (d, *J*=1.01 Hz, 1 H) 7.91 – 7.95 (m, 1 H) 7.88 – 7.91 (m, 2 H) 6.99 – 7.05 (m, 1 H) 4.10 – 4.16 (m, 2 H) 3.73 (t, *J*=5.56 Hz, 2 H) 1.90 (quin, *J*=6.19 Hz, 1 H) 0.74 – 0.84 (m, 4 H) ESI–MS:m/z 462.3 $(M+H)^+$. MP 182 – 184°C.

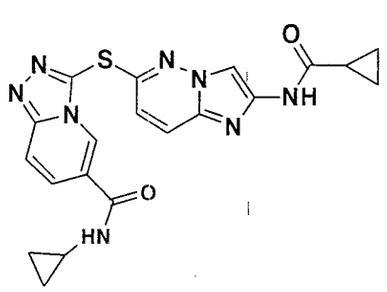
Compuesto 33: Ácido 3–(2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–iltio)–[1,2,4]triazolo[4,3–a]piridin-6–carboxílico



Ácido 3–mercapto–[1,2,4]triazolo[4,3–a]piridin-6–carboxílico: Se trató ácido 6–cloronicotínico (1.6 g) en MeOH (10ml) con NH_2NH_2 (2 g) a 140 °C durante 2 horas. Después de enfriar a –20 °C, el sólido se filtró para dar 560 mg del compuesto **33B**. El compuesto **33B** se trató con isotiocianatobenceno (141 mg) en 1,2–diclorobenceno (5 ml) a 100 °C durante 10 min, y luego 180 °C durante 1 hora. El producto se purificó por LCMS para dar ácido 3–mercapto–[1,2,4]triazolo[4,3–a]piridin-6–carboxílico (450 mg). ESI–MS:m/z 196.1 $(M+H)^+$.

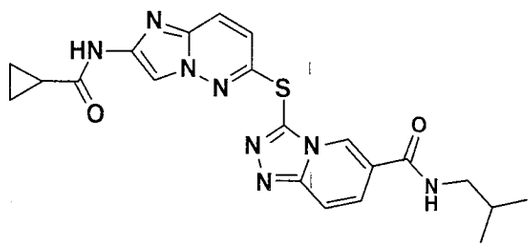
Ácido 3–(2–(Ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–iltio)–[1,2,4]triazolo[4,3–a]piridin-6–carboxílico: El compuesto **33** se preparó a partir de ácido 3–mercapto–[1,2,4]triazolo[4,3–a]piridin-6–carboxílico siguiendo el procedimiento descrito en la síntesis del compuesto **4**. ^1H NMR (400 MHz, $CDCl_3$–CD_3OD 10:1) δ ppm 9.03 (bs, 1 H), 8.01 (d, *J*=9.1 Hz, 1 H), 7.87 (d, *J*=9.6 Hz, 1 H), 7.68 (d, *J*=9.4 Hz, 1 H), 7.36 (m, 1H), 7.09 (d, *J*=9.3 Hz, 1 H), 2.84 (m, 1H), 1.72 (m, 1 H), 0.97 (m, 2 H), 0.84 (m, 2H) ESI–MS:m/z 396.1 $(M+H)^+$.

Compuesto 34: 3–(2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–iltio)–N–ciclopropil–[1,2,4]triazolo[4,3–a]piridin-6–carboxamida



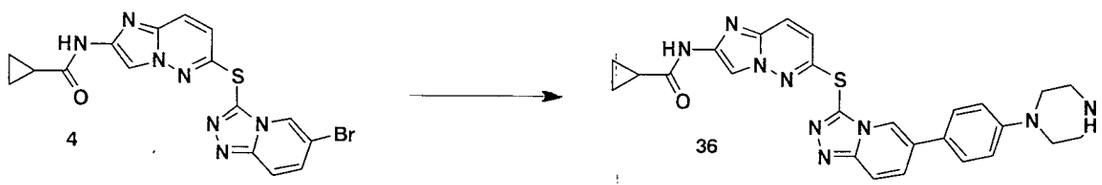
A una solución del compuesto **33** (10 mg), ciclopropanamina (30 mg) y DIEPA (100 uL) en DMF (1 ml) se añadió HATU (20 mg). La mezcla se agitó a ta durante 0.5 h y 60 °C durante 5h. El compuesto del título se aisló por LCMS preparativa. ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD 10:1) δ ppm 8.95 (bs, 1 H), 8.06 (dd, *J*=9.4, 1.6 Hz, 1 H), 7.98 (dd, *J*=9.6, 1.0 Hz, 1 H), 7.93 (s, 1 H), 7.87 (d, *J*=9.4 Hz, 1 H), 7.29 (d, *J*=9.3 Hz, 1 H), 1.77 (m, 1 H), 1.04 (m, 1 H), 0.95 (m, 2H). 0.89 (m, 2H). 0.80 (m, 2H). 0.63 (m, 2H). ESI–MS:m/z 435.1 $(M+H)^+$.

Compuesto 35: 3–(2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–iltio)–N–isobutil–[1,2,4]triazolo[4,3–a]piridin-6–carboxamida



El compuesto **35** se preparó a partir de 2–metilpropan–1–amina siguiendo el procedimiento descrito en la síntesis del compuesto **34**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.88 (bs, 1 H), 8.72 (bs, 1 H), 7.95–7.88 (m, 3H), 7.15 (bs, 1 H), 3.08 (t, *J*=6.0 Hz, 2H), 1.78 (m, 1H), 1.3–1.15 (m, 3H), 0.85 (m, 2H), 0.82 (d, *J*=6.8 Hz, 6H) ESI–MS:m/z 451.1 $(M+H)^+$.

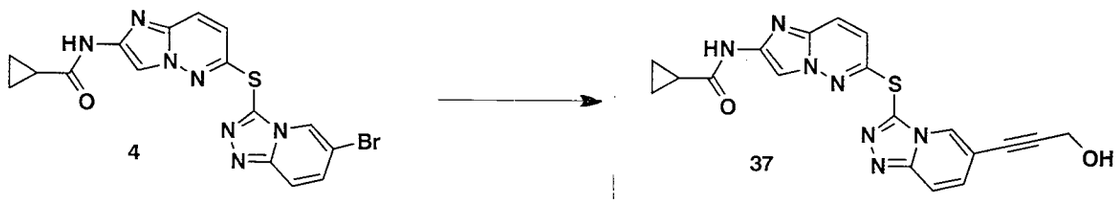
Compuesto 36: N–(6–(6–(4–(piperazin–1–il)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto **36** se preparó a partir de N–(6–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida y 4–(4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil)piperazin-1–carboxilato de ter–butilo siguiendo un procedimiento análogo al descrito en relación con la síntesis del compuesto **5**. El producto bruto se trató con 4 M HCl–dioxano a 80 °C

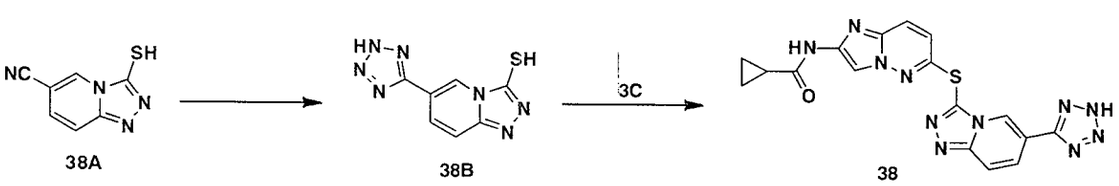
durante 1 h. La purificación de la mezcla por LCMS dio el compuesto del título en forma de sal de TFA. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.61 (bs, 1 H), 7.92–8.0 (m, 2H), 7.8 (bs, 1 H), 7.6 (m, 1H), 7.57, (d, *J*=8.9Hz, 2H), 7.21 (bs, 1H), 7.08, (d, *J*=8.8Hz, 2H), 3.47 (m, 4H), 3.36 (m, 4H), 1.82 (m, 1H), 1.3–1.15 (m, 2H), 0.85 (m, 2H). ESI–MS:m/z 512.2 $(M+H)^+$.

Compuesto 37: N–(6–(6–(3–hidroxiprop–1–ynil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



Una mezcla de N–(6–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (43mg), prop–2–in–1–ol (10 mg), Ph_3P (1.1 mg) y tetrakis(trifenilfosfina)paladio(0) (*es decir*, $Pd[P(C_6H_5)_3]_4$) (4 mg) en THF (1.5 ml), se agitó a ta durante 10 min bajo N_2, y luego se añadió CuI (1 mg). La mezcla se calentó a 60 °C toda la noche. La purificación de la mezcla por LCMS dio el compuesto del título en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO) δ ppm 11.16 (s, 1H), 8.67 (t, *J*=1.0Hz, 1H), 8.00 (dd, *J*=9.4 y 1.0 Hz, 1 H), 7.93 (dd, *J* = 9.3 y 0.7 Hz, 1 H), 7.91 (s, 1H), 7.53 (dd, *J* = 9.4 y 1.5 Hz, 1 H), 7.12 (d, *J* = 9.4 Hz, 1 H), 1.91 (m, 1 H), 1.24 (m, 2 H), 0.80 (m, 2H). ESI–MS:m/z 406.2 $(M+H)^+$.

Compuesto 38: N–(6–(6–(2H–tetrazol–5–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

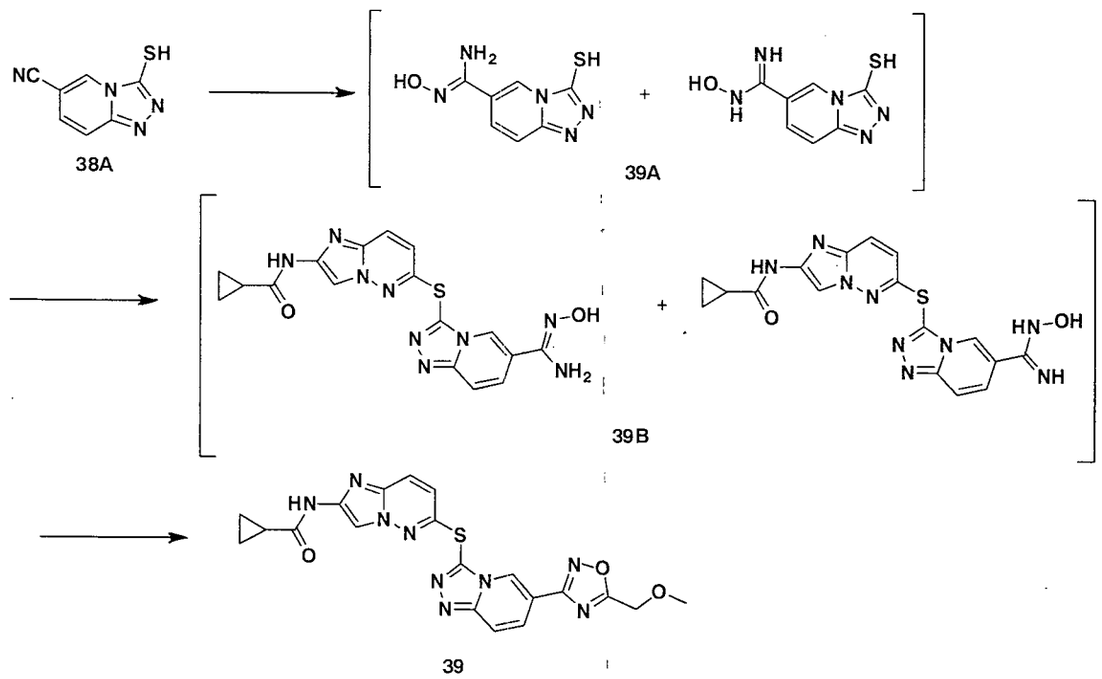


6–(2H–tetrazol–5–il)–[1,2,4]triazolo[4,3–a]piridin-3–tiol: Una mezcla de 3–

mercapto–[1,2,4]triazolo[4,3–a]piridin-6–carbonitrilo (360 mg, 2 mmol), NaN_3 y NH_4Cl en DMF (10ml) se calentó a 140 °C durante 10 h en condiciones de microonda. El producto se purificó por LCMS para dar el compuesto **38B** (320 mg). ESI–MS:m/z 220.1 $(M+H)^+$.

3–(2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–iltio)–N–isobutil–[1,2,4]triazolo[4,3–a]piridin-6–carboxamida: El compuesto **38** se preparó a partir del compuesto **38B** siguiendo el procedimiento descrito en la síntesis del compuesto **4**. ^1H NMR (400 MHz, DMSO) δ ppm 11.16 (s, 1H), 9.14 (t, *J*=1.5Hz, 1H), 8.22 (dd, *J*=9.6 y 1.0 Hz, 1 H), 8.14 (dd, *J*=9.6 y 0.7 Hz, 1 H), 7.95 (s, 1H), 7.94 (d, *J*=9.4 Hz, 1 H), 7.18 (d, *J*=9.6 Hz, 1 H), 1.90 (m, 1 H), 0.78 (bd, J=5.8Hz, 2H). ESI–MS:m/z 419.1 $(M+H)^+$.

Compuesto 39: –N–(6–(6–5-(metoximetil)-1,2,4-oxadiazol-3-il)-[(N'–hidroxicarbamimidoil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



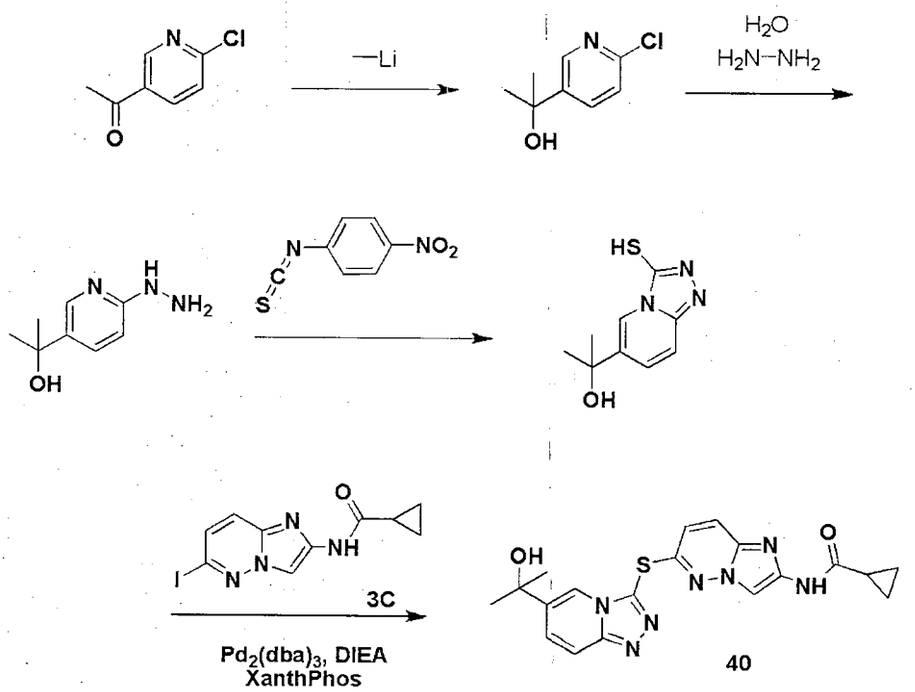
(Z)–N–hidroxi–3–mercapto–[1,2,4]triazolo[4,3–a]piridin-6–carboximidamida: Una mezcla de 3–mercapto–[1,2,4]triazolo[4,3–a]piridin-6–carbonitrilo (390 mg, 2 mmol) e hidroxilamina (50% en peso en agua, 420 mg) en EtOH (4ml) se calentó a 120 °C durante 10 h en condiciones de microonda. El producto se purificó por

LCMS para dar compuesto **39A** y su tautómero (128 mg). ESI–MS:m/z 210.0 $(M+H)^+$.

(Z)–N–(6–(6–(N'–hidroxicarbamimidoil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: El compuesto 39B y su tautómero se prepararon a partir del compuesto 39A y su tautómero siguiendo el procedimiento descrito en la síntesis del compuesto 4. ESI–MS:m/z 410.1 $(M+H)^+$.

N–(6–(6–(5–(metoximetil)–1,2,4–oxadiazol–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: A una mezcla enfriada (–10 °C) del compuesto **39B** (30mg) y DIEPA (200ml) en THF–DME (1–1, 1.5 ml) se añadió una solución de cloruro de 2–metoxiacetilo (11 mg) en THF (0.5 ml). La mezcla se agitó a esta temperatura durante 5 min, y luego ta durante 1 hora. La mezcla se calentó a 140^{0}C en condiciones de microonda durante 30 min, y se purificó por LCMS para dar el compuesto del título en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO) δ ppm 11.49 (s, 1H), 9.09 (bs, 1H), 8.19 (dd, *J*=9.6 y 1.6 Hz, 1 H), 8.11–8.12 (m, 2H), 7.92 (d, *J*=9.3 Hz, 1 H), 7.37 (d, *J*=9.4 Hz, 1 H), 4.77 (s, 1H), 3.56 (s, 3H), 1.77 (m, 1 H), 1.06 (m, 2H), 0.93 (m, 2H). ESI–MS:m/z 463.1 $(M+H)^+$.

Compuesto 40: N–(6–(6–(2–hidroxipropan–2–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



2–(6–Cloropiridin–3–il)propan–2–ol: A una solución de 1–(6–cloropiridin–3–il)etanona (2.0 g, 12.85 mmol) en THF (Volumen: 25 ml) se añadió metillitio (16.07 ml, 25.7 mmol) a 0°C. La reacción se agita durante 1 hora y se dejó calentar a temperatura ambiente. La solución rojo oscuro resultante se inactivó con agua (Volumen: 50 ml), se extrajo con EtOAc (1 x 50 ml), y la fase orgánica se secó en $MgSO_4$. La fase orgánica se filtró y el filtrado se evaporó a sequedad por medio de evaporación giratoria. El material resultante se purificó por medio de MPLC (DCM: MeOH, 95:5) para proveer 2–(6–cloropiridin–3–il)propan–2–ol (.985 g, 5.74 mmol, 44.6% de rendimiento) en forma de sólido rojo oscuro. ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 1.44 (s, 5 H) 5.32 (s, 1 H) 7.44 (d, J=8.34 Hz, 1 H) 7.90 (dd, J=8.34, 2.53 Hz, 1 H) 8.49 (d, J=2.53 Hz, 1 H). ESI–MS:m/z 172.0 $(M+H)^+$.

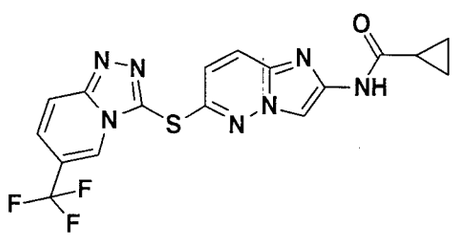
2–(6–Hidrazinilpiridin–3–il)propan–2–ol: Una mezcla de 2–(6–cloropiridin–3–il)propan–2–ol (975 mg, 5.68 mmol), e hidrato de hidrazina (5512 µl, 114 mmol) se calentó en un microondas a alta absorbancia durante 10 hora a 110°C. La mezcla se enfrió a temperatura ambiente y la hidrazina se eliminó por medio de evaporación giratoria. El residuo amarillo resultante se uso sin posterior desarrollo.

2–(3–Mercapto–[1,2,4]triazolo[4,3–a]piridin–6–il)propan–2–ol: Una mezcla de 2–(6–hidrazinilpiridin–3–il)propan–2–ol (250 mg, 1.495 mmol) y 1–isotiocianato–4–nitrobenceno (269 mg, 1.495 mmol) en ACN (Volumen: 2.0 ml) se agitó a temperatura ambiente durante 1 hora. La reacción se diluyó con Et_2O (Volumen: 5.0 ml), y el sólido resultante se filtró. En el sólido estaba presente mínima cantidad de producto. En el estacionamiento durante 1 hora, el filtrado había formado un precipitado. Este se filtró para proveer 2–(5–(2–hidroxipropan–2–il)piridin–2–il)–N–(4–nitrofenil)hidrazinacarbotioamida (175 mg, 0.504 mmol, 33.7% de rendimiento) en forma de sólido anaranjado. Una solución de 2–(5–(2–hidroxipropan–2–il)piridin–2–il)–N–(4–nitrofenil)hidrazinacarbotioamida (275 mg, 0.792 mmol) en DME (Volumen: 2.0 ml) se calentó en un microondas a alta absorbancia durante 3 hora a 110°C. La reacción se extrajo a sequedad en gel de sílice por medio de evaporación giratoria y se purificó el compuesto por MPLC con DCM:MeOH (98:2) para proveer 2–(3–mercapto–[1,2,4]triazolo[4,3–a]piridin–6–il)propan–2–ol.

N–(6–(6–(2–hidroxipropan–2–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: Una mezcla de N–

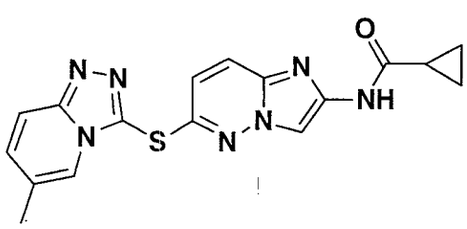
(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (62.7 mg, 0.191 mmol), $Pd_2(dba)_3$ (10.50 mg, 0.011 mmol), XANTPHOS (13.27 mg, 0.023 mmol), DIEA (0.067 ml, 0.382 mmol), y 2–(3–mercapto–[1,2,4]triazolo[4,3–a]piridin–6–il)propan–2–ol (40 mg, 0.191 mmol) en DME (Volumen: 1.5 ml) se calentó en un microondas a alta absorbancia durante 30 min a 120°C. La mezcla de reacción luego se concentró a sequedad por medio de evaporación giratoria. El material bruto resultante se reconstituyó en DMSO (Volumen: 1.0 ml) y se purificó por medio de LCMS disparada por masa preparativa usando un gradiente de elución de 20–45% ACN:0.05% TFA (ac). Las fracciones recolectadas se combinaron y el ACN se eliminó por medio de evaporación giratoria. La mezcla resultante se liofilizó para proveer la sal de TFA del compuesto del título (3.3 mg, 8.06 µmol, 4.22% de rendimiento) en forma de sólido marrón. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.72 – 0.85 (m, 3 H) 1.43 (s, 4 H) 1.91 (m, 1 H) 7.04 (d, J=9.35 Hz, 1 H) 7.70 (dd, J=9.60, 1.77 Hz, 1 H) 7.87 – 8.00 (m, 2 H) 8.32 (d, J=1.52 Hz, 1 H) 11.18 (s, 1 H). ESI–MS:m/z 410.3 $(M+H)^+$.

Compuesto 41: *N*–(6–(6–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se preparó usando un procedimiento análogo al descrito en relación con compuesto **6**. ^{1}H NMR (400MHz, DMSO–d_6) δ = 11.16 (s, 1 H), 9.03 (d, *J* = 1.3 Hz, 1 H), 8.25 – 8.17 (m, 1 H), 7.96 – 7.90 (m, 2 H), 7.83 (dd, *J* = 1.5, 9.6 Hz, 1 H), 7.17 (d, *J* = 9.6 Hz, 1 H), 1.91 (quin, *J* = 6.3 Hz, 1 H), 0.84 – 0.76 (m, 4 H) ESI–MS:m/z 420.3 $(M+H)^+$.

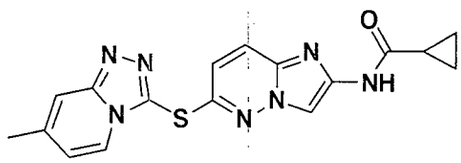
Compuesto 42: *N*–(6–(6–metil–[1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–il)ciclopropancarboxamida



000453

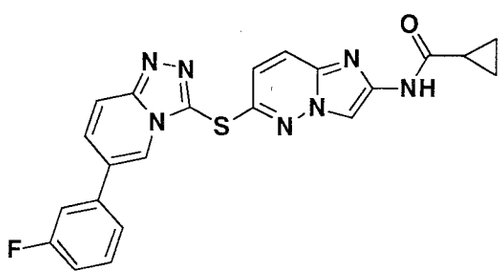
El compuesto del título se preparó usando un procedimiento análogo al descrito en relación con compuesto **6**. ^{1}H NMR (400MHz, DMSO–d_6) δ = 11.17 (s, 1 H), 8.35 (d, *J* = 1.3 Hz, 1 H), 7.96 – 7.87 (m, 3 H), 7.46 (dd, *J* = 1.5, 9.3 Hz, 1 H), 7.00 (d, *J* = 9.3 Hz, 1 H), 2.34 – 2.27 (m, 3 H), 1.95 – 1.86 (m, 1 H), 0.82 – 0.75 (m, 4 H) ESI–MS:m/z 366.3 $(M+H)^+$.

Compuesto 43: *N*–(6–(7–metil–[1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se preparó usando un procedimiento análogo al descrito en relación con compuesto **6**. ^{1}H NMR (400MHz, DMSO–d_6) δ = 11.17 (s, 1 H), 8.38 (d, *J* = 7.1 Hz, 1 H), 7.96 – 7.88 (m, 2 H), 7.76 (d, *J* = 1.3 Hz, 1 H), 7.06 (d, *J* = 9.3 Hz, 1 H), 7.00 (dd, *J* = 1.5, 7.1 Hz, 1 H), 2.44 (s, 3 H), 1.95 – 1.86 (m, 1 H), 0.83 – 0.73 (m, 4 H)ESI–MS:m/z 366.3 $(M+H)^+$.

Compuesto 44: *N*–(6–(6–(3–fluorofenil)–[1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–il)ciclopropancarboxamida

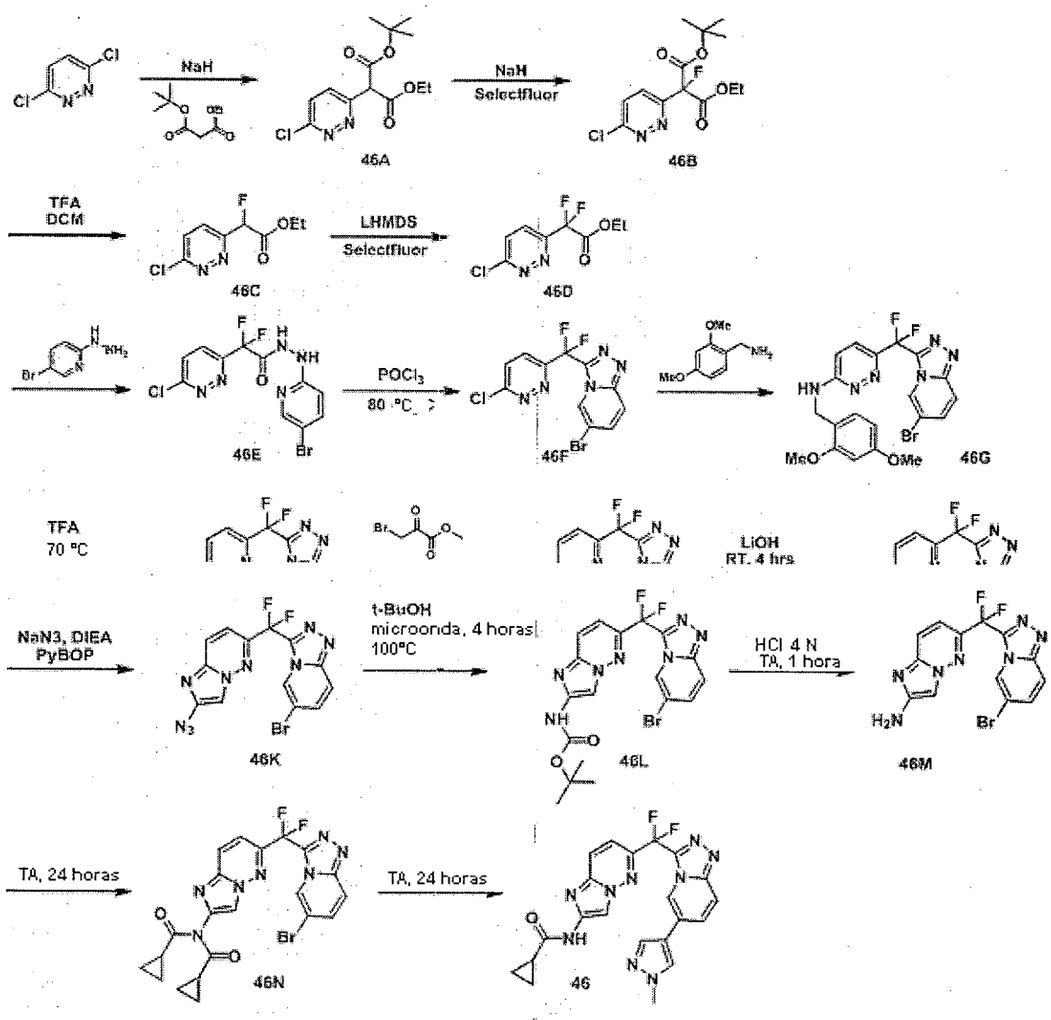


El compuesto del título se preparó usando un procedimiento análogo al descrito en relación con compuesto **6**. ^{1}H NMR (400MHz, DMSO–d_6) δ = 11.15 (s, 1 H), 8.81 (d, *J* = 1.5 Hz, 1 H), 8.11 (dd, *J* = 1.0, 9.6 Hz, 1 H), 7.99 (dd, *J* = 1.6, 9.5 Hz, 1 H), 7.95 – 7.89 (m, 1 H), 7.68 (dt, *J* = 2.1, 10.4 Hz, 2 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.53 (td, *J* = 6.2, 8.0 Hz, 1 H), 7.27 (td, *J* = 2.1, 8.3 Hz, 1 H), 7.07 (d, *J* = 9.6 Hz, 1 H),

1.89 (quin, *J* = 6.3 Hz, 1 H), 0.86 – 0.74 (m, 4 H) ESI–MS:m/z 446.3 $(M+H)^+$.

Compuesto 45: N–(6–(difluoro(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

Método A



2–(6–cloropiridazin–3–il)malonato de 1–ter–Butil 3–etilo: malonato de *ter*–Butil etilo (41.3 ml, 211 mmol) se añadió gota a gota a una suspensión de hidruro de sodio (19.33 g, 483 mmol) en dioxano (1000 ml) a 0°C. La reacción se agitó a 0°C durante 1 hora y luego se dejó calentar a temperatura ambiente. Luego se añadió 3,6–dicloropiridazina (30 g, 201 mmol) en porciones a 25°C. La reacción se agitó a reflujo durante 2 horas y luego se eliminó el solvente por medio de evaporación giratoria. El residuo resultante se disolvió en EtOAc (400 ml), y la fase orgánica se

lavó con NaHCO3 saturado (400 ml), se secó en $MgSO_4$, se filtró, y se concentró a sequedad por medio de evaporación giratoria. Esta reacción se repitió. Los residuos combinados brutos de ambos lotes se purificaron por MPLC (Hex:EtOAc, 8:2) para proveer el compuesto del título, 2–(6–cloropiridazin–3–il)malonato de 1–*ter*–butil 3–etilo (86.5 g, 288 mmol, 71.3 %). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 1.12 – 1.23 (m, 3 H) 1.36 – 1.52 (m, 9 H) 4.20 (m, *J*=10.71, 7.22, 7.22, 3.85, 3.85 Hz, 2 H) 5.29 (s, 1 H) 7.85 (d, *J*=8.84 Hz, 1 H) 7.99 (d, *J*=8.84 Hz, 1 H). ESI–MS:m/z 301.2 $(M+H)^+$.

2–(6–cloropiridazin–3–il)–2–fluoromalonato de 1–ter–Butil 3–etilo: A una solución de 2–(6–cloropiridazin–3–il)malonato de 1–*ter*–butil 3–etilo **45A** (86.5 g, 288 mmol) en THF (2400 ml) se añadió NaH (12.65 g, 316 mmol). La reacción se agitó a 0°C durante 15 min. Una solución turbia de Selectfluor (112 g, 316 mmol) en DMF (seco, 800 ml) se añadió gota a gota a 0°C y luego la reacción se dejó calentar a temperatura ambiente durante 2 horas. La reacción luego se inactivó con NH_4Cl saturado (250 ml) y se redujo en volumen a aproximadamente 1500 ml. A esta mezcla, se añadieron Et_2O (300 ml) y agua (50 ml). Las fases se separaron, y la fase acuosa se extrajo con Et_2O (3 x 300 ml). Las fases orgánicas combinadas luego se lavaron con solución de NaHCO3 saturado (3 x 150 ml), se secaron con $MgSO_4$, se filtraron y se concentraron a sequedad por medio de evaporación giratoria. El residuo se purificó por medio de MPLC (Hex:EtOAc, 8:2) para proveer 2–(6–cloropiridazin–3–il)–2–fluoromalonato de 1–*ter*–butil 3–etilo **45B** (70.2 g, 220 mmol, 77 %). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 1.24 (t, *J*=7.20 Hz, 3 H) 1.46 (s, 9 H) 4.28 – 4.43 (m, 2 H) 8.14 (s, 2 H). ESI–MS:m/z 319.2 $(M+H)^+$.

2–(6–cloropiridazin–3–il)–2–fluoroacetato de etilo: Una solución de 2–(6–cloropiridazin–3–il)–2–fluoromalonato de 1–*ter*–butil 3–etilo **45B** (60.2 g, 189 mmol) en 300 ml de TFA/DCM (1:1) se agitó a 25°C durante 2 horas y luego se concentró a sequedad por medio de evaporación giratoria. El residuo resultante se disolvió en EtOAc (300 ml), se lavó con solución de NaHCO3 saturado, se secó en $MgSO_4$, y luego se concentró a sequedad para dar el compuesto del título, 2–(6–cloropiridazin–3–il)–2–fluoroacetato de etilo **45C** (36.6 g, 167 mmol, 89%). El material se uso inmediatamente sin purificación adicional. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 1.18 (t, *J*=7.20 Hz, 3 H) 4.23 (qd, *J*=7.12, 4.42 Hz, 2 H) 6.43 –

6.62 (m, 1 H) 8.00 – 8.12 (m, 2 H). ESI–MS:m/z 219.0 $(M+H)^+$.

2–(6–cloropiridazin–3–il)–2,2–difluoroacetato de etilo: A una solución de 2–(6–cloropiridazin–3–il)–2–fluoroacetato de etilo (36.6 g, 167 mmol) en THF anhidro (500 ml) se añadió hexametildisilazida de litio (201 ml, 201 mmol) gota a gota a –78 °C. Después de 15 minutos, una solución de Selectfluor (71.2 g, 201 mmol) en DMF (183 ml) se añadió gota a gota. Después de la adición completa, la reacción se dejó calentar a temperatura ambiente durante un período de 30 min. Luego se añadió d NH_4Cl saturado (70 ml) y el THF se eliminó por medio de evaporación giratoria. El residuo resultante se diluyó con agua (500 ml), se extrajo con Et_2O (3 x 100 ml), se secó con $MgSO_4$, se filtró, y se concentró a sequedad. El material resultante se purificó por medio de MPLC (Hex:EtOAc, 8:2) para proveer 2–(6–cloropiridazin–3–il)–2,2–difluoroacetato de etilo **45D** (20.8 g, 88 mmol, 52.5%). ^1H NMR (400 MHz, DMSO–d_6) δ ppm 1.25 (t, *J*=7.07 Hz, 3 H) 4.38 (q, *J*=7.07 Hz, 2 H) 8.26 (d, *J*=9.09 Hz, 1 H) 8.33 (d, *J*=8.84 Hz, 1 H). ESI–MS:m/z 237.1 $(M+H)^+$.

N'–(5–Bromopiridin–2–il)–2–(6–cloropiridazin–3–il)–2,2–difluoroacetohidrazida: A una solución de 2–(6–cloropiridazin–3–il)–2,2–difluoroacetato de etilo (10.8 g, 45.6 mmol) y 5–bromo–2–hidrazinilpiridina (8.58 g, 45.6 mmol) en MeOH anhidro (100 ml) se añadió DIEA (5.90 g, 45.6 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. El solvente se eliminó por medio de evaporación giratoria y el material resultante se reconstituyó en EtOAc. La fase orgánica se lavó con agua y se concentró a sequedad. El residuo resultante se purificó por MPLC (EtOAc) para proveer el compuesto del título, N'–(5–bromopiridin–2–il)–2–(6–cloropiridazin–3–il)–2,2–difluoroacetohidrazida **45E** (13.3 g, 35.1 mmol, 77% de rendimiento). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.62 (d, *J*=8.84 Hz, 1 H) 7.11 (d, *J*=9.35 Hz, 1 H) 7.47 – 7.60 (m, 2 H) 8.06 (d, *J*=2.53 Hz, 1 H). ESI–MS:m/z 377.9 $(M+H)^+$.

6–Bromo–3–((6–cloropiridazin–3–il)difluorometil)–[1,2,4]triazolo[4,3–a]piridina: Una mezcla de N'–(5–bromopiridin–2–il)–2–(6–cloropiridazin–3–il)–2,2–difluoroacetohidrazida (1.0 g, 2.64 mmol) y PCl_5 (1.2 g, 8 mmol) en $POCl_3$ (40.5 g, 264 mmol) se calentó a 140°C en tubo sellado durante 18 horas. El solvente se eliminó por medio de evaporación giratoria, y el residuo resultante se reconstituyó en EtOAc. La solución orgánica se lavó con NaHCO3 saturado, se secó con $MgSO_4$, se filtró, y se concentró a sequedad. El material resultante se purificó por

medio de MPLC (Hex:EtOAc, gradiente 50–100%) para proveer el compuesto del título, 6–bromo–3–((6–cloropiridazin–3–il)difluorometil)–[1,2,4]triazolo[4,3–a]piridina **45F** (0.8 g, 2.21 mmol, 84%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 7.75 (dd, *J*=9.85, 1.77 Hz, 1 H) 8.01 (dd, *J*=9.85, 1.01 Hz, 1 H) 8.31 (d, *J*=9.09 Hz, 1 H) 8.42 – 8.51 (m, 1 H) 8.93 (s, 1 H). ESI–MS:m/z 359.9 $(M+H)^+$.

La 6-bromo-3-((6-cloropiridazin-3-il)difluorometil)-[1,2,4]triazolo[4,3-a]piridina **45F** también se preparó mezclando N'-(5-bromopiridin-2-il)-2-(6-cloropiridazin-3-il)-2,2-difluoroacetohidrazida (1.514 g, 4 mmol) y cloruro de 4-metilbencen-1-sulfonilo (0.839 g, 4.40 mmol) en acetato de etilo (Volumen: 25 ml) y enfriando la mezcla a 10 °C bajo protección de nitrógeno. 4-metilmorfolina (1.142 ml, 10.40 mmol) se adicionó durante 2 minutos. La mezcla de reacción se calentó a temperatura ambiente y se agitó por 6 horas. Se adicionó 4-metilmorfolina adicional (0.44 ml, 4 mmol). La mezcla de reacción se calentó a 60 °C por 24 horas para reducir el nivel intermediario de cloruro de imidoilo a menos de 1% por HPLC. La mezcla de reacción se enfrió a temperatura ambiente. Se agregaron EtOAc (30 ml) y agua (13ml), y la mezcla se agitó por 30 minutos. La capa acuosa se separó. La capa orgánica se concentró y el residuo se purificó por columna de gel de sílice para proporcionar 1.28g del producto (rendimiento de 89%).

6–((6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)–N–(2,4–dimetoxibencil)piridazin–3–amina: Una mezcla de reacción de 6–bromo–3–((6–cloropiridazin–3–il)difluorometil)–[1,2,4]triazolo[4,3–a]piridina (0.5 g, 1.387 mmol), (2,4–dimetoxifenil)metanamina (0.696 g, 4.16 mmol) y $NaHCO_3$ (0.58 g, 7.0 mmol) en IPA (10 ml) se calentó a 140 °C en un microondas durante 1 hora. El solvente se eliminó por medio de evaporación giratoria y el residuo resultante se reconstituyó en EtOAc. La solución orgánica se lavó con agua, se separó y pasó a través de una bolsa de sílice corta para proveer el compuesto del título, 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)–N–(2,4–dimetoxibencil)piridazin–3–amina **45G** (0.6g, 1.22 mmol, 88%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 3.71 – 3.76 (s, 3 H) 3.79 (s, 3 H) 3.85 – 3.89 (m, 2 H) 6.46 (dd, *J*=8.34, 2.53 Hz, 1 H) 6.57 (d, *J*=2.27 Hz, 1 H) 6.61 – 6.66 (m, 1 H) 7.08 (d, *J*=9.35 Hz, 1 H) 7.14 (d, *J*=8.34 Hz, 1 H) 7.81 (d, *J*=9.35 Hz, 1 H) 7.99 (dd, *J*=9.60, 1.01 Hz, 1 H) 8.70 (s, 1 H). ESI–MS:m/z 491.1 $(M+H)^+$.

6–((6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)piridazin–3–

amina: Una solución de 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)–N–(2,4–dimetoxibencil)piridazin–3–amina (16.5 g, 33.6 mmol) y anisol (5.45 g, 50.4 mmol) en TFA (150 ml) se agitó a 70 °C durante 30 min. La reacción se concentró a sequedad por medio de evaporación giratoria y el residuo resultante se sometió a sonicación en una solución de Et_2O /$NaHCO_3$ (pH=7). El sólido resultante se recolectó por filtración, se lavó con agua y luego Et_2O, y se secó al vacío sobre P_2O_5 para proveer el compuesto del título, 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)piridazin–3–amina **45H** (11.0g, 32.2 mmol, 96%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 7.14 (d, *J*=9.35 Hz, 1 H) 7.71 (dd, *J*=9.85, 1.77 Hz, 1 H) 7.92 (d, *J*=9.35 Hz, 1 H) 7.92 (*d, J*=10.20 Hz, 1) 8.02 (*d, J*=10.20, 1 H) 8.74 (s, 1 H). ESI–MS:m/z 340.9 $(M+H)^+$.

6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin-2–carboxilato de metilo: Una mezcla de reacción de 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)piridazin–3–amina (11.0 g, 32.2 mmol), 3–bromo–2–oxopropanoato de metilo (11.67 g, 64.5 mmol), y $NaHCO_3$ (10.84 g) en dioxano (150 ml) se calentó a 80 °C durante 4 horas para proveer una mezcla de reacción roja. Los sólidos se filtraron, se lavaron con dioxano, y los filtrados combinados se concentraron por medio de evaporación giratoria. El residuo resultante se disolvió en EtOAc y se lavó con NaOH 0.1 N hasta que el color rojo ya no persistió. La fase orgánica luego se separó y se concentró a sequedad. El material resultante se purificó por medio de MPLC (5:95, MeOH/EtOAc) para proveer el compuesto del título, **45I** (4.0 g, 9.45 mmol, 30%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 3.88 (s, 3 H) 7.77 (dd, *J*=9.73, 1.64 Hz, 1 H) 7.85 (d, *J*=9.60 Hz, 1 H) 7.97 – 8.08 (m, 1 H) 8.53 (d, *J*=9.60 Hz, 1 H) 8.98 (d, *J*=1.01 Hz, 1 H) 9.02 (s, 1 H). ESI–MS:m/z 423.1 $(M+H)^+$.

Ácido 6–((6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin-2–carboxílico: Una solución de 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin-2–carboxilato de 3-metilo (4.0 g, 9.45 mmol) y LiOH (0.340 g, 14.18 mmol) en 10% de H_2O/MeOH (150 ml) se agitó a temperatura ambiente durante 4 horas. El solvente se eliminó por medio de evaporación giratoria, y el residuo resultante se diluyó con H_2O (100 ml). La fase acuosa se ajustó a pH=5 con HCl concentrado. El precipitado resultante se recolectó, se lavó con agua, se lavó con EtOAc, y se

secó al vacío en P_2O_5 durante 18 horas para proveer el compuesto del título, ácido 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo–[1,2–b]piridazin-2–carboxílico **45J** (3.5 g, 8.55 mmol, 90%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 7.76 (dd, *J*=9.85, 1.77 Hz, 1 H) 7.82 (d, *J*=9.60 Hz, 1 H) 8.02 (d, J=9.60 Hz, 1H) 8.51 (d, *J*=9.85 Hz, 1 H) 8.90 (s, 1H) 8.97 (s, 1H). ESI–MS:m/z 409.0 $(M+H)^+$.

6–((6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin-2–carbonilazida: A una solución agitada de ácido 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin-2–carboxílico (3.5 g, 8.55 mmol), N–etil–N–isopropilpropan–2–amina (6.63 g, 51.3 mmol) y azida sódica (5.56 g, 86 mmol) en DMF anhidro (60 ml), PyBOP (5.34 g, 10.27 mmol) se añadió en porciones a temperatura ambiente durante 5 min. La reacción se agita durante 30 min adicionales y se diluyó con EtOAc (200 ml). La reacción luego se vertió en 10% de ácido cítrico acuoso (200 ml), y la fase orgánica se separó y se lavó con una solución de ácido cítrico (2 x 100 ml), NaHCO3 saturado (3 x 100 ml), y solución de NaCl saturada. Las fase acuosas se extrajeron nuevamente con EtOAc (200 ml) y las fases orgánicas se combinaron, se secaron con $MgSO_4$, se filtraron y concentraron a sequedad por medio de evaporación giratoria. El residuo resultante se trituró en 1:1 Et_2O/hexano, y el sólido se recolectó por filtración y se secó al vacío sobre P_2O_5 para proveer el compuesto del título, 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin-2–carbonil azida **45K** (3.2 g, 7.37 mmol, 92%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 7.77 (dd, *J*=9.85, 1.77 Hz, 1 H) 7.88 (d, *J*=9.60 Hz, 1 H) 8.00 – 8.05 (m, 1 H) 8.56 (d, *J*=9.60 Hz, 1 H) 8.98 (s, 1 H) 9.14 (s, 1 H). ESI–MS:m/z 434.0 $(M+H)^+$. ESI–MS:m/z 406.0 $(M+H)^+$.

6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–ilcarbamato de ter–butilo: 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin-2–carbonil azida (3.2 g, 7.37 mmol, dividida en 4 porciones) en t–butanol (10 ml) se calentó en horno a microondas a 100 °C durante 1 hora. El solvente se eliminó por medio de evaporación giratoria, y el residuo resultante se reconstituyó en EtOAc, se lavó con 5% de ácido cítrico, y se lavó con NaHCO3 saturado. La fase orgánica se pasó a través de una bolsa de sílice, se lavó con EtOAc:MeOH (95:5) y luego se

concentró para dar el compuesto del título, 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–ilcarbamato de ter–butilo **45L** (2.8 g, 5.83 mmol, 79%), que se uso en la próxima etapa sin purificación adicional. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 1.47 (s, 9 H) 7.66 (d, *J*=9.35 Hz, 1 H) 7.72 – 7.78 (m, 1 H) 7.96 – 8.06 (m, 2 H) 8.22 (d, *J*=9.35 Hz, 1 H) 8.93 (s, 1 H) 10.40 (br, 1H). ESI–MS:m/z 480.1 $(M+H)^+$.

6–((6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–amina: Una solución de 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–ilcarbamato de ter–butilo (2.8 g, 5.83 mmol) en HCl 4 N/dioxano (25 ml) se agitó a temperatura ambiente durante 1 hora. El solvente se eliminó por medio de evaporación giratoria y el residuo se secó al vacío para proveer el compuesto del título, 6–((6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–amina **45M** (2.2 g, 5.84 mmol, 92%), en forma de sal de HCl. Este material se uso sin purificación adicional. ESI–MS:m/z 380.1 $(M+H)^+$.

N–(6–((6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)–N–(ciclopropancarbonil)ciclopropancarboxamida: A una solución de 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–amina (2.2 g, 5.84 mmol) y DIEA (4.53 g, 35.0 mmol) en CH_2Cl_2 (250 ml), cloruro de ciclopropancarbonilo (1.831 g, 17.52 mmol) se añadió gota a gota a 0°C. La reacción se agitó a temperatura ambiente durante 18 horas. La reacción luego se lavó con 5% de ácido cítrico (2 x 100 ml) y luego se lavó con $NaHCO_3$ (2 x 100 ml). La fase orgánica luego se secó con $MgSO_4$, se filtró, y se concentró a sequedad por medio de evaporación giratoria. El material resultante se purificó por medio de MPLC (95:5, DCM:MeOH) para proveer el compuesto del título, N–(6–((6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo–[1,2–b]piridazin–2–il)–N–(ciclopropancarbonil)–ciclopropancarboxamida **45N** (2.2g, 4.27 mmol, 73%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 – 1.03 (m, 8 H) 2.05 – 2.12 (m, 2 H) 7.70 – 7.87 (m, 2 H) 7.97 – 8.06 (m, 1 H) 8.48 (d, J=9.60 Hz, 1 H) 8.65 (s, 1 H) 8.99 (s, 1 H). ESI–MS:m/z 516.1 $(M+H)^+$.

N–(6–(Difluoro(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: Una mezcla de N–

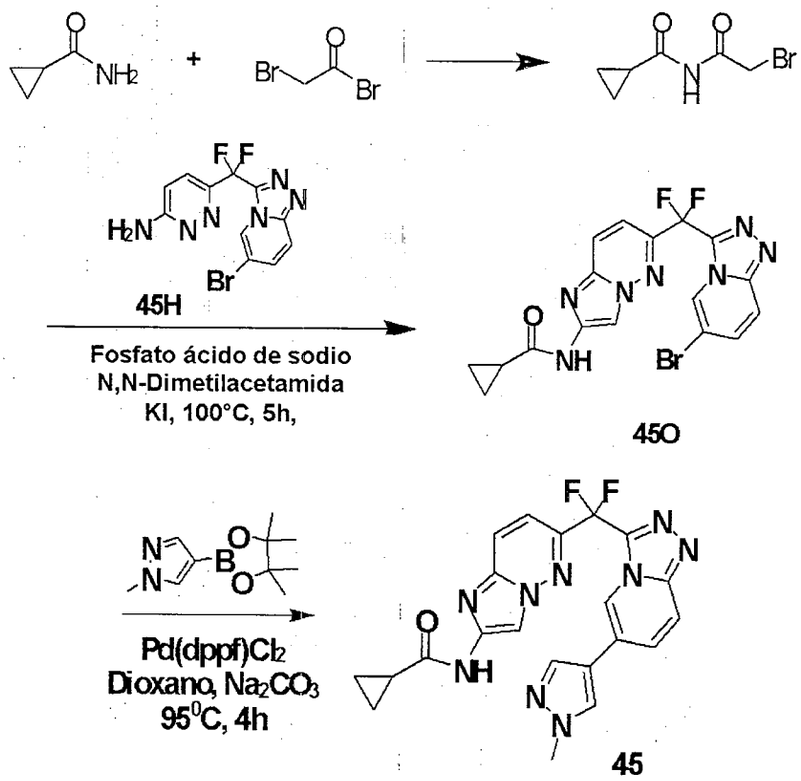
(6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)–N–(ciclopropancarbonil)ciclopropancarboxamida (0.6 g, 1.16 mmol), 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (0.242 g, 1.162 mmol), y $PdCl_2$(dppf):CH_2Cl_2 (0.048 g, 0.058 mmol) en dioxano (10 ml)/Na_2CO_3 2 N (5 ml) se calentó en un microondas a 110 °C durante 30 min. Esta reacción se repitió 4 veces y las mezclas de reacción se combinaron. La reacción se diluyó con CH_2Cl_2 (500 ml) y se lavó con H_2O (3 x 200 ml). La fase orgánica se separó y se concentró a sequedad por medio de evaporación giratoria. El residuo resultante se suspendió en EtOAc y se sometió a sonicación. El sólido resultante se recolectó por filtración y se lavó con EtOAc. El sólido luego se disolvió en MeOH/CH_2Cl_2 (5:95, 300 ml) y se filtró a través de una bolsa de sílice y se lavó con MeOH/CH_2Cl_2 (5:95). Se añadió HCl concentrado (0.5 ml) al eluyente recolectado seguido por carbón activo. La solución se agitó a temperatura ambiente durante 1 hora y se filtró a través de celite. El solvente se evaporó y el residuo resultante luego se trituró en EtOAc. El sólido se recolectó por filtración, se lavó con EtOAc y se secó al vacío para proveer el compuesto del título, clorhidrato de N–(6–(Difluoro(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (0.92 g, 1.78 mmol, 38%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.82 (d, J=6.32 Hz, 4 H) 1.91 – 2.01 (m, 1 H) 3.87 (s, 3 H) 7.70 (d, J=9.35 Hz, 1 H) 7.90 (dd, J=9.60, 1.52 Hz, 1 H) 7.98 – 8.11 (m, 2 H) 8.19 – 8.32 (m, 2 H) 8.40 (s, 1 H) 8.70 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 516.1 $(M+H)^+$. MP: 195°C dec.

El clorhidrato de N-(6-(difluoro(6-(1-metil-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida también se preparó disolviendo 0.5g de N-(6-(difluoro(6-(1-metil-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida cruda en AcOH (15ml) a 80°C para formar una solución clara. La solución se enfrió a temperatura ambiente,se agregó Sili-tiourea (comercialmente disponible de Silicycle; 0.25g) y la mezcla se agitó durante la noche. La mezcla se filtró a través de celite y se agregaron 6.5ml de solución de HCl 1.7M en MeOH a la solución de AcOH. EtOAc (18ml) luego se agregó lentamente para inducir la cristalización. La mezcla luego se agitó a ta por 1 hora hasta que se formó precipitado pesado. Se agregó EtOAc (30ml) adicional y la

mezcla se agitó por 60 min. El sólido luego se colectó vía filtración, se lavó con EtOAc (10ml) y se seco en vacío a 60°C durante la noche.

Además, clorhidrato de N-(6-(difluoro(6-(1-metil-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida se preparó suspendiendo la N-(6-(difluoro(6-(1-metil-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida cruda (2.2g; 4.9 mmol) en 333 ml de DCM. Se agregaron 50 ml de HCl 0.2 M en MeOH (10 mmol). La mezcla se agitó vigorosamente por 60 minutos y se agregó Sili-Tiourea (comercialmente disponible de Silicycle; 1.12g). La mezcla se agitó a temperatura ambiente por 14 horas, se filtró a través de Celite y se lavó con 10% MeOH en DCM (40ml) para proporcionar un volumen total de filtrado de aproximadamente 420ml. Se agregaron 15ml de una solución 2M HCl MeOH. La solución se concentró por rotovaporación a 225mbar, temperatura de baño de 22°C para remover aproximadamente 325ml de solvente. La solución se verificó para claridad para asegurar que la formación sólida se minimizó. Se agregaron 10ml de una solución 2M HCl MeOH. La solución se sembró con 25mg de sal clorhidrato de N-(6-(difluoro(6-(1-metil-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida. La solución se dejó continuar concentrando a 130mbar para remover 65 ml de solvente en la presencia de cristales simientes. Después que la solución se volvió turbia, la solución se mantuvo a temperatura por 40 minutos. La mezcla se enfrió a 0°C, se agitó por 2 horas, y los sólidos se colectaron por filtración. Los sólidos se secaron en vacío a 60°C durante la noche para proporcionar 1.75 g de un sólido amarillo pálido.

Método B



N–(6–((6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (45O): Se añadió ciclopropancarboxamida (58.7g, 690 mmol) en 1,4–dioxano (1600 ml) y bromuro de 2–bromoacetilo (59.9 ml, 690 mmol) a temperatura ambiente y se agitó durante 4 horas a 60°C. La mezcla de reacción se concentró a sequedad. El residuo se disolvió en EtOAc y se lavó cuidadosamente con. $NaHCO_3$ saturado, luego se añadió agua con solución de salmuera, se secó en Na_2SO_4 y se concentró para obtener N–(2–bromoacetil)ciclopropancarboxamida (138 g, 670 mmol, 97 % de rendimiento) en forma de sólido blanco. Este material se uso sin purificación posterior. ESI–MS:m/z 208.0 $(M+2H)^+$.

A una mezcla de 6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)piridazin–3–amina (21.8 g, 63.9 mmol) y fosfato ácido de sodio (27.2 g, 192 mmol) en N,N–Dimetilacetamida (250 ml) se añadieron N–(2–bromoacetil)ciclopropancarboxamida (19.75 g, 96 mmol) y yoduro de potasio (10.61 g, 63.9 mmol) a temperatura ambiente. La mezcla de reacción se agitó

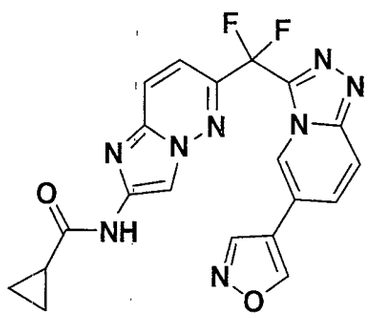
durante 5 horas a 100 °C. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con EtOAc (1000ml) y se lavó con solución de salmuera (5X), se secó en Na_2SO_4, los productos volátiles se evaporaron y el residuo se purificó por combiflash (2 a 30% de MeOH en diclorometano durante 120 min). Las fracciones que contienen producto se combinaron y concentraron para obtener N–(6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (13.9 g, 31.0 mmol, 48.5% de rendimiento) en forma de un sólido blanco. ^{1}H NMR (400 MHz, DMSO–d_6) δ 11.31 (s, 1H), 8.92 (s, 1H), 8.18 – 8.35 (m, 2H), 7.92 – 8.06 (m, 1H), 7.61 – 7.80 (m, 2H), 1.91 – 2.02 (m, 1H), 0.78 – 0.89 (m, 4H). ESI–MS: m/z 450.0 $(M+2H)^+$.

N–(6–(Difluoro(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (45): Una mezcla de N–(6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (7.2 g, 16.06 mmol), 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (5.01 g, 24.10 mmol) y $PdCl_2$(dppf):CH_2Cl_2 (0.655 g, 0.803 mmol) en 1,4–dioxano:1M de Na_2CO_3 (relación: 2.1, Volumen: 100 ml) se calentó a 95 °C durante 4 horas. La mezcla de reacción se enfrió y concentró a sequedad por medio de evaporación giratoria, se diluyó con EtOAc y agua. El sólido resultante se recolectó por filtración, se lavó con H_2O seguido por EtOAc. El sólido color gris se disolvió en 20% de MeOH en cloroformo y se trató con carbón activado toda la noche, se filtró a través de un lecho de celite y el lecho de celite se lavó con 20% de MeOH en cloroformo hasta que no se detectó compuesto por HPLC. Esta solución se pasó a través de una columna de gel de sílice. El solvente se evaporó y el sólido resultante se lavó con EtOAc, MeOH, seguido por EtOAc y luego Et_2O, se secó al vacío para proporcionar N–(6–(difluoro(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (5.13 g, 11.41 mmol, 71.1 % de rendimiento) en forma de sólido blanco. ^{1}H NMR (400 MHz, DMSO–d_6) δ 11.35 (s, 1H), 8.71 (s, 1H), 8.41 (s, 1H), 8.19 – 8.34 (m, 2H), 8.00 – 8.12 (m, 2H), 7.91 (dd, J = 1.64, 9.47 Hz, 1H), 7.71 (d, J = 9.35 Hz, 1H), 3.88 (s, 3H), 1.88 – 2.02 (m, 1H), 0.83 (d, J = 6.32 Hz, 4H). ESI–MS:m/z 450.1 $(M+H)^+$. MP: 274.9°C.

La sal bis HCl de Compuesto 45 se preparó de la siguiente manera: bis

clorhidrato de N–(6–(Difluoro(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: A N–(6–(difluoro(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (2.100 g, 4.67 mmol) en una mezcla de MeOH y DCM (Relación: 1:2, Volumen: 100 ml) se añadió cloruro de hidrógeno (12N, 0.973 ml, 11.68 mmol) a temperatura ambiente y se agitó durante 2 horas. Los productos volátiles se evaporaron a sequedad y el sólido se lavó con EtOAc y éter luego se secó al vacío para proporcionar N–(6–(difluoro(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida, 2HCl (2.4 g, 4.59 mmol, 98 % de rendimiento) en forma de sólido blanco. ^{1}H NMR (400 MHz, DMSO–d_6) δ 12.21 (br. s., 2H), 11.32 (s, 1H), 8.66 (s, 1H), 8.36 (s, 1H), 8.14 – 8.27 (m, 2H), 7.94 – 8.08 (m, 2H), 7.87 (dd, J = 1.52, 9.60 Hz, 1H), 7.65 (d, J = 9.35 Hz, 1H), 3.82 (s, 3H), 1.84 – 1.99 (m, 1H), 0.77 (d, J = 6.32 Hz, 4H). ESI–MS:m/z 450.1 $(M+H)^+$. MP: 208°C.

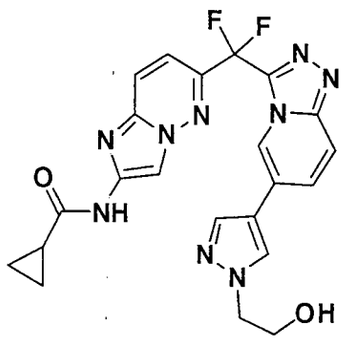
Compuesto 46: N–(6–(difluoro(6–(isoxazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



Una mezcla de N–(6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)–N (ciclopropancarbonil)ciclopropancarboxamida (**45N**, 0.200 g, 0.38 mmol), 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)isoxazol (0.1 g, 0.5 mmol) y $PdCl_2$(dppf):CH_2Cl_2 (5 mg, 0.006 mmol) en Na_2CO_3 (2N, 1 ml)/dioxano (2 ml) se calentó a 110 °C en un microondas durante 30 min. La mezcla de reacción se filtró y los sólidos se lavaron con EtOAc. El filtrado luego se lavó con NaCl saturado, se secó con $MgSO_4$, se filtró, y se concentró a sequedad por medio de evaporación

giratoria. El residuo resultante se purificó por LCMS preparativa. Las fracciones recolectadas se combinaron y la mezcla resultante se trató con dos gotas de HCl concentrado. La solución se liofilizó para proveer la sal de HCl del compuesto del título, N–(6–(difluoro(6–(isoxazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (20 mg, 0.04 mmol, 12%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.82 (d, J=6.32 Hz, 4 H) 1.91 – 2.01 (m, 1 H) 7.67 (dd, J=9.47, 5.43 Hz, 1 H) 7.75 (dd, J=9.73, 1.64 Hz, 1 H) 7.84 (dd, J=9.85, 1.77 Hz, 1 H) 7.98 – 8.07 (m, 1 H) 8.23 – 8.34 (m, 2 H) 8.46 (s, 1 H) 9.02 (s, 1 H) 11.36 (d, J=2.27 Hz, 1 H). ESI–MS:m/z 437.2 $(M+H)^+$.

Compuesto 47: N–(6–(difluoro(6–(1–(2–hidroxietil)–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



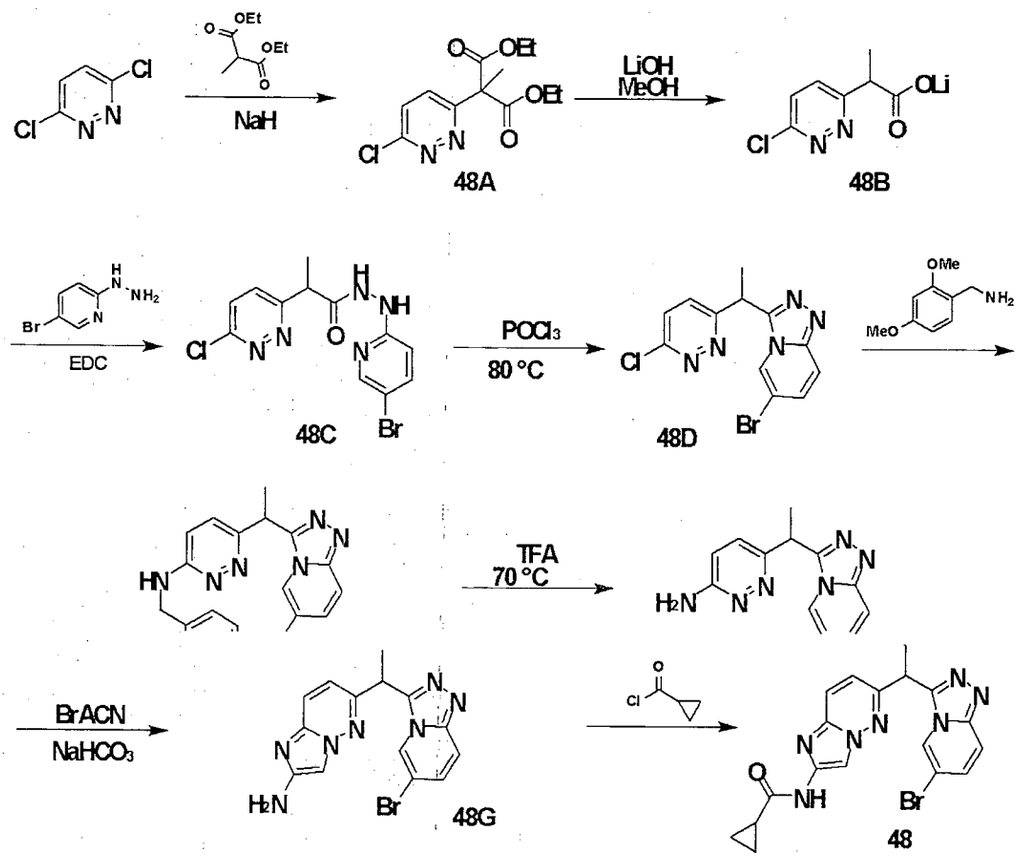
Una mezcla de N–(6–((6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)–N-(ciclopropancarbonil)ciclopropancarboxamida (**45N**, 0.067 g, 0.13 mmol), 1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (0.042 g, 0.130 mmol) y $PdCl_2$(dppf) (5 mg, 0.006 mmol) en Na_2CO_3 (2N, 1 ml)/dioxano (2 ml) se calentó a 110 °C en un microondas durante 30 min. La mezcla de reacción se filtró y se lavó con EtOAc. La fase orgánica se lavó con NaCl saturado, se secó con $MgSO_4$, se filtró, y se concentró a sequedad. El residuo resultante se disolvió en 4 N HCl/dioxano y se agitó a temperatura ambiente durante 30 min y luego se concentró a sequedad. El material resultante se purificó por LCMS preparativa. Las fracciones recolectadas se combinaron y la mezcla resultante se trató con dos gotas de HCl concentrado. La solución se liofilizó para proveer la sal de HCl del compuesto del título, (18 mg, 0.037 mmol,

000487

29%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.95 (d, *J*=5.81 Hz, 1 H) 3.77 (t, *J*=5.43 Hz, 2 H) 4.10 – 4.21 (m, 2 H) 7.71 (d, *J*=9.35 Hz, 1 H) 7.87 – 7.98 (m, 1 H) 8.00 – 8.07 (m, 1 H) 8.11 (s, 1 H) 8.20 – 8.33 (m, 2 H) 8.44 (s, 1 H) 8.73 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 480.2 $(M+H)^+$.

Compuesto 48: N–(6–(1–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

Método A



2–(6–cloropiridazin–3–il)–2–metilmalonato de dietilo: A una mezcla de NaH (13.42 g, 336 mmol) en dioxano (800 ml) se añadió 2–metilmalonato de dietilo (42.9 ml, 252 mmol) gota a gota a 0 °C. La reacción se agitó a 0 °C durante 1 hora y se dejó calentar a temperatura ambiente. Luego se añadió en porciones 3,6–dicloropiridazina (25 g, 168 mmol) a 25 °C. La reacción luego se agitó a reflujo durante 1 hora. El solvente se eliminó por medio de evaporación giratoria y el residuo resultante se disolvió en EtOAc. La solución orgánica se lavó con

NaHCO3 saturado (100 ml) seguido por 5% ácido cítrico. La fase orgánica luego se secó con $MgSO_4$, se filtró, y se concentró a sequedad. El residuo resultante se purificó por medio de MPLC (Hex:EtOAc, 3:1) para proveer el compuesto del título, 2–(6–cloropiridazin–3–il)–2–metilmalonato de dietilo **48A** (12 g, 25% de rendimiento) en forma de un aceite amarillo. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 1.18 (s, 6 H) 1.81 (s, 3 H) 4.21 (dd, *J*=7.07, 2.27 Hz, 4 H) 8.00 (s, 2 H). ESI–MS:m/z 287.1 $(M+H)^+$.

2–(6–cloropiridazin–3–il)propanoato de litio: Una solución de 2–(6–cloropiridazin–3–il)–2–metilmalonato de dietilo (19.8 g, 69.1 mmol) y LiOH (3.31 g, 138 mmol) en MeOH:agua (3:1, 200 ml) se agitó a 25 °C durante 3 horas. El MeOH se eliminó de la reacción por medio de evaporación giratoria, y el residuo resultante se reconstituyó en H_2O (300 ml). La mezcla acuosa se lavó con Et_2O (3 x 100 ml) y luego se liofilizó a sequedad para proveer 2–(6–cloropiridazin–3–il)propanoato de litio **48B** en rendimiento cuantitativo. El material se uso sin desarrollo posterior. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 1.36 (3 H, d, *J*=7.33 Hz) 3.63 (1 H, q, *J*=7.24 Hz) 7.71 (2 H, s). ESI–MS:m/z 187.0 $(M+H)^+$.

N'–(5–Bromopiridin–2–il)–2–(6–cloropiridazin–3–il)propanehidrazida: Una mezcla de 2–(6–cloropiridazin–3–il)propanoato de litio (7.2 g, 37.4 mmol), 5–bromo–2–hidrazinilpiridina (7.03 g, 37.4 mmol), 1*H*–benzo[d][1,2,3]triazol–1–ol (5.05 g, 37.4 mmol), y clorhidrato de *N*–1–((etilimino)metilen)–*N*3,*N*3–dimetilpropano–1,3–diamina (7.89 g, 41.1 mmol) en DMF (Volumen: 320 ml) se agita durante 4 horas a 25 °C. La reacción se vertió en H_2O (2 L) y se extrajo con EtOAc (3 x 500 ml). La fase orgánica se secó en $MgSO_4$, se filtró, y se evaporó a sequedad. El residuo resultante se purificó por MPLC $CHCl_3$:MeOH (9:1) para proveer el compuesto del título, N'–(5–bromopiridin–2–il)–2–(6–cloropiridazin–3–il)propanohidrazida **48C** (5.5 g, 15.42 mmol, 41.2% de rendimiento). ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 1.52 (d, *J*=7.33 Hz, 3 H) 4.17 (d, *J*=7.07 Hz, 1 H) 6.52 (d, *J*=8.84 Hz, 1 H) 7.67 (dd, *J*=8.84, 2.53 Hz, 1 H) 7.87 (d, *J*=9.09 Hz, 1 H) 7.94 (d, *J*=8.84 Hz, 1 H) 8.11 (d, *J*=1.77 Hz, 1 H) 8.66 (d, *J*=1.52 Hz, 1 H) 10.20 (d, *J*=1.52 Hz, 1 H). ESI–MS:m/z 356.1 $(M+H)^+$.

6–bromo–3–(1–(6–cloropiridazin–3–il)etil)–[1,2,4]triazolo[4,3–a]piridina: Una solución de N'–(5–bromopiridin–2–il)–2–(6–cloropiridazin–3–il)propanohidrazida (5.0 g, 14.02 mmol) y tricloruro de fosforilo (100 ml, 1073 mmol) se agitó a 90 °C

durante 5 horas. La reacción se enfrió, se extrajo a sequedad, y el material resultante se reconstituyó en una mezcla de EtOAc y NaHCO3 saturado (400 ml, 1:1)). La fase orgánica se aisló, se lavó con NaHCO3 saturado (1 x 100 ml), y se secó en $MgSO_4$. La fase orgánica se eliminó por medio de evaporación giratoria para proveer el compuesto del título, 6–bromo–3–(1–(6–cloropiridazin–3–il)etil)–[1,2,4]triazolo[4,3–a]piridina **48D** (2.2 g, 6.50 mmol, 46.3% de rendimiento). Este material se uso sin purificación adicional. ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 1.86 (d, *J*=7.07 Hz, 3 H) 5.27 (d, *J*=7.33 Hz, 1 H) 7.49 (dd, *J*=9.60, 1.77 Hz, 1 H) 7.78 (dd, J=9.85, 1.01 Hz, 1 H) 7.94 (s, 2 H) 8.79 (s, 1 H). ESI–MS:m/z 339.1 $(M+H)^+$.

N–(2,4–dimetoxibencil)–6–(1–(6–metil–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)piridazin–3–amina: Una mezcla de 6–bromo–3–(1–(6–cloropiridazin–3–il)etil)–[1,2,4]triazolo[4,3–a]piridina (650 mg, 1.920 mmol), (2,4–dimetoxifenil)metanamina (0.577 ml, 3.84 mmol), y $NaHCO_3$ (645 mg, 7.68 mmol) en IPA (10.0 ml) se calentó en un microondas a alta absorbancia durante 18 horas a 140 °C. La reacción se enfrió a temperatura ambiente, se extrajo a sequedad por medio de evaporación giratoria, y se reconstituyó en EtOAc (25 ml). Los producto insolubles se filtraron y el filtrado se redujo a sequedad. El residuo resultante se purificó por medio de MPLC (DCM:MeOH, 98:2) para proveer el compuesto del título, 6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)–N–(2,4–dimetoxibencil)piridazin–3–amina **48E** (750 mg, 1.598 mmol, 83% de rendimiento) en forma de sólido amarillo. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 1.77 (d, *J*=7.07 Hz, 3 H) 3.72 (s, 3 H) 4.37 (d, *J*=5.81 Hz, 2 H) 4.95 (d, *J*=7.07 Hz, 1 H) 6.44 (dd, *J*=8.34, 2.53 Hz, 1 H) 6.54 (d, *J*=2.27 Hz, 1 H) 6.85 (d, *J*=9.35 Hz, 1 H) 7.03 (s, 1 H) 7.12 (d, *J*=8.34 Hz, 1 H) 7.29 (d, *J*=9.35 Hz, 1 H) 7.45 (dd, *J*=9.73, 1.64 Hz, 1 H) 7.69 – 7.79 (m, 1 H) 8.59 (s, 1 H). ESI–MS:m/z 469.2 $(M+H)^+$.

6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)piridazin–3–amina: Una mezcla de 6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)–N–(2,4–dimetoxibencil)piridazin–3–amina (750 mg, 1.598 mmol), anisol (0.349 ml, 3.20 mmol), y TFA (1.0 ml, 12.98 mmol) en DCM (5.0 ml) se calentó en un microondas a alta absorbancia durante 2 horas a 75 °C. La reacción se extrajo a sequedad por medio de evaporación giratoria, y el aceite resultante se trató con Et_2O para producir un sólido. El sólido se filtró y se secó al vacío para proveer el compuesto

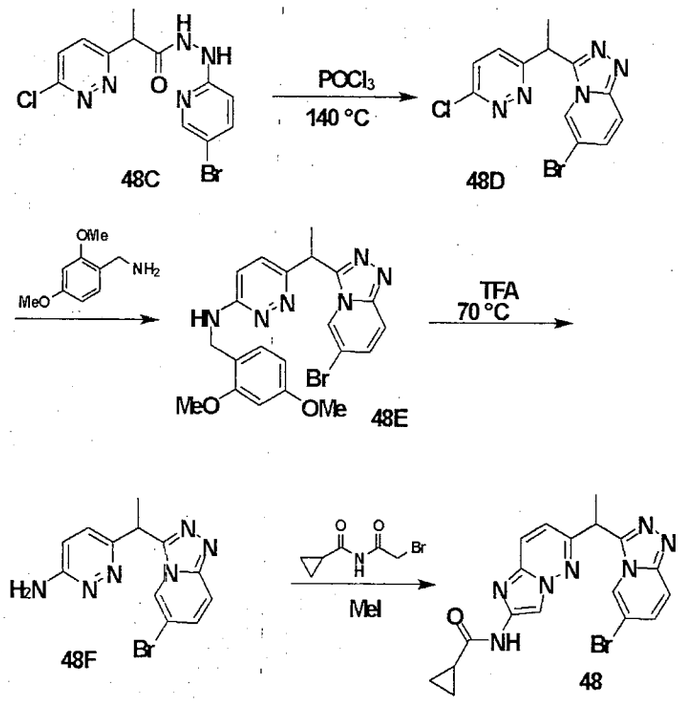
del título, 2,2,2–trifluoroacetato de 6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)piridazin–3–amina (400 mg, 0.923 mmol, 57.8% de rendimiento) en forma de sólido amarillo. ^{1}H NMR **48F** (400 MHz, DMSO–d6) δ ppm 1.77 (d, J = 7.07 Hz, 3 H) 5.05 (d, J = 7.07 Hz, 1 H) 7.44 (d, J=9.60 Hz, 1 H) 7.50 (dd, J = 9.73, 1.64 Hz, 1 H) 7.73 – 7.84 (m, 1 H) 7.92 (d, J = 9.60 Hz, 1 H) 8.56 (br. s., 2 H) 8.81 (s, 1 H). ESI–MS: m/z 319.1 $(M+H)^+$.

6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–amina: Una mezcla de 6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)piridazin–3–amina (1.0 g, 3.13 mmol), 2–bromoacetonitrilo (0.251 ml, 3.76 mmol) y $NaHCO_3$ (0.053 g) en IPA (10 ml) se calentó a 100 °C en tubo sellado durante 2 horas. El sólido se filtró, se lavó con IPA, y se extrajo a sequedad por medio de evaporación giratoria. El residuo resultante se purificó por LCMS y se liofilizó en forma de sal de TFA para proveer el compuesto del título, 6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–amina **48G** (0.62 mg, 1.73 mmol, 55%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 1.85 (d, *J*=7.07 Hz, 3 H) 5.17 (d, *J*=7.07 Hz, 1 H) 7.38 – 7.57 (m, 3 H) 7.80 (d, *J*=9.60 Hz, 1 H) 7.99 (d, *J*=9.09 Hz, 1 H) 8.78 (s, 1 H). ESI–MS:m/z 358.1 $(M+H)^+$.

N–(6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: A una solución de sal de TFA de 6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–amina (250 mg, 0.52 mmol) en CH_2Cl_2 se añadió DIEA (0.65 g, 5.0 mmol) seguido por cloruro de ciclopropancarbonilo (0.16 g, 1.5 mmol). La reacción se agitó a temperatura ambiente durante 30 min. El solvente se eliminó por medio de evaporación giratoria y el residuo resultante se reconstituyó en MeOH (10 ml). Se añadió NH_4OH (0.5 ml) y la reacción se agitó a temperatura ambiente durante 1 hora. La reacción luego se concentró a sequedad y el material resultante se disolvió en EtOAc, se lavó con NaHCO3 saturado, se secó con $MgSO_4$, se filtró y se concentró a sequedad. El material bruto se purificó por medio de MPLC (5%MeOH/0.1% NH_4OH/EA) para proveer el compuesto del título, N–(6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida **48** (0.22 g, 0.52 mmol, 100%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm, 73 – 0.87 (m, 4 H) 1.83 – 1.99 (m, 4 H) 5.17 (d, *J*=7.07 Hz, 1 H) 7.38 – 7.57 (m, 3 H) 7.80 (d, *J*=9.60 Hz, 1 H) 7.99 (d, *J*=9.09 Hz, 1 H) 8.78 (s, 1 H)

11.14 (s, 1 H). ESI–MS:m/z 426.2 $(M+H)^+$.

Método B



6–Bromo–3–(1–(6–cloropiridazin–3–il)etil)–[1,2,4]triazolo[4,3–a]piridina (48D): Una solución de N'–(5–bromopiridin–2–il)–2–(6–cloropiridazin–3–il)propanehidrazida (13 g, 36.5 mmol) en tricloruro de fosforilo (84 ml, 901 mmol) se calentó en microondas a 140 °C durante 15 min. La reacción se concentró por evaporación giratoria y la mezcla resultante se añadió gota a gota a una mezcla de EtOAc:bicarbonato saturado (ac) (4:6, 1L). La fase orgánica se separó y la fase acuosa se extrajo con EtOAc (3 x 75 ml). Las soluciones en EtOAc se combinaron y evaporaron a sequedad. El residuo resultante se purificó por MPLC (DCM:MeOH, 97:3) para proporcionar el compuesto del título, 6–Bromo–3–(1–(6–cloropiridazin–3–il)etil)–[1,2,4]triazolo[4,3–a]piridina (48D, 3.3g, 26.7%). ^{1}H NMR (400MHz, DMSO–d_6) δ ppm 1.86 (d, *J*=7.07 Hz, 3 H) 5.27 (d, *J*=7.33 Hz, 1 H) 7.49 (dd, *J*=9.60, 1.77 Hz, 1 H) 7.78 (dd, J=9.85, 1.01 Hz, 1 H) 7.94 (s, 2 H) 8.79 (s, 1 H). ESI–MS:m/z 339.1 $(M+H)^+$.

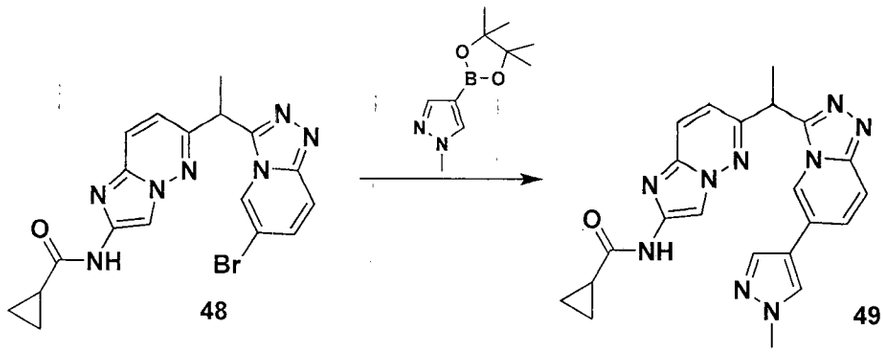
6–(1–(6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)–N–(2,4–dimetoxibencil)piridazin–3–amina (48E): El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del

Compuesto 48E del método A.

6–(1–(6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)piridazin–3–amina (48F): El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto 48E del método A.

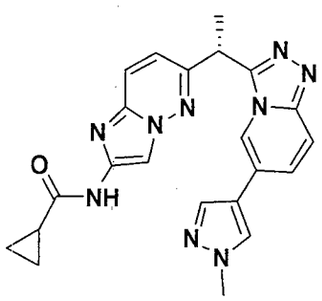
N–(6–(1–(6–Bromo–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (48): El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto 45O.

Compuesto 49: N–(6–(1–(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



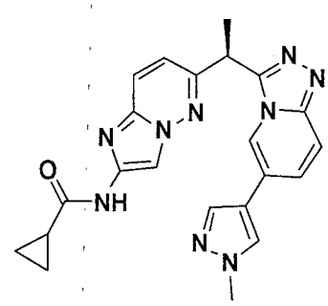
Una mezcla de N–(6–(1–(6–bromo–[1,2,4]triazolo[4,3–a]–piridin–3–il)imidazol[1,2–b]piridazin–2–il)ciclopropancarboxamida(0.23 g, 0.54 mmol), 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (0.16 g, 0.8 mmol) y $PdCl_2$(dppf)–CH_2Cl_2 (0.02 g, 0.02 mmol) en Na_2CO_3 (2 N, 1 ml)/dioxano (2 ml) se calentó en microondas a 110 °C durante 45 min. La mezcla de reacción se filtró, se lavó con EtOAc y se concentró a sequedad por medio de evaporación giratoria. El material resultante se purificó por LCMS preparativa. Las fracciones recolectadas se combinaron y la mezcla resultante se trató con dos gotas de HCl concentrado. La solución se liofilizó para proveer la sal de HCl del compuesto del título, N–(6–(1–(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida **49** (0.11 g, 0.25 mmol, 47%). ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.80 (d, *J*=6.32 Hz, 4 H) 1.84 – 1.99 (m, 4 H) 3.87 (s, 3 H) 5.35 (d, *J*=7.07 Hz, 1 H) 7.43 (d, *J*=9.35 Hz, 1 H) 8.02 (d, *J*=9.35 Hz, 1 H) 8.05 – 8.13 (m, 3 H) 8.19 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.38 (s, 1 H) 9.01 (s, 1 H) 11.18 (s, 1 H). MS:m/z 428.2 $(M+H)^+$.

Compuesto 50: (S)–N–(6–(1–(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



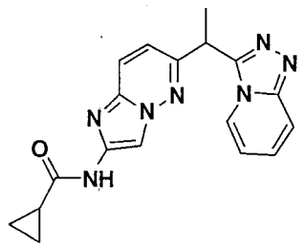
El compuesto **50** se obtuvo de la separación quiral del compuesto **49** en las siguientes condiciones: Un sistema SFC/UV se uso con las fases móviles de 25% de EtOH (más 10 mM de NH_4OAc) en CO_2 en una columna de ChiralCel AS–H (21 x 250 mm) a una velocidad de flujo de 50 ml/min con detección UV a 220 nm. ^1H NMR (400 MHz, DMSO–d_6) δ ppm 0.73 – 0.88 (m, 3 H) 1.81 – 1.99 (m, 4 H) 3.87 (s, 3 H) 5.08 – 5.21 (m, 1 H) 7.27 (d, *J*=9.35 Hz, 1 H) 7.63 (dd, *J*=9.60, 1.52 Hz, 1 H) 7.80 (dd, *J*=9.60, 1.01 Hz, 1 H) 7.91 – 8.00 (m, 2 H) 8.12 (s, 1 H) 8.23 (s, 1 H) 8.62 (s, 1 H) 11.13 (s, 1 H). MS:m/z 428.2 $(M+H)^+$.

Compuesto 51: (R)–N–(6–(1–(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



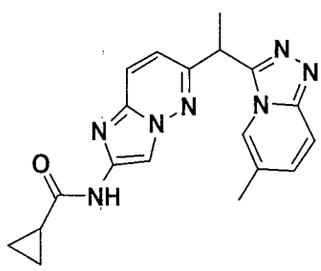
El compuesto **51** se obtuvo de la separación quiral del compuesto **49** en las siguientes condiciones: Un sistema SFC/UV se uso con las fases móviles de 25% de EtOH (más 10 mM de NH_4OAc) en CO_2 en una columna ChiralCel AS–H (21 x 250 mm) a una velocidad de flujo de 50 ml/min con detección UV a 220 nm. ^1H NMR (400 MHz, DMSO–d_6) δ ppm 0.73 – 0.88 (m, 3 H) 1.81 – 1.99 (m, 4 H) 3.87 (s, 3 H) 5.08 – 5.21 (m, 1 H) 7.27 (d, *J*=9.35 Hz, 1 H) 7.63 (dd, *J*=9.60, 1.52 Hz, 1 H) 7.80 (dd, *J*=9.60, 1.01 Hz, 1 H) 7.91 – 8.00 (m, 2 H) 8.12 (s, 1 H) 8.23 (s, 1 H) 8.62 (s, 1 H) 11.13 (s, 1 H). MS:m/z 428.2 $(M+H)^+$.

Compuesto 52: N–(6–(1–([1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



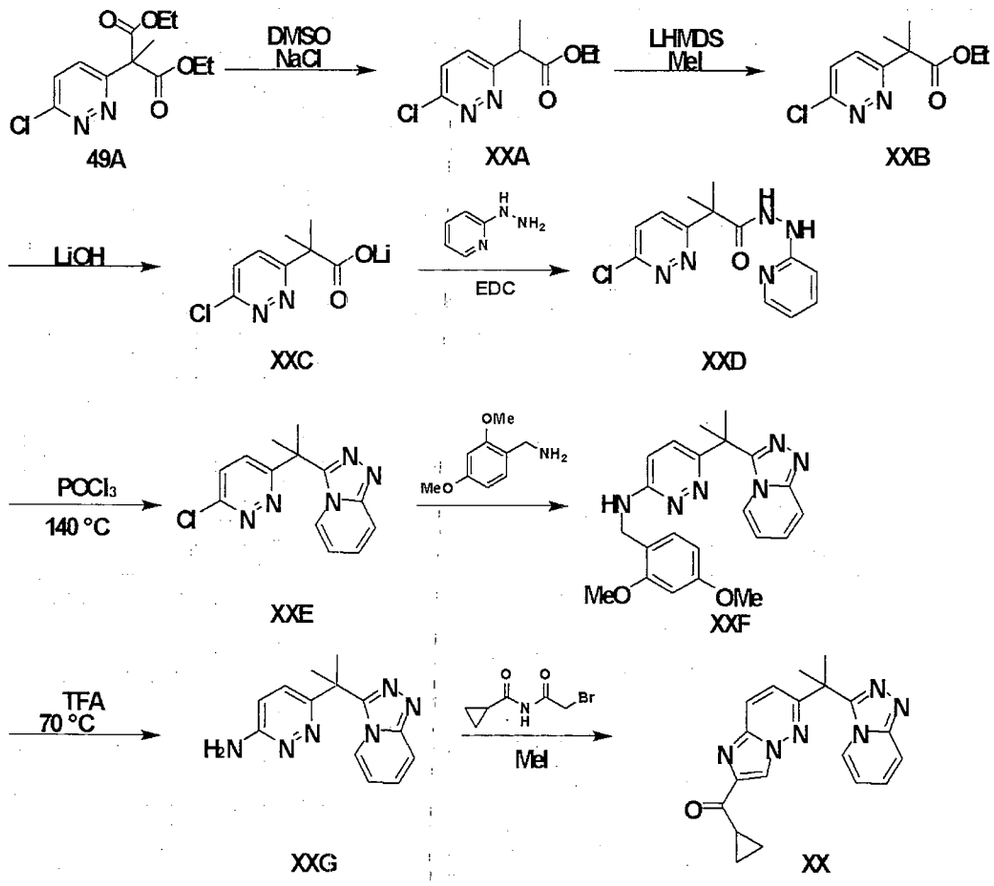
El compuesto del título se sintetizó usando un procedimiento análogo al que se describe en la preparación del compuesto **48,** (método A) usando 2–hidrazinilpiridina. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.73 – 0.87 (m, 4 H) 1.83 – 1.99 (m, 4 H) 5.04 – 5.15 (m, 1 H) 6.94 – 7.04 (m, 1 H) 7.19 (d, *J*=9.35 Hz, 1 H) 7.38 – 7.47 (m, 1 H) 7.80 (d, *J*=9.35 Hz, 1 H) 7.94 (d, *J*=9.85 Hz, 1 H) 8.10 (s, 1 H) 8.35 (d, *J*=7.07 Hz, 1 H) 11.14 (s, 1 H). MS:m/z 348.2 $(M+H)^+$.

Compuesto 53: N–(6–(1–(6–metil–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describe en la preparación del compuesto **48,** (método A) usando 2–hidrazinil–5–metilpiridina. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.76 – 0.86 (m, 4 H) 1.85 (d, *J*=7.07 Hz, 3 H) 1.92 (m, 1 H) 3.56 (s, 3 H) 5.02 (d, *J*=7.07 Hz, 1 H) 7.18 (d, *J*=9.35 Hz, 1 H) 7.23 – 7.31 (m, 1 H) 7.70 (d, *J*=8.84 Hz, 1 H) 7.93 (d, *J*=9.85 Hz, 1 H) 8.10 (s, 1 H) 8.20 (s, 1 H) 11.13 (s, 1 H). MS:m/z 362.2 $(M+H)^+$.

Compuesto 54: (6–(2–([1,2,4]Triazolo[4,3–a]piridin–3–il)propan–2–il)imidazo[1,2–b]piridazin–2–il)(ciclopropil)metanona



2–(6–cloropiridazin–3–il)propanoato de etilo (54A***)***: Una solución del 2–(6–cloropiridazin–3–il)–2–metilmalonato de dietilo (11 g, 38.4 mmol) y NaCl (2.69 g, 46.0 mmol) en DMSO (91 ml) y H_2O (1.382 ml) se dividió en ocho viales de microonda separados y cada reacción se calentó en un microondas a 175°C durante 90 min a absorbancia alta. Las reacciones se combinaron y luego se vertieron en H_2O (300 ml). La fase acuosa se extrajo con EtOAc (2 x 100 ml) y luego la fase orgánica se lavó con salmuera (2 x 100 ml). La fase orgánica se secó con $MgSO_4$, se filtró y concentró a sequedad por evaporación giratoria. El aceite resultante se purificó por medio de MPLC (3:1, Hex:EtOAc) para proporcionar el compuesto del título, 2–(6–cloropiridazin–3–il)propanoato de etilo (54A, 2.9g, 35%). ^{1}H NMR (400 MHz, DMSO–d_6) δppm 1.13 (s, 3 H) 1.49 (d, *J*=7.33 Hz, 3 H) 4.09 (dd, *J*=7.07, 2.02 Hz, 2 H) 4.23 (d, *J*=7.33 Hz, 1 H) 7.83 (d, *J*=8.84 Hz, 1 H) 7.93 (d, *J*=8.84 Hz, 1 H). ESI–MS:m/z 215.0 $(M+H)^+$.

2–(6–cloropiridazin–3–il)–2–metilpropanoato de etilo (54B): A una solución de 2–(6–cloropiridazin–3–il)propanoato de etilo (2.8 g, 13.04 mmol) en TF (28 ml) se añadió hexametlidisilazida de litio (1.0 molar en TF, 15.65 ml, 15.65 mmol) a –70 °C en forma de goteo. La reacción se agitó a –70 durante 30 min y luego se añadió yodometano (0.816 ml, 13.04 mmol). La reacción se agitó durante 2 horas para permitir calentar a temperatura ambiente. La reacción se concentró a sequedad por evaporación giratoria y el material resultante se purificó por MPLC (98:2, DCM:MeOH) para proporcionar el compuesto del título, 2–(6–cloropiridazin–3–il)–2–metilpropanoato de etilo (54B, 2.82g, 95%). ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 1.11 (t, *J*=7.07 Hz, 3 H) 1.58 (s, 6 H) 4.08 (q, *J*=7.07 Hz, 2 H) 7.83 – 7.97 (m, 2 H).

2–(6–cloropiridazin–3–il)–2–metilpropanoao de litio (54C): El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **48B**.

2–(6–Cloropiridazin–3–il)–2–metil–N'–(piridin–2–il)propanehidrazida (54D): El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **48C** usando 2–hidrazinilpiridina.

3–(2–(6–cloropiridazin–3–il)propan–2–il)–[1,2,4]triazolo[4,3–a]piridina (54E): Una mezcla de 2–(6–cloropiridazin–3–il)–N'–(piridin–2–il)propanohidrazida (1.2 g, 4.32 mmol) y tricloruro de fosforilo (10.0 ml, 107 mmol) se calentó en un microondas a absorbancia alta durante 15 min a 140 °C. La reacción resultante se extrajo a sequedad por evaporación giratoria. El residuo resultante se reconstituyó en EtOAc (50 ml) y se lavó con bicarbonato saturado (3 x 50 ml). La fase orgánica se separó y se secó con $MgSO_4$ y el EtOAc se eliminó por evaporación giratoria para proporcionar el compuesto del título, 3–(2–(6–cloropiridazin–3–il)propan–2–il)–[1,2,4]triazolo[4,3–a]piridina (54E, 0.750 g, 2.74 mmol, 63.4 % de rendimiento). $_1$H NMR (400 MHz, DMSO–*d*6) δppm 1.94 (6 H, s) 6.75 – 6.82 (1 H, m) 7.33 (1 H, ddd, *J*=9.35, 6.57, 1.01 Hz) 7.72 – 7.82 (2 H, m) 7.87 – 7.99 (2 H, m). ESI–MS:m/z 274.1 $(M+H)^+$.

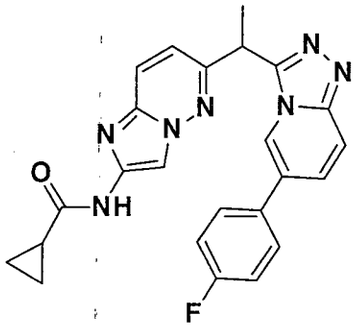
6–(2–([1,2,4]Triazolo[4,3–a]piridin–3–il)propan–2–il)–N–(2,4–dimetoxibencil)piridazin–3–amina (54F): El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del

Compuesto **48E**.

6–(2–([1,2,4]Triazolo[4,3–a]piridin–3–il)propan–2–il)piridazin–3–amina (54G): El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **48F**.

(6–(2–([1,2,4]Triazolo[4,3–a]piridin–3–il)propan–2–il)imidazo[1,2–b]piridazin–2–il)(ciclopropil)metanona (54): Una mezcla de 2,2,2–trifluoroaceto de 6–(2–([1,2,4]triazolo[4,3–a]piridin–3–il)propan–2–il)piridazin–3–amina (50 mg, 0.136 mmol), N–(2–bromoacetil)ciclopropancarboxamida (28.0 mg, 0.136 mmol), fosfato ácido de sodio (57.8 mg, 0.407 mmol), y yoduro de potasio (22.54 mg, 0.136 mmol) en DMA (Volumen: 1160 µl) se calentó en un microondas a absorbancia alta durante 1 hora a 100 °C. La reacción se purificó por LCMS preparativa para proporcionar el compuesto del título, (6–(2–([1,2,4]triazolo[4,3–a]piridin–3–il)propan–2–il)imidazo[1,2–b]piridazin–2–il)(ciclopropil)metanona (54, 13 mg, 26%) en forma de sal de TFA. $_1$H NMR (400 MHz, DMSO–d_6) δppm 0.81 (d, *J*=6.06 Hz, 4 H) 1.87 – 2.00 (m, 7 H) 6.92 – 6.97 (m, 1 H) 7.12 (d, *J*=9.60 Hz, 1 H) 7.55 (dd, *J*=8.97, 6.69 Hz, 1 H) 7.87 – 8.01 (m, 3 H) 8.04 (s, 1 H) 11.16 (s, 1 H). ESI–MS:m/z 362.1 $(M+H)^+$.

Compuesto 55: N–(6–(1–(6–(4–fluorofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

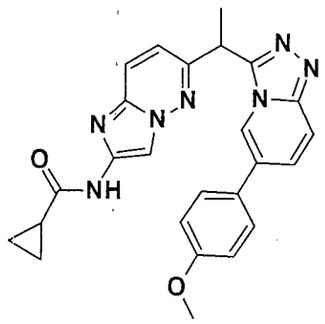


El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–fluorofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d6*) δ ppm 0.72 – 0.88 (m, 4 H) 1.81 – 1.98 (m, 4 H) 5.30 (d, *J*=7.07 Hz, 1 H) 7.30 (d, *J*=9.35 Hz, 1 H) 7.32 – 7.40 (m, 2H) 7.76 – 7.82 (m, 2 H) 7.82 – 7.88 (m, 1 H) 7.95 (t, *J*=9.09 Hz, 2

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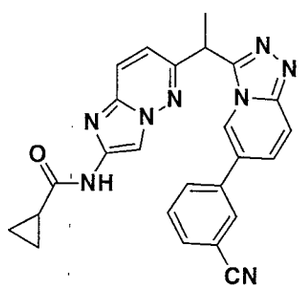
H) 8.09 (s, 1 H) 8.78 (s, 1 H) 11.14 (s, 1 H). ESI–MS:m/z 442.2 $(M+H)^+$.

Compuesto 56: N–(6–(1–(6–(4–metoxifenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–metoxifenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.73 – 0.87 (m, 5 H) 1.84 – 2.00 (m, 5 H) 5.30 (d, *J*=7.33 Hz, 1 H) 7.02 – 7.14 (m, 3 H) 7.29 (d, *J*=9.35 Hz, 1H) 7.61 – 7.72 (m, 3 H) 7.83 – 8.00 (m, 4 H) 8.10 (s, 1 H) 8.71 (s, 1 H) 11.15 (s, 1 H). ESI–MS:m/z 454.2 $(M+H)^+$.

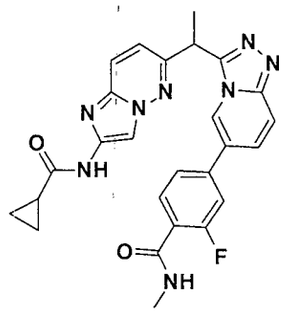
Compuesto 57: N–(6–(1–(6–(3–cianofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 3–cianofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.71 – 0.86 (m, 4 H) 1.82 – 1.97 (m, 4 H) 5.24 – 5.37 (m, 1 H) 7.31 (d, *J*=9.60 Hz, 1 H) 7.69 – 7.75 (m, 1 H) 7.87 – 7.99 (m, 4 H) 8.05 – 8.13 (m, 2 H) 8.31 (t, *J*=1.52 Hz, 1 H)

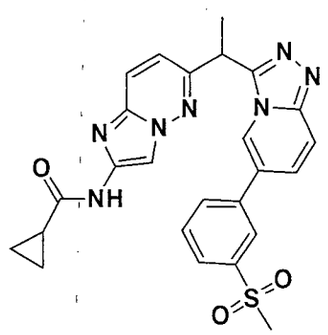
8.94 (s, 1 H) 11.12 (s, 1 H). ESI–MS:m/z 449.2 $(M+H)^+$.

Compuesto 58: 4–(3–(1–(2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–il)etil)–[1,2,4]triazolo[4,3–a]piridin–6–il)–2–fluoro–N–metilbenzamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 3–fluoro–4–(metilcarbamoil)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.72 – 0.86 (m, 4 H) 1.84 – 1.98 (m, 4 H) 2.80 (d, *J*=4.55 Hz, 3 H) 5.31 (d, *J*=7.07 Hz, 1 H) 7.30 (d, *J*=9.35 Hz, 1 H) 7.66 – 7.71 (m, 1 H) 7.71 – 7.81 (m, 2 H) 7.83 – 7.88 (m, 1 H) 7.89 – 7.98 (m, 2 H) 8.09 (s, 1 H) 8.30 (dd, *J*=4.55, 2.53 Hz, 1 H) 8.89 (s, 1 H) 11.13 (s, 1 H). ESI–MS:m/z 499.2 $(M+H)^+$.

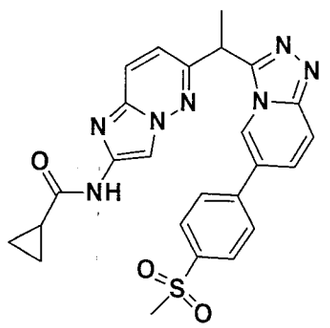
Compuesto 59: N–(6–(1–(6–(3–(metilsulfonil)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 3–(metilsulfonil)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.74 – 0.85 (m, 5 H) 1.83 – 1.98 (m, 5 H) 5.34 (d, *J*=7.07 Hz, 1

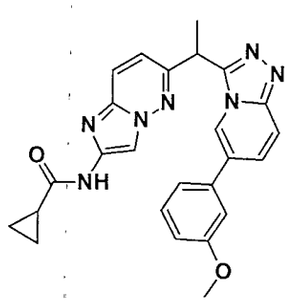
H) 7.32 (d, *J*=9.35 Hz, 1 H) 7.73 – 7.85 (m, 1 H) 7.89 – 8.03 (m, 5 H) 8.05 – 8.14 (m, 2 H) 8.27 (t, *J*=1.64 Hz, 1 H) 8.93 (s, 1 H) 11.13 (s, 1 H). ESI–MS:m/z 502.2 $(M+H)^+$.

Compuesto 60: N–(6–(1–(6–(4–(metilsulfonil)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–(metilsulfonil)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.73 – 0.87 (m, 5 H) 1.83 – 1.98 (m, 5 H) 5.31 (d, *J*=7.07 Hz, 1 H) 7.30 (d, *J*=9.35 Hz, 1 H) 7.85 – 7.90 (m, 1 H) 7.93 – 7.99 (m, 2 H) 7.99 – 8.07 (m, 5 H) 8.09 (s, 1 H) 8.90 (s, 1 H) 11.13 (s, 1 H). ESI–MS:m/z 502.2 $(M+H)^+$.

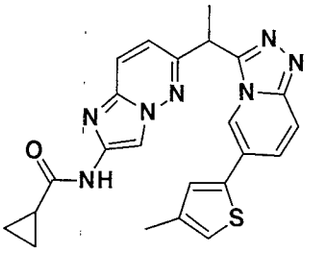
Compuesto 61: N–(6–(1–(6–(3–metoxifenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 3–metoxifenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz,

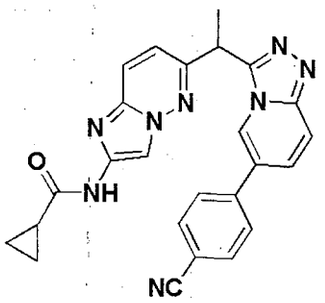
DMSO–*d*6) δ ppm 0.74 – 0.85 (m, 4 H) 1.90 (d, *J*=7.33 Hz, 4 H) 3.61 (s, 3 H) 5.32 (d, *J*=7.07 Hz, 1 H) 7.02 (ddd, *J*=8.21, 2.40, 0.76 Hz, 1 H) 7.21 – 7.34 (m, 3 H) 7.37 – 7.49 (m, 1 H) 7.87 – 8.00 (m, 3 H) 8.09 (s, 1 H) 8.77 (s, 1 H) 11.14 (s, 1 H). ESI–MS:m/z 454.2 $(M+H)^+$.

Compuesto 62: N–(6–(1–(6–(4–metiltiofen–2–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–metiltiofen–2–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.75 – 0.87 (m, 4 H) 1.82 – 1.98 (m, 4 H) 2.24 (d, *J*=0.76 Hz, 3 H) 5.24 (d, *J*=7.33 Hz, 1 H) 7.17 – 7.30 (m, 2 H) 7.45 (d, *J*=1.26 Hz, 1 H) 7.71 (dd, *J*=9.60, 1.52 Hz, 1 H) 7.86 (dd, *J*=9.47, 0.88 Hz, 1 H) 7.95 (d, *J*=9.60 Hz, 1 H) 8.13 (s, 1 H) 8.64 (s, 1 H) 11.15 (s, 1 H). ESI–MS:m/z 444.2 $(M+H)^+$.

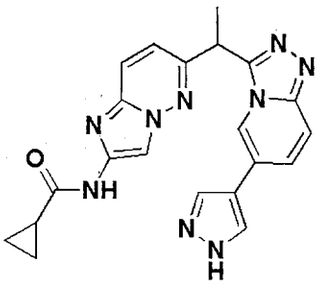
Compuesto 63: N–(6–(1–(6–(4–cianofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–cianofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.73 – 0.87

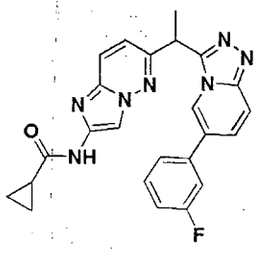
(m, 4 H) 1.83 – 2.00 (m, 4 H) 5.29 (d, *J*=7.07 Hz, 1 H) 7.29 (d, *J*=9.35 Hz, 1 H) 7.80 – 7.89 (m, 1 H) 7.90 – 8.04 (m, 6 H) 8.08 (s, 1 H) 8.90 (s, 1 H) 11.13 (s, 1 H). ESI–MS:m/z 449.2 $(M+H)^+$.

Compuesto 64: N–(6–(1–(6–(1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 1H–pirazol–4–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.73 – 0.86 (m, 4 H) 1.82 – 1.99 (m, 4 H) 5.21 (d, *J*=7.33 Hz, 1 H) 7.31 (d, *J*=9.60 Hz, 1 H) 7.88 (d, *J*=6.06 Hz, 2 H) 7.97 (d, *J*=9.35 Hz, 1 H) 8.11 (s, 1 H) 8.19 (s, 2 H) 8.75 (s, 1 H) 11.13 (s, 1 H). ESI–MS:m/z 414.2 $(M+H)^+$.

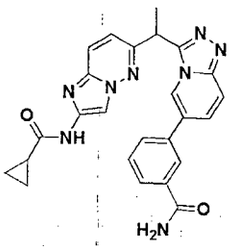
Compuesto 65: N–(6–(1–(6–(3–fluorofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–fluorofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.72 – 0.87 (m, 4 H) 1.83 – 1.97 (m, 4 H) 5.29 (d, *J*=7.33 Hz, 1 H) 7.51 – 7.61 (m, 2 H) 7.64 (dt, *J*=10.29, 2.05 Hz, 1 H) 7.81 (dd, *J*=9.73, 1.64 Hz, 1 H) 7.87 – 7.92 (m, 1 H) 7.94

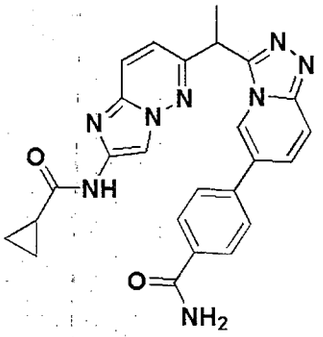
(d, *J*=9.35 Hz, 1 H) 8.09 (s, 1 H) 8.80 (s, 1 H) 11.08 (s, 1 H). ESI–MS:m/z 442.2 $(M+H)^+$.

Compuesto 66: 3–(3–(1–(2–(ciclopropancarboxamido) imidazo[1,2–b]piridazin–6–il)etil)–[1,2,4]triazolo[4,3–a]piridin–6–il)benzamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 3–carbamoilfenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.71 – 0.89 (m, 4 H) 1.83 – 2.00 (m, 4 H) 7.31 (d, *J*=9.35 Hz, 1 H) 7.46 (br. s., 1 H) 7.60 (t, *J*=7.71 Hz, 1 H) 7.82 – 8.03 (m, 5 H) 8.04 – 8.14 (m, 2 H) 8.22 (t, *J*=1.52 Hz, 1 H) 8.86 (s, 1 H) 11.09 (s, 1 H). ESI–MS:m/z 467.2 $(M+H)^+$.

Compuesto 67: 4–(3–(1–(2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–il)etil)–[1,2,4]triazolo[4,3–a]piridin–6–il)benzamida

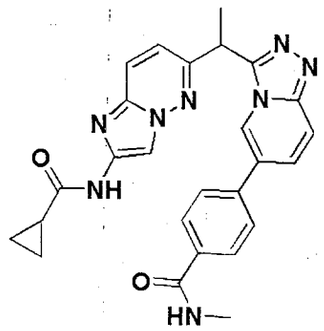


El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–carbamoilfenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.73 – 0.89 (m, 4 H) 1.83 – 1.99 (m, 4 H) 5.29 (d, *J*=7.33 Hz, 1 H) 7.28 (d, *J*=9.35 Hz, 1 H) 7.77 – 7.86 (m, 3 H) 7.87 – 7.92 (m, 1 H) 7.94 (d,

000484

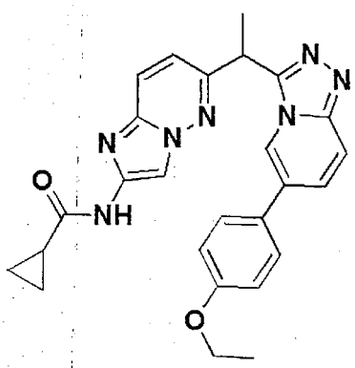
J=9.35 Hz, 1 H) 7.97 – 8.06 (m, 3 H) 8.10 (s, 1 H) 8.79 (s, 1 H) 11.08 (s, 1 H). ESI–MS:m/z 467.2 $(M+H)^+$.

Compuesto 68: 4–(3–(1–(2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–il)etil)–[1,2,4]triazolo[4,3–a]piridin–6–il)–N–metilbenzamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–(metilcarbamoil)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.72 – 0.88 (m, 4 H) 1.83 – 1.99 (m, 4 H) 2.81 (d, *J*=4.55 Hz, 3 H) 5.30 (d, *J*=7.07 Hz, 1 H) 7.28 (d, *J*=9.35 Hz, 1 H) 7.78 – 7.87 (m, 3 H) 7.87 – 8.00 (m, 4 H) 8.10 (s, 1 H) 8.49 (d, *J*=4.55 Hz, 1 H) 8.81 (s, 1 H) 11.09 (s, 1 H). ESI–MS:m/z 481.2 $(M+H)^+$.

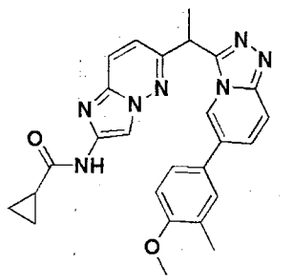
Compuesto 69: N–(6–(1–(6–(4–etoxifenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–etoxifenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se

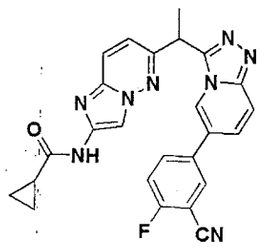
aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.72 – 0.87 (m, 4 H) 1.34 (t, *J*=6.95 Hz, 3 H) 1.82 – 1.98 (m, 4 H) 5.27 (d, *J*=7.07 Hz, 1 H) 6.99 – 7.10 (m, 2 H) 7.26 (d, *J*=9.35 Hz, 1 H) 7.57 – 7.69 (m, 2 H) 7.74 – 7.83 (m, 1 H) 7.84 – 7.91 (m, 1 H) 7.94 (d, *J*=9.60 Hz, 1 H) 8.10 (s, 1 H) 8.64 (s, 1 H) 11.09 (s, 1 H). ESI–MS:m/z 468.2 $(M+H)^+$.

Compuesto 70: N–(6–(1–(6–(4–metoxi–3–metilfenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–metoxi–3–metilfenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.74 – 0.86 (m, 5 H) 1.85 – 1.99 (m, 5 H) 2.21 (s, 4 H) 5.29 (d, *J*=7.33 Hz, 2 H) 7.06 (d, *J*=8.59 Hz, 1 H) 7.28 (d, *J*=9.35 Hz, 1 H) 7.42 – 7.57 (m, 2 H) 7.78 – 7.99 (m, 4 H) 8.12 (s, 1 H) 8.65 (s, 1 H) 11.10 (s, 1 H). ESI–MS:m/z 468.2 $(M+H)^+$.

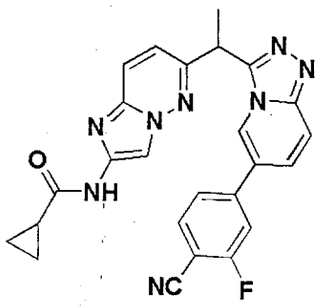
Compuesto 71: N–(6–(1–(6–(3–ciano–4–fluorofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 3–ciano–4–fluorofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ

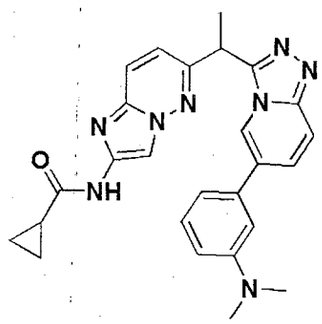
ppm 0.73 – 0.86 (m, 4 H) 1.84 – 1.99 (m, 5 H) 5.26 (d, *J*=7.33 Hz, 1 H) 7.29 (d, *J*=9.60 Hz, 1 H) 7.68 (t, *J*=8.97 Hz, 1 H) 7.75 – 7.84 (m, 1 H) 7.87 – 7.98 (m, 2 H) 8.08 (s, 1 H) 8.12 – 8.22 (m, 1 H) 8.38 (dd, *J*=6.19, 2.40 Hz, 1 H) 8.86 (s, 1 H) 11.08 (s, 1 H). ESI–MS:m/z 467.2 $(M+H)^+$.

Compuesto 72: N–(6–(1–(6–(4–ciano–3–fluorofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 4–ciano–3–fluorofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.73 – 0.86 (m, 4 H) 1.82 – 2.00 (m, 4 H) 5.29 (d, *J*=7.33 Hz, 1 H) 7.29 (d, *J*=9.60 Hz, 1 H) 7.82 – 7.88 (m, 2 H) 7.89 – 7.97 (m, 2 H) 8.02 (dd, *J*=10.99, 1.64 Hz, 1 H) 8.05 – 8.10 (m, 2 H) 8.95 (s, 1 H) 11.08 (s, 1 H). ESI–MS:m/z 467.2 $(M+H)^+$.

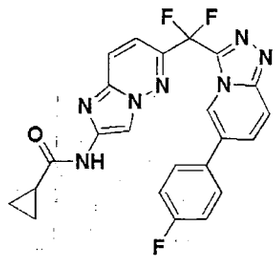
Compuesto 73: N–(6–(1–(6–(3–(dimetilamino)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)etil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **49** usando ácido 3–(dimetilamino)fenilborónico. La mezcla de reacción bruta se purificó por LCMS

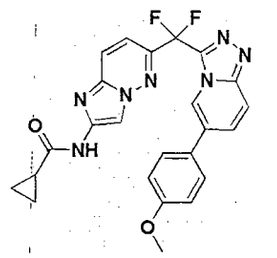
preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–*d*6) δ ppm 0.74 – 0.86 (m, 4 H) 1.91 (d, *J*=7.07 Hz, 4 H) 2.94 (s, 6 H) 5.29 (d, *J*=7.33 Hz, 1 H) 6.82 (dd, *J*=8.21, 2.15 Hz, 1 H) 6.90 (s, 1 H) 6.97 (d, *J*=7.83 Hz, 1 H) 7.25 – 7.34 (m, 2 H) 7.83 – 7.89 (m, 1 H) 7.89 – 7.98 (m, 2 H) 8.09 (s, 1 H) 8.62 (s, 1 H) 11.09 (s, 1 H). ESI–MS:m/z 467.2 $(M+H)^+$.

Compuesto 74: N–(6–(difluoro(6–(4–fluorofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 4–fluorofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.19 Hz, 1 H) 7.37 (t, *J*=8.84 Hz, 2 H) 7.71 (d, *J*=9.35 Hz, 1 H) 7.79 – 7.85 (m, 2 H) 7.96 (dd, *J*=9.73, 1.39 Hz, 1 H) 8.12 (d, *J*=9.60 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.74 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 464.2 $(M+H)^+$.

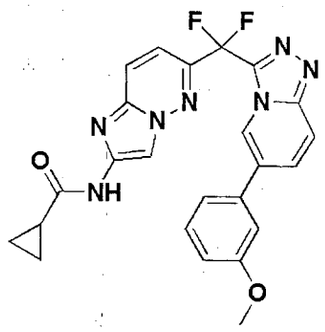
Compuesto 75: N–(6–(difluoro(6–(4–metoxifenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** (*Método B*) usando ácido 4–metoxifenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz,

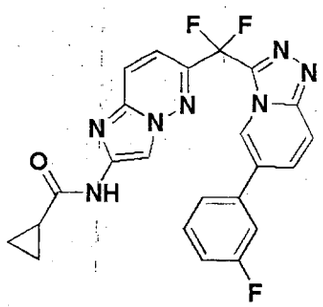
DMSO–d_6) δ ppm 0.83 (d, *J*=6.32 Hz, 4 H) 1.92 – 2.00 (m, 1 H) 3.82 (s, 3 H) 7.09 (d, *J*=8.84 Hz, 2 H) 7.70 (d, 2 H) 7.72 (s, 1 H) 7.95 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.08 (d, *J*=9.60 Hz, 1 H) 8.25 (s, 1 H) 8.27 (d, *J*=9.60 Hz, 1 H) 8.66 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 476.2 $(M+H)^+$.

Compuesto 76: N–(6–(difluoro(6–(3–metoxifenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 3–metoxifenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.91 – 2.01 (m, 1 H) 3.83 (s, 3 H) 7.05 (dd, *J*=8.21, 1.89 Hz, 1 H) 7.26 (d, *J*=2.02 Hz, 1 H) 7.30 (d, *J*=7.58 Hz, 1 H) 7.44 (t, 1 H) 7.71 (d, *J*=9.35 Hz, 1 H) 7.98 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.11 (d, *J*=8.84 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.73 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 476.2 $(M+H)^+$.

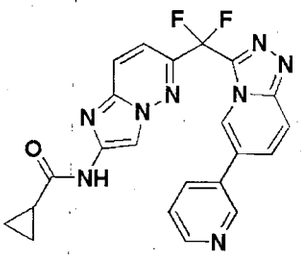
Compuesto 77: N–(6–(difluoro(6–(3–fluorofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se

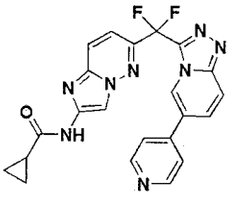
describió en la preparación del Compuesto **45** usando ácido 3–fluorofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, J=6.06 Hz, 4 H) 1.96 (quin, J=6.19 Hz, 1 H) 7.32 (dt, 1 H) 7.54 – 7.59 (m, 1 H) 7.62 (t, J=7.58 Hz, 1 H) 7.68 (dt, 1 H) 7.71 (d, 1 H) 8.00 (dd, J=9.60, 1.52 Hz, 1 H) 8.13 (d, J=9.60 Hz, 1 H) 8.23 (s, 1 H) 8.28 (d, J=9.60 Hz, 1 H) 8.81 (s, 1 H) 11.34 (s, 1 H). ESI–MS:m/z 464.2 $(M+H)^+$.

Compuesto 78: N–(6–(difluoro(6–(piridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido piridin–3–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, J=6.06 Hz, 4 H) 1.96 (quin, J=6.13 Hz, 1 H) 7.61 (dd, J=7.96, 4.93 Hz, 1 H) 7.73 (d, J=9.35 Hz, 1 H) 8.02 (dd, J=9.60, 1.52 Hz, 1 H) 8.17 (d, J=9.09 Hz, 1 H) 8.22 (s, 1 H) 8.25 (s, 1 H) 8.26 – 8.32 (m, 1 H) 8.69 (d, J=4.29 Hz, 1 H) 8.90 (s, 1 H) 9.00 (br. s., 1 H) 11.34 (s, 1 H). ESI–MS:m/z 447.2 $(M+H)^+$.

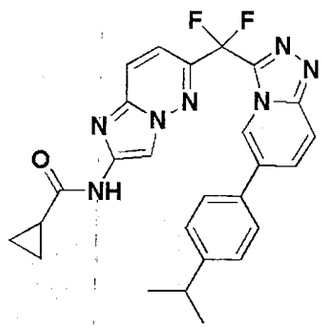
Compuesto 79: N–(6–(difluoro(6–(piridin–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido piridin–4–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se

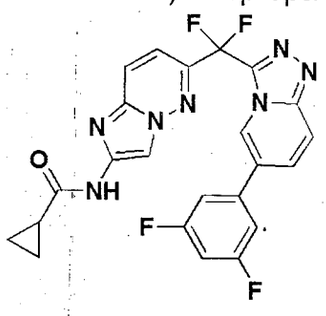
aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, J=5.31 Hz, 4 H) 1.96 (quin, J=6.13 Hz, 1 H) 7.69 – 7.77 (m, 1 H) 7.93 (d, J=5.05 Hz, 2 H) 8.07 (dd, J=9.60, 1.52 Hz, 1 H) 8.19 (d, J=9.85 Hz, 1 H) 8.23 (s, 1 H) 8.29 (d, J=9.35 Hz, 1 H) 8.76 (br. s., 2 H) 8.98 (s, 1 H) 11.34 (s, 1 H). ESI–MS:m/z 447.2 $(M+H)^+$.

Compuesto 80: N–(6–(difluoro(6–(4–isopropilfenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 4–isopropilfenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.84 (d, J=6.06 Hz, 4 H) 1.24 (d, J=6.82 Hz, 6 H) 1.95 (q, 1 H) 2.96 (spt, J=6.86 Hz, 1 H) 7.40 (d, J=8.34 Hz, 2 H) 7.67 (d, J=8.34 Hz, 2 H) 7.71 (d, J=9.35 Hz, 1 H) 7.96 (dd, J=9.60, 1.26 Hz, 1 H) 8.11 (d, J=9.60 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, J=9.35 Hz, 1 H) 8.70 (s, 1 H) 11.36 (s, 1 H). ESI–MS:m/z 488.2 $(M+H)^+$.

Compuesto 81: N–(6–((6–(3,5–difluorofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

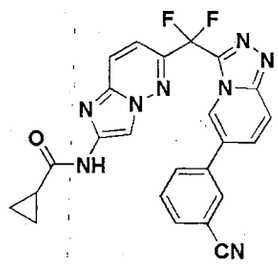


El compuesto del título se sintetizó usando un procedimiento análogo al que se

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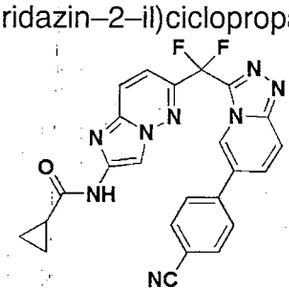
describió en la preparación del Compuesto **45** usando ácido 3,5–difluorofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=5.81 Hz, 4 H) 1.95 (quin, 1 H) 7.32 – 7.42 (m, 1 H) 7.56 – 7.66 (m, 2 H) 7.73 (d, *J*=9.60 Hz, 1 H) 8.01 (dd, *J*=9.73, 1.39 Hz, 1 H) 8.14 (d, *J*=9.60 Hz, 1 H) 8.21 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.88 (s, 1 H) 11.34 (s, 1 H). ESI–MS:m/z 482.2 $(M+H)^+$.

Compuesto 82: N–(6–((6–(3–cianofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 3–cianofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.13 Hz, 1 H) 7.68 – 7.77 (m, 2 H) 7.94 (d, *J*=7.83 Hz, 1 H) 8.03 (dd, *J*=9.73, 1.14 Hz, 1 H) 8.12 (d, *J*=8.34 Hz, 1 H) 8.16 (d, *J*=9.60 Hz, 1 H) 8.23 (s, 1 H) 8.29 (d, *J*=9.35 Hz, 1 H) 8.33 (s, 1 H) 8.93 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 471.2 $(M+H)^+$.

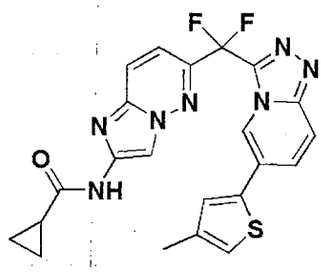
Compuesto 83: N–(6–((6–(4–cianofenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 4–cianofenilborónico.

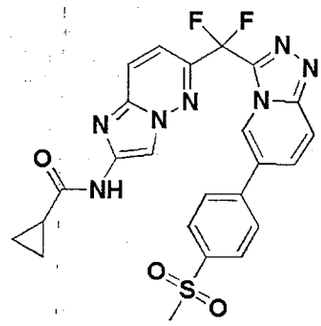
La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.19 Hz, 1 H) 7.72 (d, *J*=9.60 Hz, 1 H) 8.00 (s, 4 H) 8.03 (d, *J*=9.60 Hz, 1 H) 8.16 (d, *J*=9.60 Hz, 1 H) 8.20 – 8.24 (m, 1 H) 8.28 (d, *J*=9.60 Hz, 1 H) 8.89 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 471.2 $(M+H)^+$.

Compuesto 84: N–(6–(difluoro(6–(4–metiltiofen–2–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 4–metiltiofen–2–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.84 (d, *J*=6.32 Hz, 4 H) 1.95 (q, 1 H) 2.26 (s, 3 H) 7.29 (s, 1 H) 7.59 (s, 1 H) 7.70 (d, *J*=9.35 Hz, 1 H) 7.91 (dd, *J*=9.73, 1.64 Hz, 1 H) 8.07 (d, *J*=9.60 Hz, 1 H) 8.26 (s, 1 H) 8.25 – 8.30 (m, 1 H) 8.69 (s, 1 H) 11.36 (s, 1 H). ESI–MS:m/z 466.2 $(M+H)^+$.

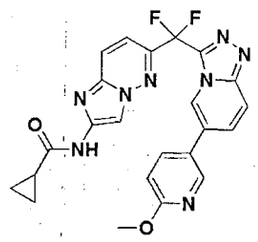
Compuesto 85: N–(6–(difluoro(6–(4–(metilsulfonil)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 4–

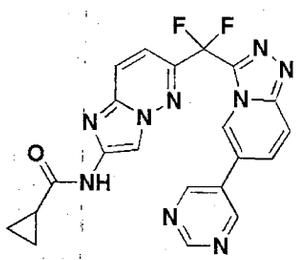
(metilsulfonil)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, J=6.06 Hz, 4 H) 1.96 (q, 1 H) 3.28 (s, 3 H) 7.72 (d, J=9.35 Hz, 1 H) 8.02 (dd, 1 H) 8.05 (s, 4 H) 8.17 (d, J=9.60 Hz, 1 H) 8.23 (s, 1 H) 8.28 (d, J=9.60 Hz, 1 H) 8.88 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 524.2 $(M+H)^+$.

Compuesto 86: N–(6–(difluoro(6–(6–metoxipiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 6–metoxipiridin–3–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, J=6.06 Hz, 4 H) 1.96 (quin, J=6.19 Hz, 1 H) 3.91 (s, 3 H) 6.97 (d, J=8.59 Hz, 1 H) 7.72 (d, J=9.35 Hz, 1 H) 7.97 (dd, J=9.60, 1.52 Hz, 1 H) 8.09 – 8.15 (m, 2 H) 8.22 (s, 1 H) 8.28 (d, J=9.35 Hz, 1 H) 8.56 (d, J=2.53 Hz, 1 H) 8.78 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 477.2 $(M+H)^+$.

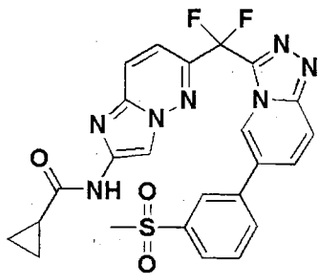
Compuesto 87: N–(6–(difluoro(6–(pirimidin–5–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido pirimidin–5–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm

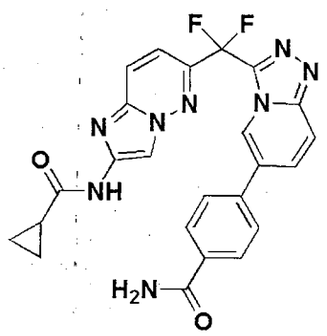
0.83 (d, *J*=5.56 Hz, 4 H) 1.90 – 2.00 (m, 1 H) 7.74 (d, *J*=9.60 Hz, 1 H) 8.06 (dd, *J*=9.60, 1.26 Hz, 1 H) 8.17 – 8.25 (m, 2 H) 8.29 (d, *J*=9.35 Hz, 1 H) 9.03 (s, 1 H) 9.21 (s, 2 H) 9.24 – 9.29 (m, 1 H) 11.34 (s, 1 H). ESI–MS:m/z 448.2 $(M+H)^+$.

Compuesto 88: N–(6–(difluoro(6–(3–(metilsulfonil)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 3–(metilsulfonil)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.91 – 2.01 (m, 1 H) 3.32 (s, 3 H) 7.72 (d, *J*=9.35 Hz, 1 H) 7.81 (t, *J*=7.83 Hz, 1 H) 8.02 (d, *J*=7.83 Hz, 1 H) 8.06 (dd, *J*=9.60, 1.52 Hz, 1 H) 8.13 (d, *J*=7.83 Hz, 1 H) 8.18 (d, *J*=9.60 Hz, 1 H) 8.23 – 8.31 (m, 3 H) 8.92 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 524.2 $(M+H)^+$.

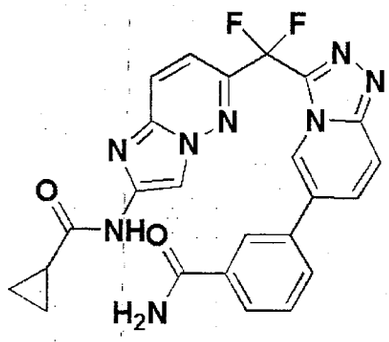
Compuesto 89: 4–(3–((2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–il)difluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il)benzamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 4–carbamoilfenilborónico. La mezcla de reacción bruta se purificó por LCMS

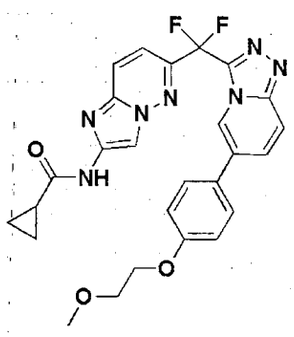
preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=6.32 Hz, 4 H) 1.90 – 2.01 (m, 1 H) 7.48 (br. s., 1 H) 7.72 (d, *J*=9.35 Hz, 1 H) 7.87 (d, *J*=8.34 Hz, 2 H) 7.98 – 8.06 (m, 3 H) 8.10 (br. s., 1 H) 8.11 – 8.17 (m, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.82 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 489.2 $(M+H)^+$.

Compuesto 90: 3–(3–((2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–il)difluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il)benzamida



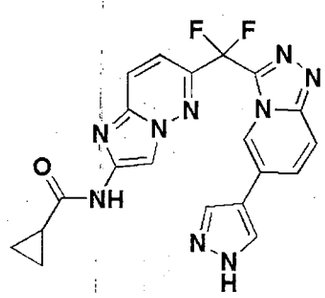
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 3–carbamoilfenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.84 (d, *J* = 6.06 Hz, 4 H) 1.96 (quin, *J* = 6.13 Hz, 1 H) 7.53 (s, 1 H) 7.62 (t, *J* = 7.70 Hz, 1 H) 7.72 (d, *J* = 9.60 Hz, 1 H) 7.90 – 7.98 (m, 2 H) 8.04 (dd, *J* = 9.73, 1.39 Hz, 1 H) 8.16 (d, *J* = 9.60 Hz, 1 H) 8.19 (br. s., 1 H) 8.22 (s, 1 H) 8.25 (s, 1 H) 8.28 (d, *J* = 9.35 Hz, 1 H) 8.85 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 489.2 $(M+H)^+$.

Compuesto 91: N–(6–(difluoro(6–(4–(2–metoxietoxi)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



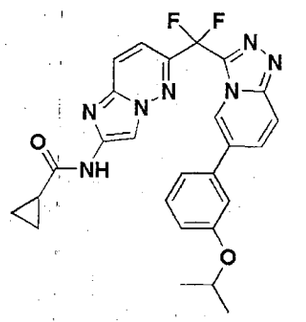
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 4–(2–metoxietoxi)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.84 (d, J = 6.32 Hz, 4 H) 1.96 (quin, J = 6.13 Hz, 1 H) 3.32 (s, 3 H) 3.66 – 3.71 (m, 2 H) 4.13 – 4.19 (m, 2 H) 7.09 (d, J = 8.59 Hz, 2 H) 7.70 (dd, J = 9.09, 2.78 Hz, 3 H) 7.95 (dd, J = 9.60, 1.52 Hz, 1 H) 8.08 (d, J = 9.60 Hz, 1 H) 8.25 (s, 1 H) 8.28 (d, J = 9.35 Hz, 1 H) 8.67 (s, 1 H) 11.36 (s, 1 H). ESI–MS: m/z 520.2 $(M+H)^+$.

Compuesto 92: N–(6–((6–(1H–pirazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



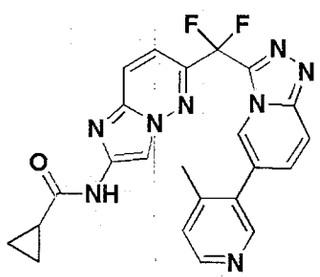
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 1H–pirazol–4–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.84 (d, J=6.06 Hz, 4 H) 1.96 (quin, J=6.19 Hz, 1 H) 7.71 (d, J=9.35 Hz, 1 H) 7.97 (dd, 1 H) 8.03 – 8.08 (m, 1 H) 8.17 – 8.43 (m, 2 H) 8.25 (s, 1 H) 8.28 (d, J=9.35 Hz, 1 H) 8.75 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 436.2 $(M+H)^+$.

Compuesto 93: N–(6–(difluoro(6–(3–isopropoxifenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



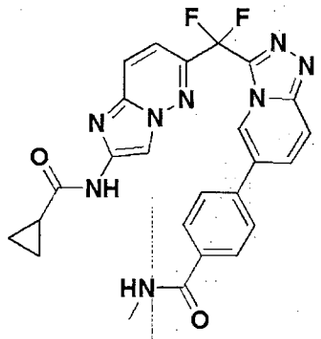
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 3–isopropoxifenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.28 (d, *J*=6.06 Hz, 6 H) 1.96 (quin, *J*=6.13 Hz, 1 H) 4.65 – 4.76 (m, 1 H) 7.02 (dd, *J*=8.21, 1.89 Hz, 1 H) 7.21 (s, 1 H) 7.26 (d, *J*=7.83 Hz, 1 H) 7.38 – 7.46 (m, 1 H) 7.71 (d, *J*=9.35 Hz, 1 H) 7.96 (dd, *J*=9.60, 1.26 Hz, 1 H) 8.10 (d, *J*=9.60 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.71 (s, 1 H) 11.36 (s, 1 H). ESI–MS:m/z 504.2 $(M+H)^+$.

Compuesto 94: N–(6–(difluoro(6–(4–metilpiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



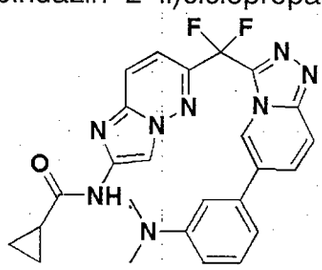
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 4–metilpiridin–3–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.79 – 0.89 (m, 4 H) 1.19 – 1.29 (m, 3 H) 1.89 – 2.00 (m, 1 H) 6.87 (s, 1 H) 7.43 (br. s., 1 H) 7.68 – 7.76 (m, 2 H) 8.11 (d, *J*=8.84 Hz, 1 H) 8.22 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.51 (br. s., 1 H) 8.68 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 461.2 $(M+H)^+$.

Compuesto 95: 4–(3–((2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–il)difluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il)–N–metilbenzamida



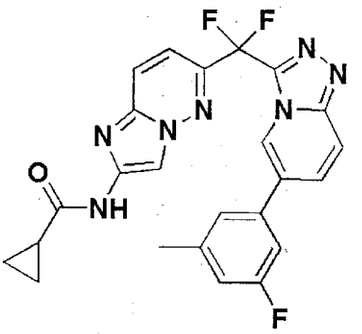
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 4–(metilcarbamoil)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.13 Hz, 1 H) 2.76 – 2.86 (m, 3 H) 7.72 (d, *J*=9.60 Hz, 1 H) 7.88 (d, *J*=8.34 Hz, 2 H) 7.93 – 8.00 (m, 2 H) 8.03 (dd, *J*=9.73, 1.39 Hz, 1 H) 8.14 (d, *J*=9.35 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, *J*=9.35 Hz, 1 H) 8.57 (d, *J*=4.55 Hz, 1 H) 8.83 (s, 1 H) 11.35 (s, 1 H). ESI–MS:m/z 503.2 $(M+H)^+$.

Compuesto 96: N–(6–((6–(3–(dimetilamino)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)difluorometil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



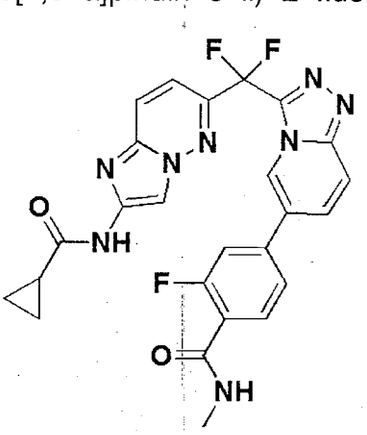
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 3–(dimetilamino)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.84 (d, *J*=6.06 Hz, 4 H) 1.96 (quin, *J*=6.13 Hz, 1 H) 2.96 (s, 6 H) 6.85 (d, *J*=8.34 Hz, 1 H) 6.94 (br. s., 1 H) 6.98 (d, *J*=7.33 Hz, 1 H) 7.33 (t, *J*=7.83 Hz, 1 H) 7.68 – 7.74 (m, 1 H) 7.93 – 7.99 (m, 1 H) 8.09 (d, *J*=9.60 Hz, 1 H) 8.25 (s, 1 H) 8.28 (d, *J*=9.60 Hz, 1 H) 8.65 (s, 1 H) 11.32 – 11.40 (m, 1 H). ESI–MS:m/z 489.2 $(M+H)^+$.

Compuesto 97: N–(6–(difluoro(6–(3–fluoro–5–metilfenil)–[1,2,4]triazolo[4,3–a]piridin–3–il)metil)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 3–fluoro–5–metilfenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, J = 6.06 Hz, 4 H) 1.95 (q, 1 H) 2.41 (s, 3 H) 7.15 (d, J = 9.60 Hz, 1 H) 7.42 – 7.50 (m, 2 H) 7.72 (d, J = 9.35 Hz, 1 H) 7.98 (dd, J = 9.73, 1.39 Hz, 1 H) 8.12 (d, J = 9.60 Hz, 1 H) 8.24 (s, 1 H) 8.28 (d, J = 9.60 Hz, 1 H) 8.80 (s, 1 H) 11.36 (s, 1 H). ESI–MS: m/z 478.2 $(M+H)^+$.

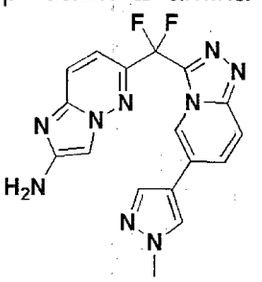
Compuesto 98: 4–(3–((2–(ciclopropancarboxamido)imidazo[1,2–b]piridazin–6–il)difluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il)–2–fluoro–N–metilbenzamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **45** usando ácido 3–fluoro–4–(metilcarbamoil)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 0.83 (d, J = 5.81 Hz, 4 H) 1.90 – 2.00 (m, 1 H) 2.80 (d, J = 4.55

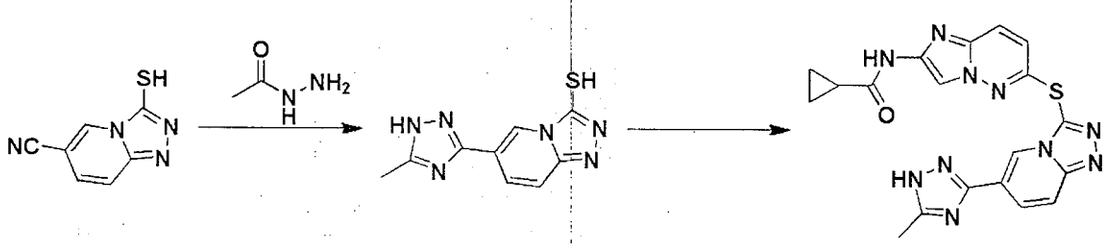
Hz, 3 H) 7.68 – 7.78 (m, 2 H) 7.81 (d, *J* = 11.87 Hz, 1 H) 8.00 – 8.07 (m, 1 H) 8.11 – 8.18 (m, 1 H) 8.22 (s, 1 H) 8.28 (d, *J* = 9.35 Hz, 1 H) 8.33 (d, *J* = 4.55 Hz, 1 H) 8.88 (s, 1 H) 11.35 (s, 1 H). ESI–MS: m/z 521.2 $(M+H)^+$.

Compuesto 99: 6–(difluoro(6–(1–metil–1*H*–pirazol–4–il)–[1,2,4]triazolo[4,3–*a*]piridin–3–il)metil)imidazo[1,2–*b*]piridazin–2–amina



Una solución de **45** (100 mg) en HCl 3N:50% MeOH:agua se calentó a 50 °C durante 3 horas . La reacción se concentró y purificó por LCMS preparativa para proporcionar el compuesto del título, 6–(difluoro(6–(1–metil–1*H*–pirazol–4–il)–[1,2,4]triazolo[4,3–*a*]piridin–3–il)metil)imidazo[1,2–*b*]piridazin–2–amina (30 mg) en forma de sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 3.89 (s, 3 H) 7.46 (br. s., 1 H) 7.51 – 7.58 (m, 1 H) 7.90 (dd, *J*=9.47, 1.39 Hz, 1 H) 7.93 – 7.99 (m, 1 H) 8.04 (d, *J*=9.60 Hz, 1 H) 8.08 (s, 1 H) 8.39 – 8.43 (m, 2 H) 8.67 (s, 1 H). ESI–MS:m/z 382.2 $(M+H)^+$.

Compuesto 100: N–(6–(6–(5–metil–1H–1,2,4–triazol–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



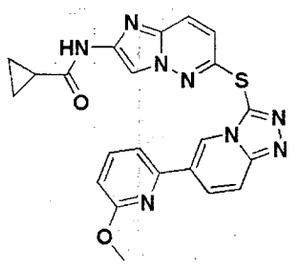
6–(5–metil–1H–1,2,4–triazol–3–il)–[1,2,4]triazolo[4,3–a]piridin-3–tiol: Una mezcla de 3–mercapto–[1,2,4]triazolo[4,3–a]piridin-6–carbonitrilo (**38A**, 450 mg, 2.56 mmol), acetohidrazida (400mg, 5.4 mmol), y 2–metilpropan–2–olato de sodio (200 mg, 2.08 mmol) en propan–2–ol (2.5 ml) se calentó a 180°C en condiciones de microondas durante 2 horas. El producto se purificó por LCMS preparativa para proporcionar el compuesto del título, 6–(5–metil–1H–1,2,4–triazol–3–il)–

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[1,2,4]triazolo[4,3–a]piridin-3–tiol.

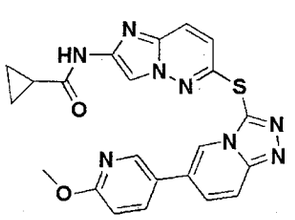
N–(6–(6–(5–metil–1H–1,2,4–triazol–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto 4 usando 6–(5–metil–1H–1,2,4–triazol–3–il)–[1,2,4]triazolo[4,3–a]piridin-3–tiol. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (DMSO–d_6, 400MHz): δ = 11.26 (s, 1 H), 9.25 (s, 1 H), 8.19 – 8.29 (m, 2 H), 8.00 (d, J = 9.6 Hz, 1 H), 7.85 – 7.93 (m, 1 H), 7.40 (d, J = 9.3 Hz, 1 H), 2.43 (s, 3 H), 1.96 (br. s., 1 H), 0.75 – 0.93 ppm (m, 5 H). ESI–MS: m/z 433.1 $(M+H)^+$.

Compuesto 101: N–(6–(6–(6–metoxipiridin–2–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



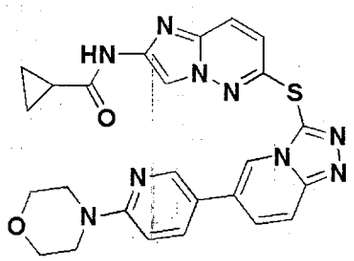
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **5** usando ácido 6–metoxipiridin–2–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (METANOL–d_4, 400MHz): δ = 9.09 (s, 1 H), 8.35 (d, *J*=9.9 Hz, 1 H), 7.95 – 8.04 (m, 2 H), 7.84 (d, *J*=9.3 Hz, 1 H), 7.71 – 7.78 (m, 1 H), 7.55 (d, *J*=7.3 Hz, 1 H), 7.23 (d, *J*=9.1 Hz, 1 H), 6.79 (d, *J*=8.3 Hz, 1 H), 3.85 (s, 3 H), 1.84 (m, 1 H), 0.82 – 0.96 ppm (m, 4 H). ESI–MS:m/z 459.2 $(M+H)^+$.

Compuesto 102: N–(6–(6–(6–metoxipiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



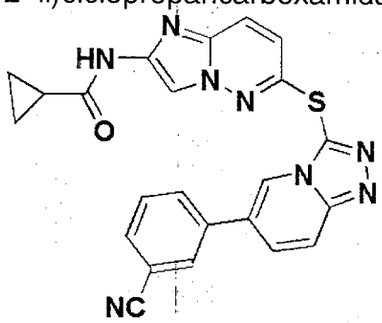
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **5** usando ácido 6–metoxipiridin–3–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (METANOL–d_4, 400MHz): δ = 8.71 (br. s., 1 H), 8.40 (br. s., 1 H), 7.86 – 8.16 (m, 4 H), 7.80 (br. s., 1 H), 7.20 (br. s., 1 H), 6.87 (d, *J*=8.8 Hz, 1 H), 3.92 (s, 3 H), 1.85 (br. s., 1 H), 0.73 – 1.02 ppm (m, 4 H). ESI–MS:m/z 459.2 $(M+H)^+$.

Compuesto 103: N–(6–(6–(6–morfolinopiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **5** usando 4–(5–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)piridin–2–il)morfolina. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA.

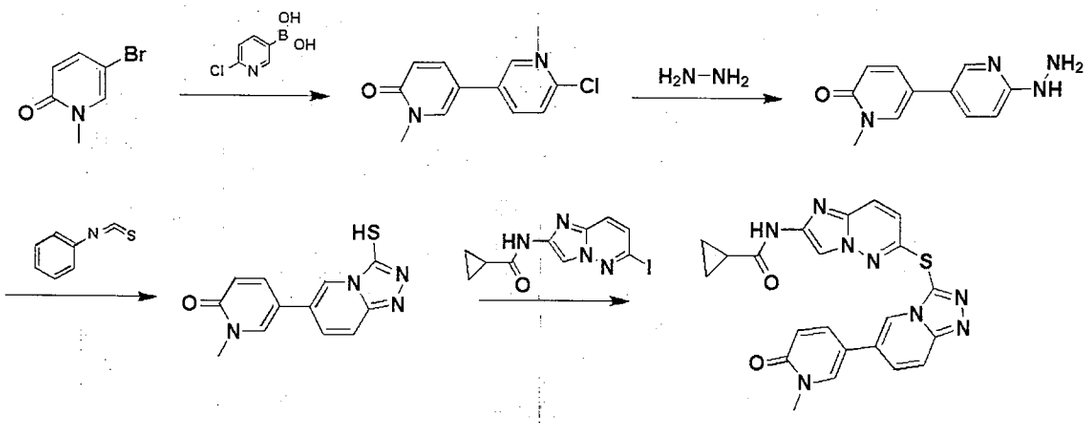
Compuesto 104: N–(6–(6–(3–cianofenil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **5** usando ácido 3–cianofenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (METANOL–d_4, 400MHz): δ = 8.72 (s, 1

H), 8.34 (d, *J* = 2.3 Hz, 1 H), 8.12 (dd, *J* = 9.2, 2.4 Hz, 1 H), 8.04 (d, *J* = 9.6 Hz, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.82 (s, 2 H), 7.16 – 7.27 (m, 2 H), 3.80 – 3.89 (m, 4 H), 3.61 – 3.69 (m, 4 H), 1.85 (br. s., 1 H), 0.95 (m, 2 H), 0.80 – 0.92 ppm (m, 2 H). ESI–MS:m/z 514.2 $(M+H)^+$.

Compuesto 105: N–(6–(6–(1–metil–6–oxo–1,6–dihidropiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



5–(6–Cloropiridin–3–il)–1–metilpiridin–2(1H)–ona: Una mezcla de 5–bromo–1–metilpiridin–2(1H)–ona (2.2 g, 11.7 mmol), 6–cloropiridin–3–ilborónico (1.57 g, 9.98 mmol), Na_2CO_3 (2.2 g, 20.76 mmol), y tetrakis(trifenilfosfina)paladio (0) (500 mg, 0.05 mmol) en dioxano:agua (15:1, 20 ml) se desgasificó y calentó a 110°C en un microondas durante 1 hora. La reacción se diluyó con EtOAc y se lavó con agua. La fase orgánica se secó con Na_2SO_4, filtró, y concentró a sequedad. El residuo resultante se purificó por cromatografía en gel de sílice (AcOEt–Hexanos) para proporcionar el compuesto del título, 5–(6–Cloropiridin–3–il)–1–metilpiridin–2(1H)–ona (1.6 g, 73% de rendimiento).

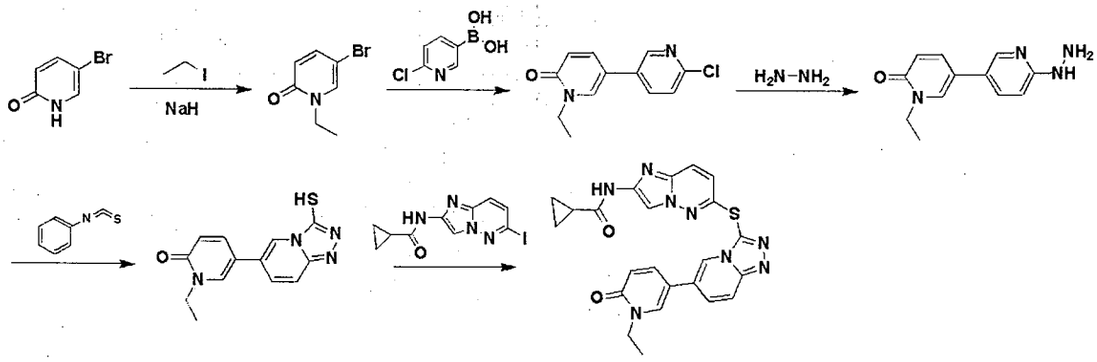
5–(6–hidrazinilpiridin–3–il)–1–metilpiridin–2(1H)–ona: Una mezcla de 5–(6–cloropiridin–3–il)–1–metilpiridin–2(1H)–ona (1.2 g, 5.44 mmol) y hidrazina (870 mg, 2.2 mmol) en 2–propanol (5 ml) se calentó en un microondas a 140 °C durante 5 horas . La mezcla de reacción se co–evaporó con MeOH (3x) y luego se suspendió en agua (50 ml). El producto sólido se recolectó por filtración y se secó bajo alto vacío durante 24 horas para proporcionar el compuesto del título, 5–(6–hidrazinilpiridin–3–il)–1–metilpiridin–2(1H)–ona (600 mg, 51% de rendimiento).

5–(3–mercapto–[1,2,4]triazolo[4,3–a]piridin–6–il)–1–metilpiridin–2(1H)–ona:

Una mezcla de 5–(6–hidrazinilpiridin–3–il)–1–metilpiridin–2(1H)–ona (600 mg, 2.78 mmol) y isotiocianatobenceno (450 mg, 3.33 mmol) en NMP–1,3–diclorobenceno (1:1, 10 ml) se calentó en un microondas a 160 °C durante 1 hora y luego se purificó por LCMS preparativa para proporcionar el compuesto del título, 5–(3–mercapto–[1,2,4]triazolo[4,3–a]piridin–6–il)–1–metilpiridin–2(1H)–ona (310 mg, 43% de rendimiento).

N–(6–(6–(1–metil–6–oxo–1,6–dihidropiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: El compuesto del título se preparó a partir de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida y 5–(3–mercapto–[1,2,4]triazolo[4,3–a]piridin–6–il)–1–metilpiridin–2(1H)–ona siguiendo el procedimiento para la síntesis del compuesto 4. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. El producto luego se disolvió en MeOH, se trató con HCl 4M en dioxano y se concentró a sequedad para proporcionar la sal de HCl del compuesto del título. ^{1}H NMR (METANOL–d_4, 400MHz): δ = 8.83 (s, 1 H), 8.18 (d, J=9.9 Hz, 2 H), 8.11 (d, J=9.6 Hz, 1 H), 7.98 (d, J=9.3 Hz, 1 H), 7.77 – 7.92 (m, 2 H), 7.55 (d, J=9.1 Hz, 1 H), 6.58 (d, J=9.3 Hz, 1 H), 3.52 – 3.59 (m, 3 H), 1.73 (br. s., 1 H), 0.80 – 0.90 ppm (m, 4 H). ESI–MS:m/z 459.2 $(M+H)^+$.

Compuesto 106: N–(6–(6–(1–etil–6–oxo–1,6–dihidropiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



5–bromo–1–etilpiridin–2(1H)–ona: Una solución de 5–bromopiridin–2–ol (1.74 g, 10.00 mmol) en DMF (20ml) se trató con NaH a temperatura ambiente y luego se agitó durante 30 min. Se añadió yodoetano (0.823 ml, 12.00 mmol) a la mezcla y la reacción se agitó toda la noche a temperatura ambiente. La reacción se diluyó

con DCM, se lavó con agua, se secó con Na_2SO_4,y se concentró a sequedad por evaporación giratoria para proporcionar el compuesto del título en forma de producto bruto que se uso sin purificación posterior.

5–(6–cloropiridin–3–il)–1–etilpiridin–2(1H)–ona: Una mezcla de 5–bromo–1–etilpiridin–2(1H)–ona (1.9 g, 9.45 mmol), ácido 6–cloropiridin–3–ilborónico (1.8 g, 11.46 mmol), Cs_2CO_3 (9.9 g, 30.37 mmol) y tetrakis(trifenilfosfina)paladio (0) (543 mg, 0.55 mmol) se suspendieron en dioxano:agua (15:1, 20 ml). Después de desgasificar, la mezcla se calentó en un microondas a 140 °C durante 30 min. La reacción luego se diluyó con EtOAc y se lavó con agua. La fase orgánica se secó con Na_2SO_4, se filtró y se concentró a sequedad por evaporación giratoria. El residuo resultante se purificó por LCMS para proporcionar el compuesto del título, 5–(6–cloropiridin–3–il)–1–etilpiridin–2(1H)–ona (1.2 g, 51% de rendimiento).

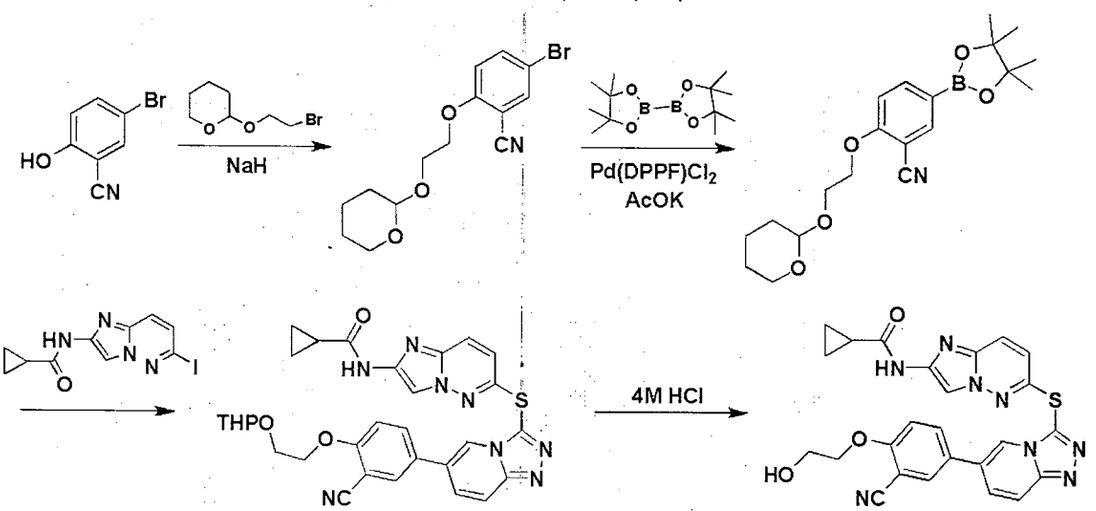
5–(6–hidrazinilpiridin–3–il)–1–etilpiridin–2(1H)–ona: Una mezcla de 5–(6–cloropiridin–3–il)–1–etilpiridin–2(1H)–ona (1.2g, 5.44 mmol) e hidrazina (820 mg, 25.62 mmol) en 2–propanol (5 ml) se calentó en un microondas a 140 °C durante 4 horas. La mezcla se coevaporó con MeOH (3x) y luego se suspendió en agua (50 ml). El sólido resultante se recolectó por filtración y se secó bajo alto vacío durante un día para dar el compuesto del título bruto, 5–(6–hidrazinilpiridin–3–il)–1–etilpiridin–2(1H)–ona (1.2 g, 95.9% de rendimiento).

5–(3–mercapto–[1,2,4]triazolo[4,3–a]piridin–6–il)–1–etilpiridin–2(1H)–ona: Una mezcla de 5–(6–hidrazinilpiridin–3–il)–1–etilpiridin–2(1H)–ona (1.2 g, 5.22 mmol) e isotiocianatobenceno (775 mg, 5.74 mmol) en NMP (3 ml) y DCM (10 ml) se agitó a temperatura ambiente durante 30 min. El DCM se eliminó por evaporación giratoria y la reacción se diluyó con 1,3–diclorobenceno (7ml). La mezcla luego se calentó en un microondas a 160 °C durante 1 hora. Se añadió éter (10 ml) a la reacción y el sólido resultante se recolectó por filtración y se lavó con éter para proporcionar el compuesto del título, **5–(**3–mercapto–[1,2,4]triazolo[4,3–a]piridin–6–il)–1–etilpiridin–2(1H)–ona (600 mg, 42.3% de rendimiento).

N–(6–(6–(1–etil–6–oxo–1,6–dihidropiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: El compuesto del título se preparó a partir de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida y 5–(3–mercapto–[1,2,4]triazolo[4,3–a]piridin–6–il)–1–

etilpiridin–2(1H)–ona siguiendo el procedimiento de la síntesis del compuesto 4. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. El producto luego se disolvió en MeOH, se trató con HCl 4 M en dioxano, y se concentró a sequedad para proporcionar la sal de HCl del compuesto del título. ^{1}H NMR (DMSO–d_6, 400MHz): δ = 11.15 (s, 1 H), 8.66 – 8.72 (m, 1 H), 8.24 (d, J=2.5 Hz, 1 H), 8.08 (dd, J=9.6, 1.0 Hz, 1 H), 7.93 (s, 2 H), 7.90 – 7.92 (m, 1 H), 7.87 (dd, J=9.5, 2.9 Hz, 1 H), 7.06 (d, J=9.3 Hz, 2 H), 6.47 (d, J=9.3 Hz, 1 H), 3.96 (q, J=7.1 Hz, 2 H), 1.92 (t, J=6.1 Hz, 1 H), 1.24 (t, J=7.2 Hz, 3 H), 0.75 – 0.82 ppm (m, 4 H). ESI–MS:m/z 473.2 $(M+H)^+$.

Compuesto 107: N–(6–(6–(3–ciano–4–(2–hidroxietoxi)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



5–bromo–2–(2–(tetrahidro–2H–piran–2–iloxi)etoxi)benzonitrilo: Una solución de 5–bromo–2–hidroxibenzonitrilo (1g, 5.05 mmol) en DMF se trató con 95% NaH (242 mg, 9.6 mmol) durante 20 min a temperatura ambiente. Luego se añadió 2–(2–Bromoetoxi)tetrahidro–2H–pirano (0.839 ml, 5.56 mmol) a la reacción y la mezcla se agitó a temperatura ambiente durante 5 horas. La reacción luego se diluyó con DCM y se lavó con agua. La fase orgánica se secó con Na_2SO_4, filtró y se concentró a sequedad para proporcionar el compuesto del título bruto, 5–bromo–2–(2–(tetrahidro–2H–piran–2–iloxi)etoxi)benzonitrilo (1.6 g, 9.75% de rendimiento) que se uso sin purificación posterior.

2–(2–(tetrahidro–2H–piran–2–iloxi)etoxi)–5–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)benzonitrilo: Una mezcla de 5–bromo–2–(2–(tetrahidro–2H–

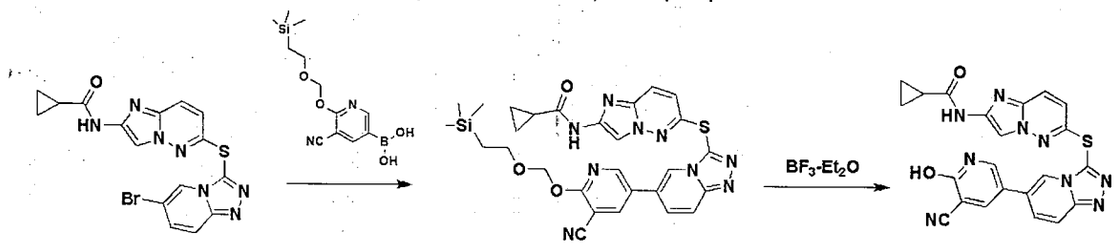
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piran–2–iloxi)etoxi)benzonitrilo (1.6 g, 4.92 mmol), 4,4,4',4',5,5,5',5'–octametil–2,2'–bi(1,3,2–dioxaborolano) (1.9 g, 7.48 mmol), AcOK (1.47 g, 15 mmol) y Pd(DPPF)Cl_2 (366 mg, 0.5 mmol) en dioxano (50 ml) se calentó a 110 °C durante 60 min. La reacción se evaporó a sequedad por evaporación giratoria y el residuo resultante se purificó por cromatografía en gel de sílice (DCM–hxano) para proporcionar el compuesto del título, 2–(2–(tetrahidro–2H–piran–2–iloxi)etoxi)–5–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)benzonitrilo (1.7 g, 92.6% de rendimiento).

N–(6–(6–(3–ciano–4–(3–(tetrahidro–2H–piran–2–iloxi)propil)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: El compuesto del título se preparó a partir del compuesto 4 y 2–(2–(tetrahidro–2H–piran–2–iloxi)etoxi)–5–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)benzonitrilo siguiendo el procedimiento para la síntesis de compuesto 5. La mezcla de reacción se uso sin purificación posterior.

N–(6–(6–(3–ciano–4–(2–hidroxietoxi)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: En forma de mezcla de reacción bruta, N–(6–(6–(3–ciano–4–(3–(tetrahidro–2H–piran–2–iloxi)propil)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida se trató con [HCl]:dioxano (1:5) at 70 °C durante 30 min. La reacción se concentró y purificó por LCMS para proporcionar el compuesto del título en forma de sal de TFA. El producto luego se disolvió en MeOH, se trató con HCl 4 M en dioxano, y se concentró a sequedad para proporcionar la sal de HCl del compuesto del título. ^{1}H NMR (METANOL–d_4, 400MHz): δ = 9.00 (br. s., 1 H), 8.36 (br. s., 1 H), 8.24 (br. s., 1 H), 8.08 (br. s., 2 H), 8.01 (br. s., 1 H), 7.94 (br. s., 1 H), 7.66 – 7.74 (m, 1 H), 7.36 (br. s., 1 H), 4.27 (br. s., 2 H), 3.95 (br. s., 2 H), 1.83 (br. s., 1 H), 0.84 – 1.04 ppm (m, 4 H). ESI–MS:m/z 513.4 $(M+H)^+$.

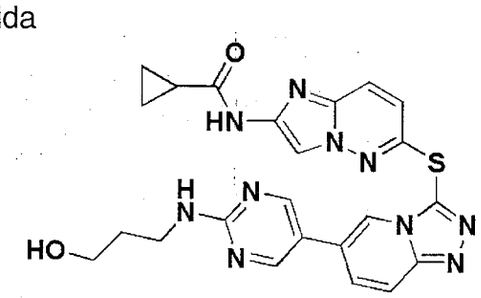
Compuesto 108: N–(6–(6–(5–ciano–6–hidroxipiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



N–(6–(6–(5–ciano–6–((2–(trimetilsilil)etoxi)metoxi)piridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto 5 usando 5–ciano–6–((2–(trimetilsilil)etoxi)metoxi)piridin–3–ilborónico. La reacción bruta se uso en el paso próximo sin purificación posterior.

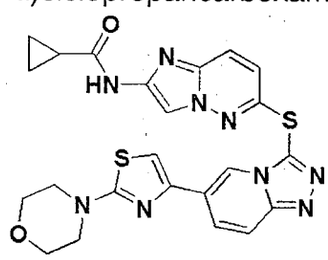
N–(6–(6–(5–ciano–6–hidroxipiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: en forma de mezcla de reacción bruta N–(6–(6–(5–ciano–6–((2–(trimetilsilil)etoxi)metoxi)piridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida se sometió a reflujo en TFA:DCM (1:1, 5 ml) durante 30 min. La reacción luego se concentró y se purificó por LCMS preparativa para proporcionar el compuesto del título, N–(6–(6–(5–ciano–6–hidroxipiridin–3–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida en forma de sal de TFA. El producto luego se disolvió en MeOH, se trató con HCl 4 M en dioxano, y se concentró a sequedad para proporcionar la sal de HCl del compuesto del título. ^{1}H NMR (METANOL–d_4, 400MHz): δ = 8.80 (br. s., 1 H), 8.51 (d, J=2.5 Hz, 1 H), 8.13 (d, J=2.8 Hz, 1 H), 8.04 (d, J=9.6 Hz, 1 H), 7.79 – 7.96 (m, 3 H), 7.27 (d, J=7.8 Hz, 1 H), 1.83 (br. s., 1 H), 0.91 ppm (d, J=16.7 Hz, 4 H). ESI–MS:m/z 513.4 $(M+H)^+$.

Compuesto 109: N–(6–(6–(2–(3–hidroxipropilamino)pirimidin–5–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



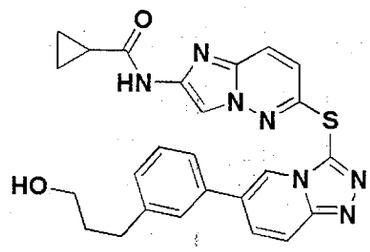
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **5** usando 2–(3–hidroxipropilamino)pirimidin–5–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (ACETONITRILO–d_3, 400MHz): δ = 8.50 (s, 2 H), 8.44 (s, 1 H), 7.89 – 8.00 (m, 2 H), 7.67 – 7.78 (m, 2 H), 7.62 (s, 3 H), 7.01 (d, *J*=9.3 Hz, 1 H), 3.55 (t, *J*=6.1 Hz, 2 H), 3.45 (t, *J*=6.6 Hz, 2 H), 1.70 – 1.79 (m, 3 H), 0.85 ppm (d, *J*=16.2 Hz, 4 H). ESI–MS:m/z 503.3 $(M+H)^+$.

Compuesto 110: N–(6–(6–(2–morfolinotiazol–4–il)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



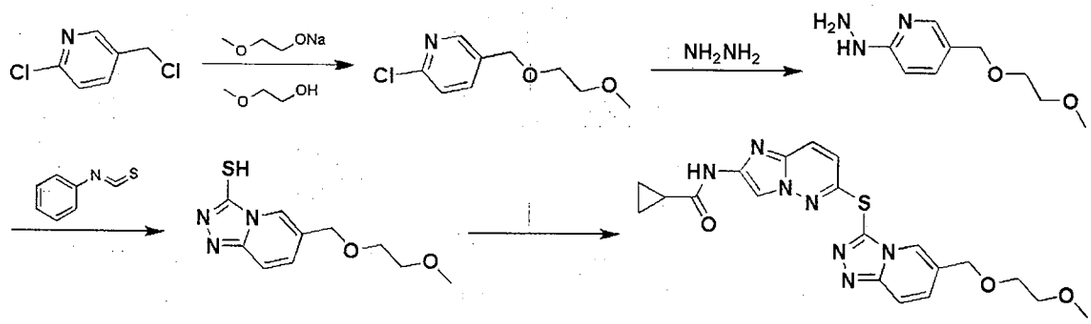
El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **5** usando ácido 2–morfolinotiazol–4–ilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (ACETONITRILO–d_3, 400MHz): δ = 8.74 (s, 1 H), 8.03 (br. s., 1 H), 7.91 – 7.97 (m, 1 H), 7.83 – 7.90 (m, 1 H), 7.71 (br. s., 1 H), 7.15 (s, 1 H), 7.03 (br. s., 1 H), 3.75 (s, 4 H), 3.39 – 3.45 (m, 4 H), 1.78 (dt, *J*=5.0, 2.4 Hz, 1 H), 0.81 – 0.92 ppm (m, 4 H). ESI–MS:m/z 520.2 $(M+H)^+$.

Compuesto 111: N–(6–(6–(3–(3–hidroxipropil)fenil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



El compuesto del título se sintetizó usando un procedimiento análogo al que se describió en la preparación del Compuesto **5** usando ácido 3–(3–hidroxipropil)fenilborónico. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. ^{1}H NMR (METANOL–d_4, 400MHz): δ = 8.54 (s, 1 H), 7.84 – 7.94 (m, 3 H), 7.72 (d, *J*=9.3 Hz, 1 H), 7.33 – 7.39 (m, 2 H), 7.25 – 7.32 (m, 1 H), 7.18 (d, *J*=7.6 Hz, 1 H), 7.10 (d, *J*=9.3 Hz, 1 H), 3.46 (t, *J*=6.3 Hz, 2 H), 2.58 – 2.67 (dd, *J*=8.0 y 7.6, 2 H), 1.67 – 1.79 (m, 3 H), 0.72 – 0.87 ppm (m, 4 H). ESI–MS:m/z 486.3 $(M+H)^+$.

Compuesto 112: N–(6–(6–((2–metoxietoxi)metil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

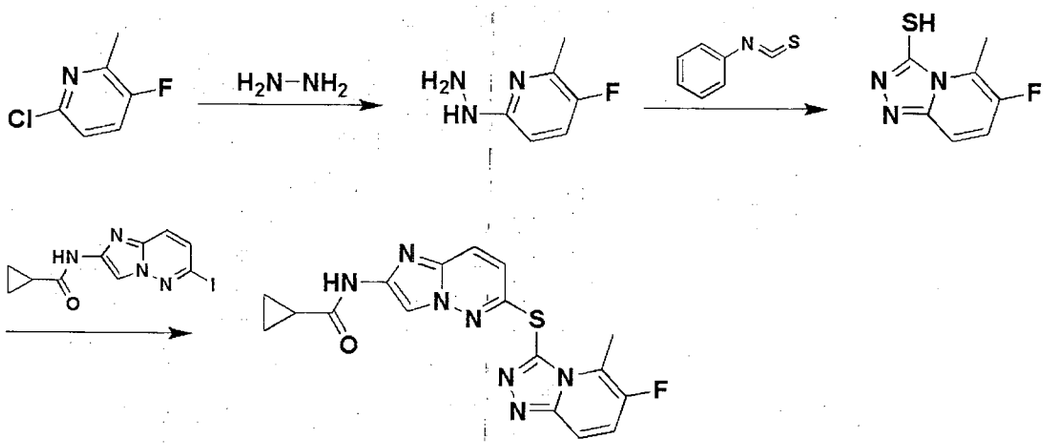


2–hidrazinil–5–((2–metoxietoxi)metil)piridina: A una solución de 2–cloro–5–(clorometil)piridina (1620 mg, 10 mmol) en 2–metoxietanol (10ml) se añadió 2–metoxietanolato de de sodio (5.9 g, 12.00 mmol). La mezcla se agitó a temperatura ambiente durante 10 min y luego a 50 °C durante 2 horas. Luego se añadió hidrazina (1.6 g, 50.0 mmol) a la mezcla y la reacción se calentó a 120 °C durante 1 hora. La mezcla se purificó por LCMS preparativa para proporcionar el compuesto del título, 2–hidrazinil–5–((2–metoxietoxi)metil)piridina (540 mg, 27.4% de rendimiento).

6–((2–metoxietoxi)metil)–[1,2,4]triazolo[4,3–a]piridin-3–tiol: El compuesto del título se preparó a partir del 2–hidrazinil–5–((2–metoxietoxi)metil)piridina e isotiocianatobenceno siguiendo el procedimiento descrito en la síntesis del compuesto **4A**.

N–(6–(6–((2–metoxietoxi)metil)–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: El compuesto del título se preparó a partir del N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida y 6–((2–metoxietoxi)metil)–[1,2,4]triazolo[4,3–a]piridin-3–tiol siguiendo el procedimiento descrito en la síntesis del Compuesto 4. ^{1}H NMR (METANOL–d_4, 400MHz): δ = 8.75 – 8.78 (m, 1 H), 8.15 (dd, *J*=9.3, 1.0 Hz, 1 H), 8.04 – 8.11 (m, 1 H), 8.02 (d, *J*=9.3 Hz, 1 H), 7.94 (s, 1 H), 7.56 (d, *J*=9.3 Hz, 1 H), 4.71 (d, *J*=1.0 Hz, 2 H), 3.61 – 3.67 (m, 2 H), 3.47 – 3.53 (m, 2 H), 3.29 (s, 3 H), 1.80 – 1.87 (m, 1 H), 0.88 – 1.01 ppm (m, 4 H). ESI–MS:m/z 440.2 $(M+H)^+$.

Compuesto 113: N–(6–(6–fluoro–5–metil–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



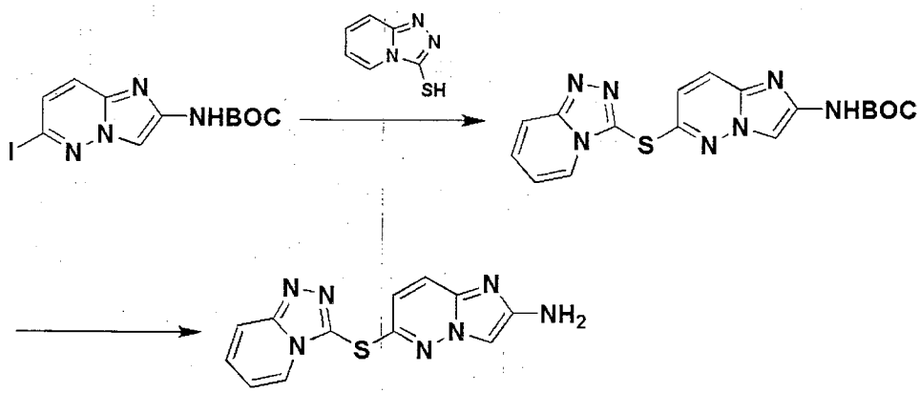
3–fluoro–6–hidrazinil–2–metilpiridina: A una mezcla de 6–cloro–3–fluoro–2–metilpiridina (4.7g, 32.3 mmol) en isopropanol (100 ml) se añadió hidrato de hidrazina (5 g, 100 mmol). Después de someter a reflujo la mezcla durante 5 horas se añadió hidrato de hidracina adicional (5 g, 100 mmol), y la reacción se sometió a reflujo durante 3 días. La mezcla luego se concentró a sequedad y se alamacenó al vacío toda la noche. Este material se uso sin purificación posterior.

6–fluoro–5–metil–[1,2,4]triazolo[4,3–a]piridin-3–tiol: El compuesto del título se preparó a partir del 3–fluoro–6–hidrazinil–2–metilpiridina e isotiocianatobenceno

siguiendo el procedimiento descrito en la síntesis del compuesto **4A**.

N–(6–(6–fluoro–5–metil–[1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida: El compuesto del título se preparó a partir del N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida y 6–fluoro–5–metil–[1,2,4]triazolo[4,3–a]piridin-3–tiol siguiendo el procedimiento descrito en la síntesis del compuesto **4**. La mezcla de reacción bruta se purificó por LCMS preparativa, y el producto se aisló en forma de sal de TFA. El producto luego se disolvió en MeOH, se trató con HCl 4 M en dioxano, y se concentró a sequedad para proporcionar la sal de HCl del compuesto del título. ^{1}H NMR (METANOL–d_4, 400MHz): δ = 8.00 (s, 1 H), 7.83 – 7.89 (m, 3 H), 7.63 (dd, *J*=9.9, 8.3 Hz, 1 H), 7.22 (d, *J*=9.6 Hz, 1 H), 2.96 (d, *J*=3.5 Hz, 4 H), 1.81 – 1.91 (m, 1 H), 0.96 (dt, *J*=4.5, 3.0 Hz, 2 H), 0.86 – 0.92 (m, 2 H). ESI–MS:m/z 384.3 $(M+H)^+$.

Compuesto 114: 6–([1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–amina



6–([1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–ilcarbamato de ter–Butilo: El compuesto del título se preparó a partir del 6–yodoimidazo[1,2–b]piridazin–2–ilcarbamato de ter–butilo y [1,2,4]triazolo[4,3–a]piridin-3–tiol siguiendo el procedimiento para la síntesis de compuesto **4.**

6–([1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–amina: Una solución de 6–([1,2,4]triazolo[4,3–a]piridin–3–iltio)imidazo[1,2–b]piridazin–2–ilcarbamato de ter-butilo (300 mg, 0.78 mmol) en dioxano (5 ml) se trató con HCl 4 M en dioxano (5ml) a 80 °C durante 1 hora. La mezcla se concentró y se purificó por LCMS para dar el compuesto del título, 6–([1,2,4]triazolo[4,3–*a*]piridin–3–iltio)imidazo[1,2–*b*]piridazin–2–amina (201 mg, 68% de rendimiento) en forma de

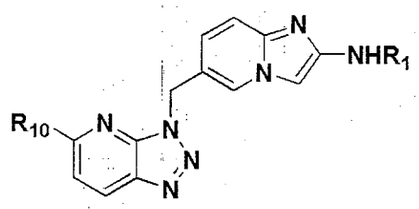
sal de TFA. ^{1}H NMR (400 MHz, DMSO–d_6) δ ppm 7.00 (d, J=9.35 Hz, 1 H) 7.16 (t, J=6.44 Hz, 1 H) 7.22 (s, 1 H) 7.54 – 7.65 (m, 1 H) 7.73 (d, J=9.35 Hz, 1 H) 8.00 (d, J=9.09 Hz, 1 H) 8.47 (d, J=6.82 Hz, 1 H). ESI–MS:m/z 284.2 $(M+H)^+$.

Procedimiento General para la Formación de Base Libre y Sal de HCl

Las formas de base de libre de los anteriores ejemplos de compuestos se pueden preparar por la purificación del material bruto por MPLC usando Hex:EtOAc (9:1 → 4:6) o DCM:MeOH (99:1 → 9:1) como eluyente. En forma específica, se prepararon las formas de base libre de los compuestos 3, 13, 45 y 49.

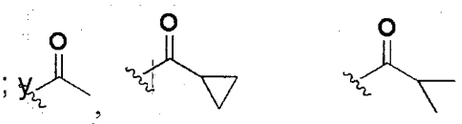
Las sales de HCl de los anteriores ejemplos de compuestos se pueden preparar por la disolución de la sal de TFA en agua, tratamiento de la solución con HCl concentrado, y liofilización a sequedad. En forma específica, se prepararon las sales de HCl de los compuestos 3, 13, 45, 49 y 112.

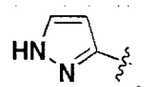
Además de lo precedente, se pueden usar los anteriores esquemas de reacción y sus variaciones para preparar los compuestos que tiene la fórmula:

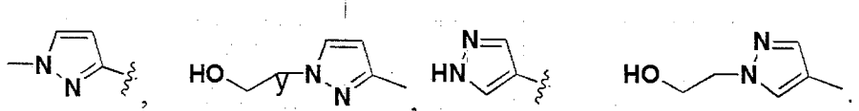


en donde

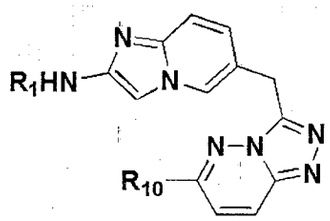
R_1 se selecciona del grupo que consiste en

hidrógeno, y  ;

R_{10} se selecciona del grupo que consiste en  ,

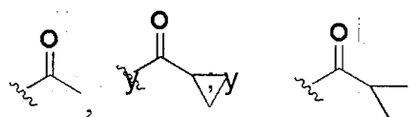


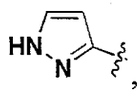
Además, los anteriores esquemas de reacción y sus variaciones se pueden usar para preparar los compuestos que tienen la fórmula:

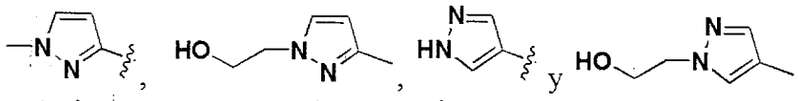


en donde

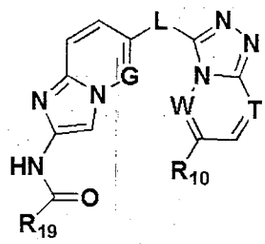
R_1 se selecciona del grupo que consiste en hidrógeno,



R_{10} se selecciona del grupo que consiste en  ,



Además, los anteriores esquemas de reacción y sus variaciones se pueden usar para preparar los compuestos que tienen la fórmula:



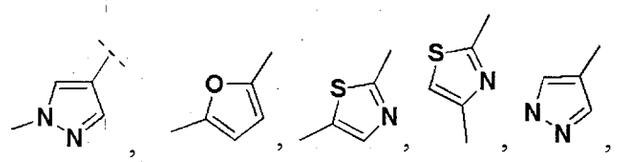
en donde

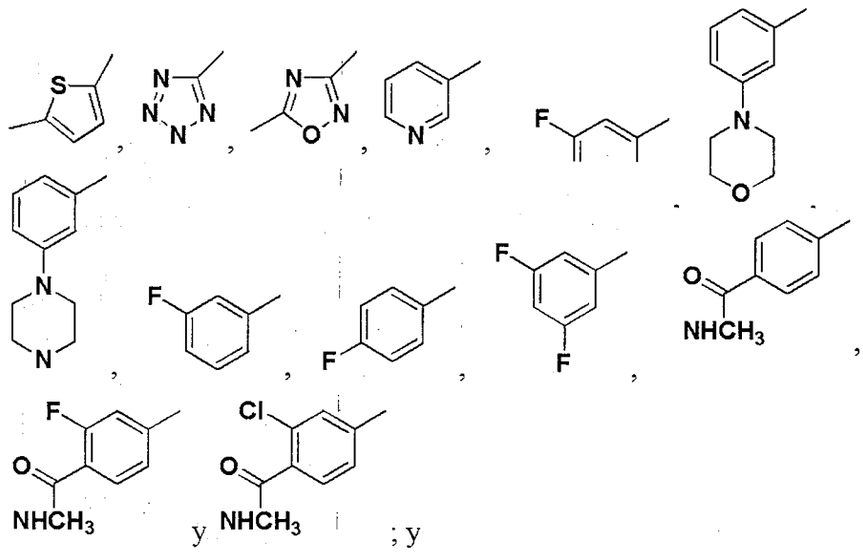
L se selecciona del grupo que consiste en S, CH_2, $CH(CH_3)$, $C(CH_3)_2$ y CF_2;

G, T y W se selecciona de modo independiente del grupo que consiste en CH y N;

R_1 se selecciona del grupo que consiste en Cl, Br, I,

CH_3, CF_3, CN,

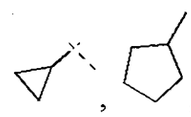


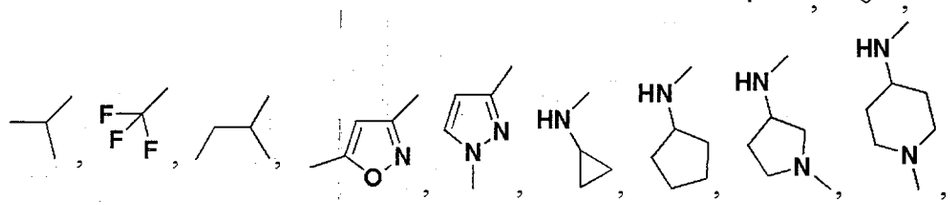


y

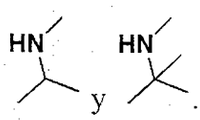
; y

R_{19} se selecciona del grupo que consiste en



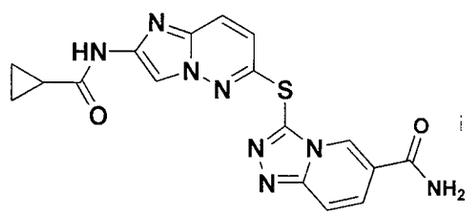
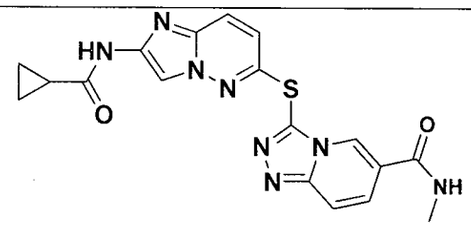
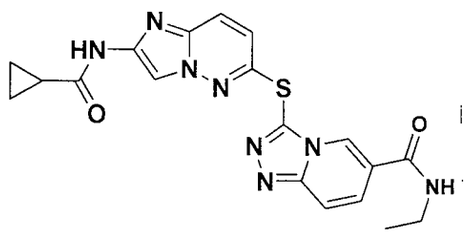
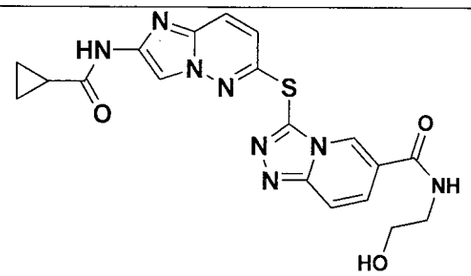
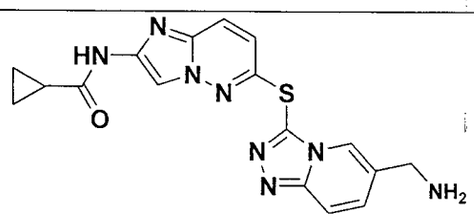
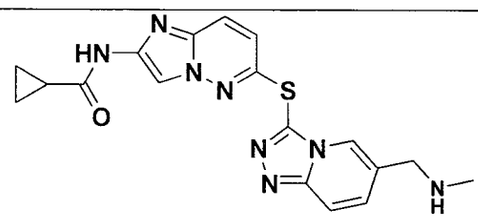


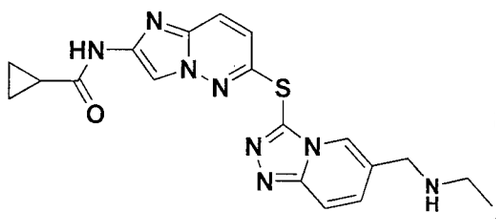
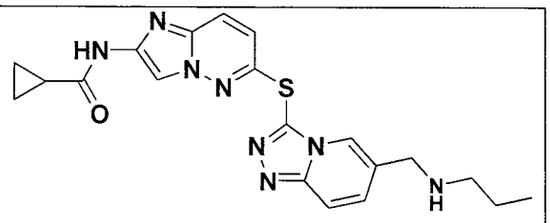
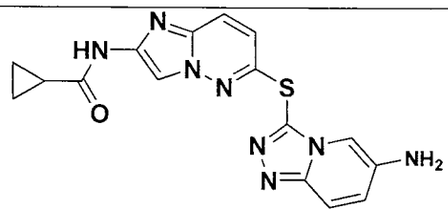
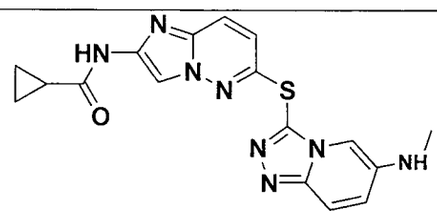
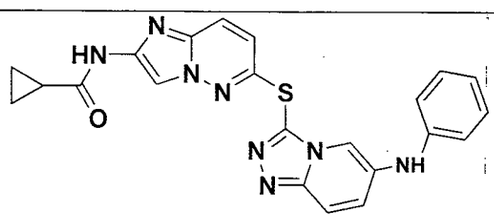
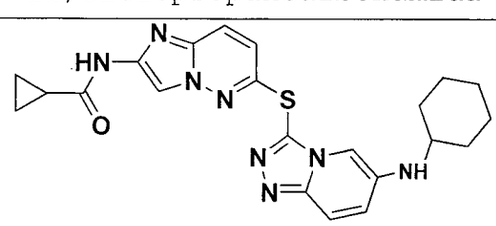
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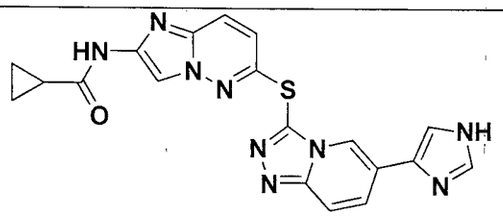
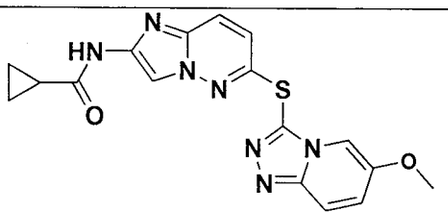
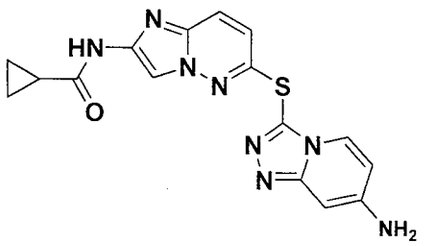
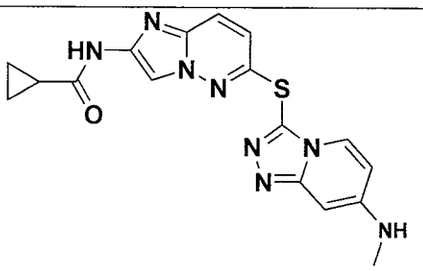
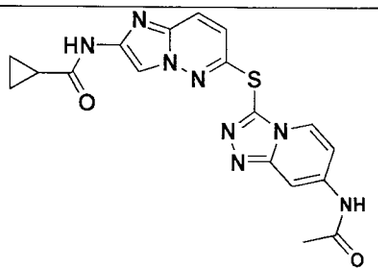
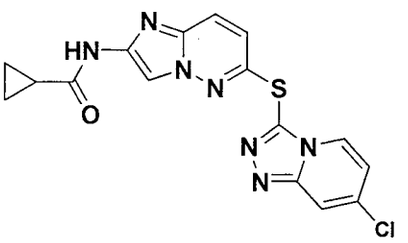


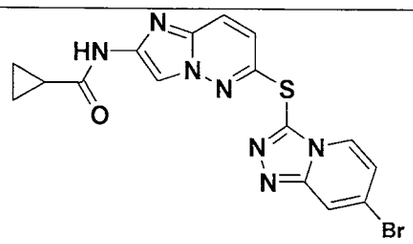
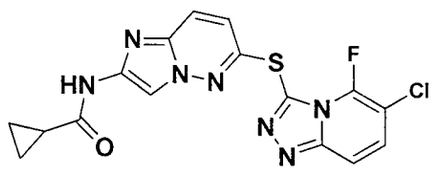
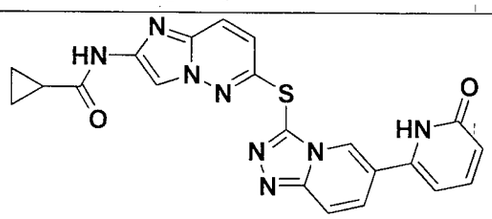
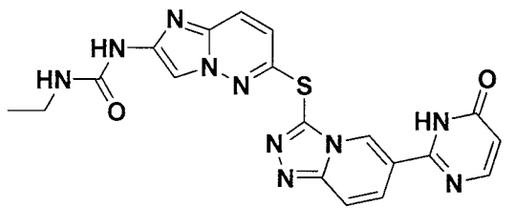
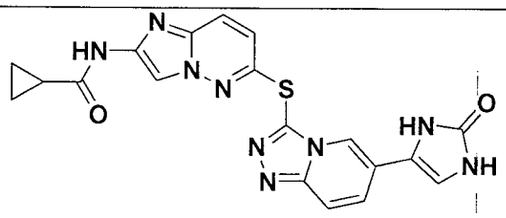
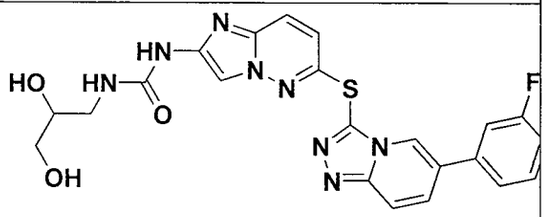
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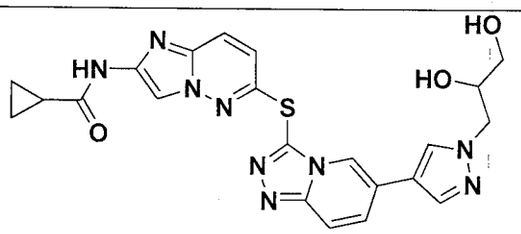
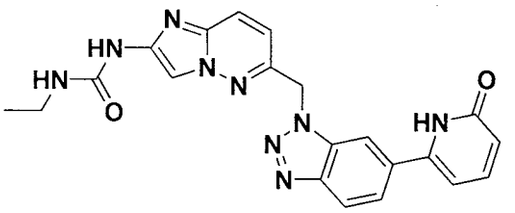
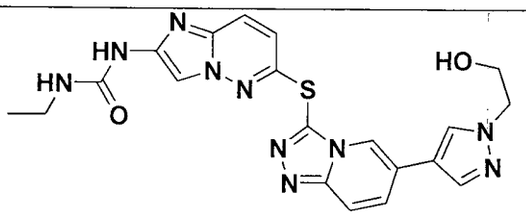
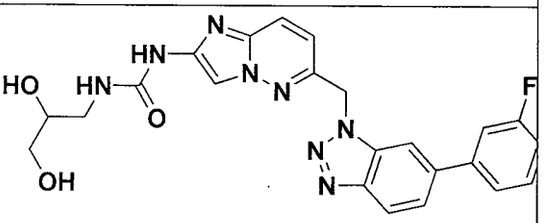
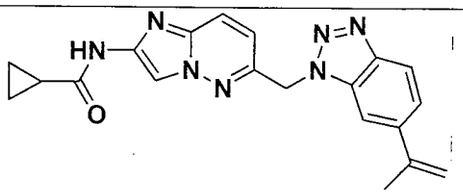
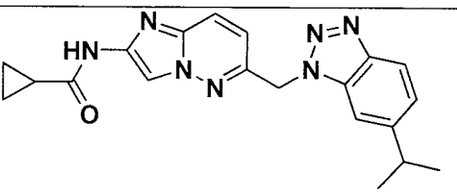
Además de lo precedente, los anteriores esquemas de reacción y sus variaciones se pueden usar para preparar los siguientes compuestos:

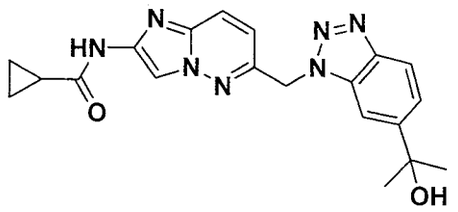
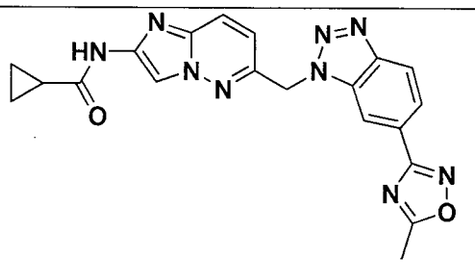
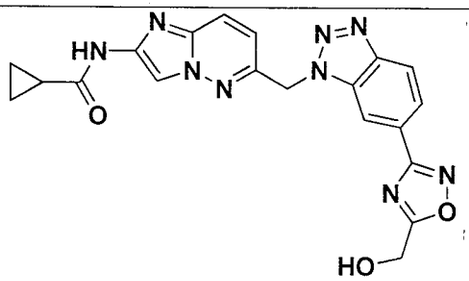
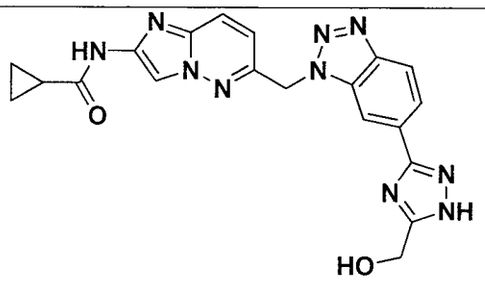
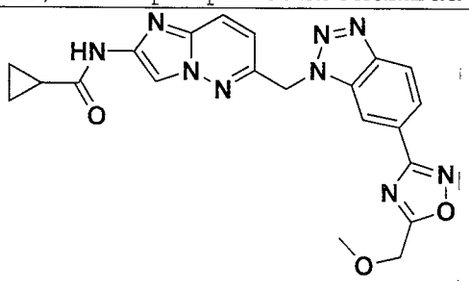
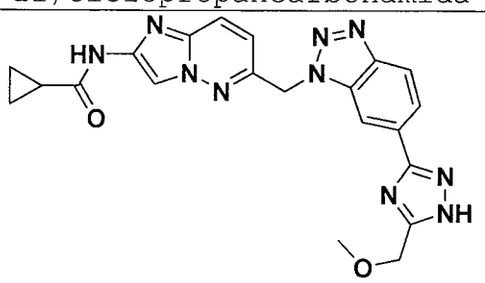
 3-(2-(ciclopropancarboxamido)imidazo[1,2-b]piridazin-6-iltio)-[1,2,4]triazolo[4,3-a]piridin-6-carboxamida	 3-(2-(ciclopropancarboxamido)imidazo[1,2-b]piridazin-6-iltio)-N-metil-[1,2,4]triazolo[4,3-a]piridin-6-carboxamida
 3-(2-(ciclopropancarboxamido)imidazo[1,2-b]piridazin-6-iltio)-N-etil-[1,2,4]triazolo[4,3-a]piridin-6-carboxamida	 3-(2-(ciclopropancarboxamido)imidazo[1,2-b]piridazin-6-iltio)-N-(2-hidroxietil)-[1,2,4]triazolo[4,3-a]piridin-6-carboxamida
 N-(6-(6-(aminometil)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-((metilamino)metil)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

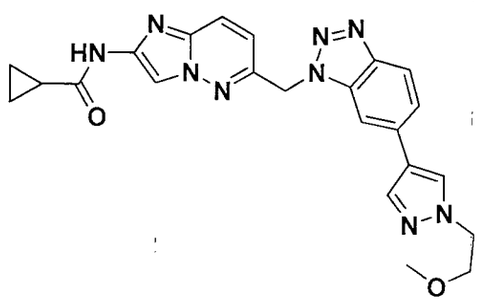
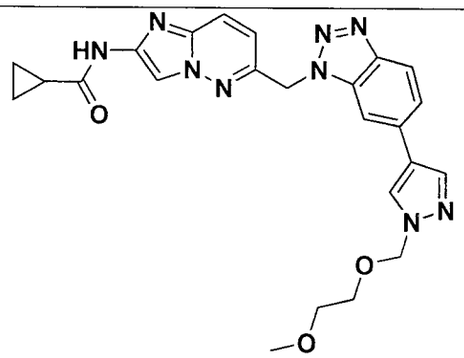
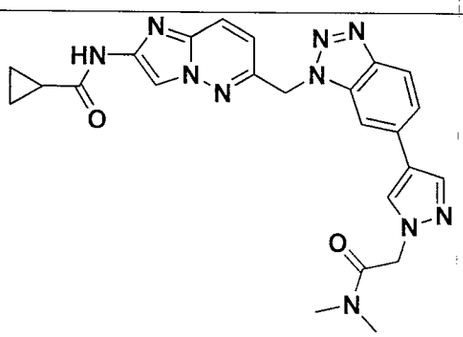
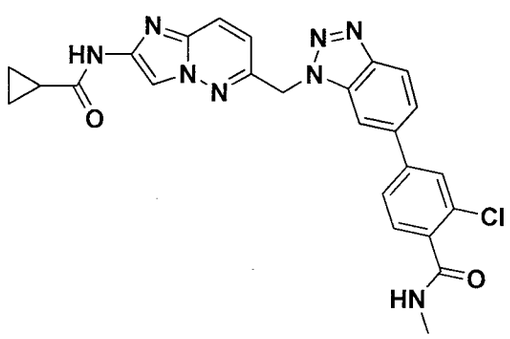
 N-(6-(6-((etilamino)metil)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-((propilamino)metil)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-amino-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(metilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(fenilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(ciclohexilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

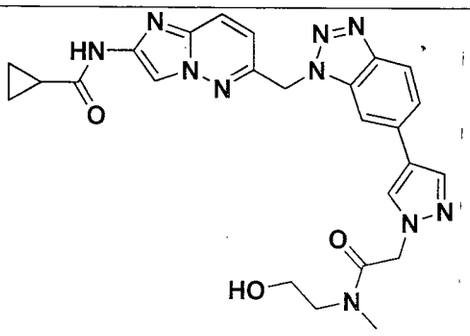
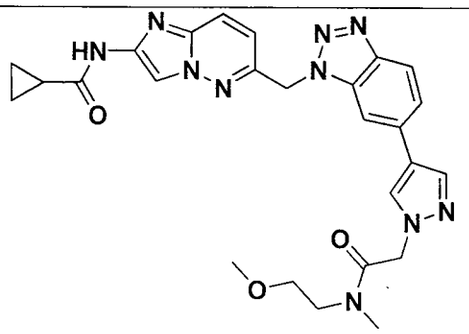
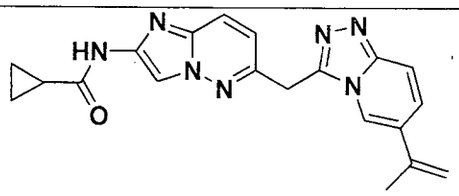
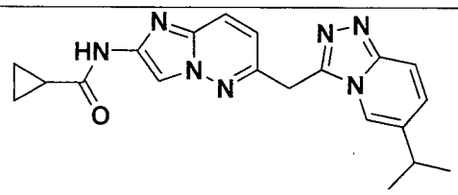
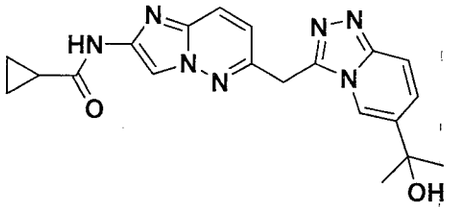
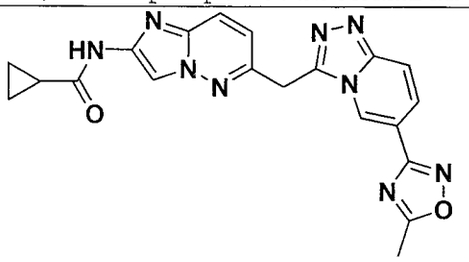
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 N-(6-(7-amino-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(7-(metilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(7-acetamido-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(7-cloro-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

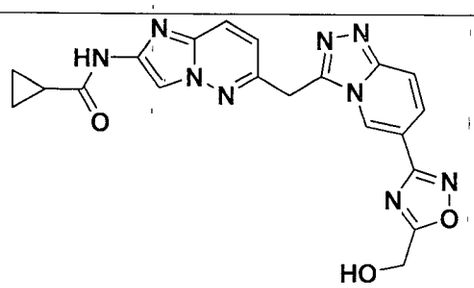
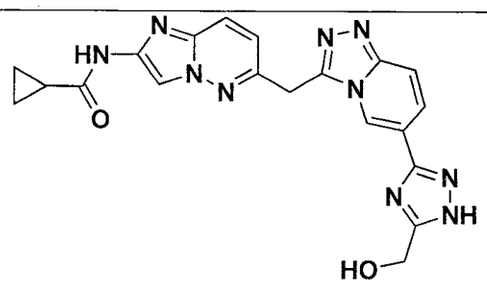
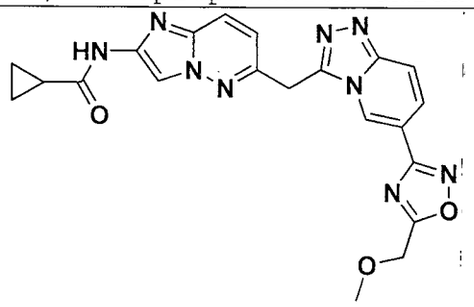
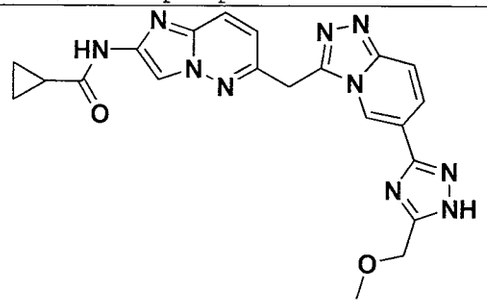
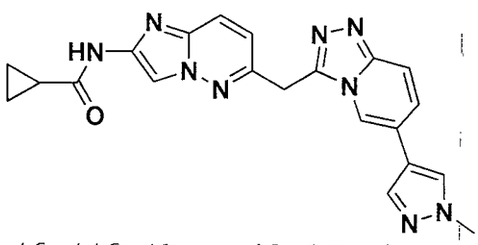
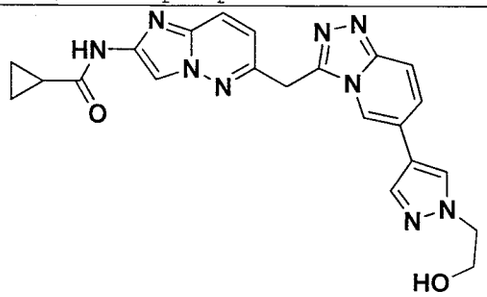
 N-(6-(7-bromo-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-cloro-5-fluoro-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 3-(2N-(6-(6-(6-oxo-1,6-dihidropiridin-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 3-(21-etil-3-(6-(6-(6-oxo-1,6-dihidropirimidin-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)urea
 3-(2N-(6-(6-(2-oxo-2,3-dihidro-1H-imidazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 1-(2,3-dihidroxipropil)-3-(6-(6-(3-fluorofenil)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)urea

 N-(6-(6-(1-(2,3-dihidroxipropil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 1-etil-3-(6-((6-(6-oxo-1,6-dihidropiridin-2-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)urea
 1-etil-3-(6-(6-(1-(2-hidroxietil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)urea	 1-(2,3-dihidroxipropil)-3-(6-((6-(3-fluorofenil)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)urea
 N-(6-((6-(prop-1-en-2-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-isopropil-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

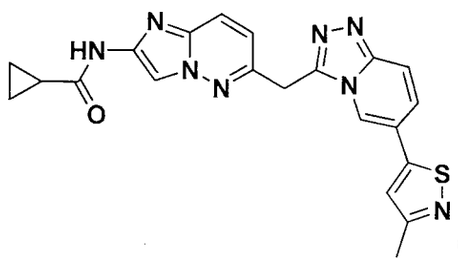
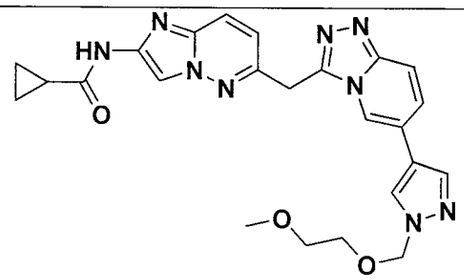
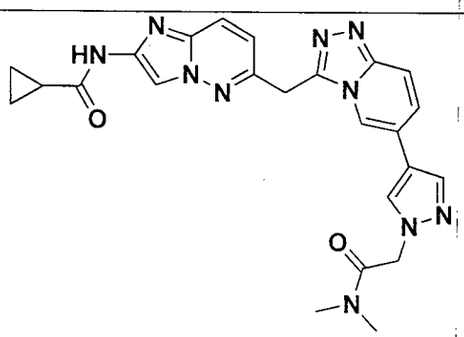
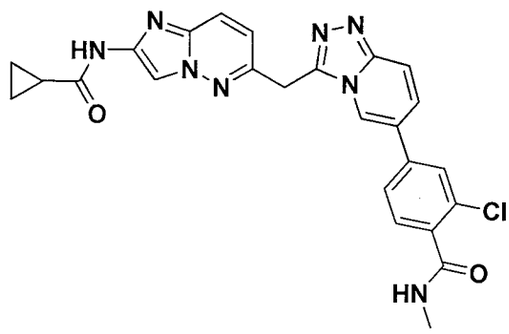
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 N-(6-((6-(5-(hidroximetil)-1,2,4-oxadiazol-3-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-(5-(hidroximetil)-1H-1,2,4-triazol-3-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-((6-(5-(metoximetil)-1,2,4-oxadiazol-3-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-(5-(metoximetil)-1H-1,2,4-triazol-3-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

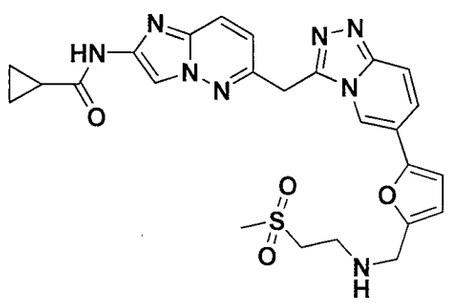
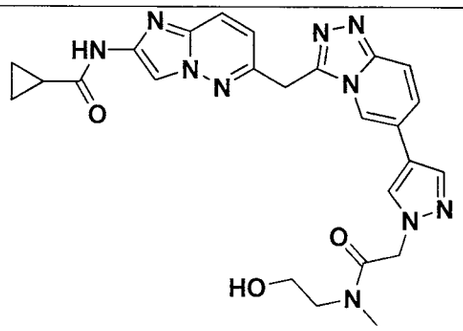
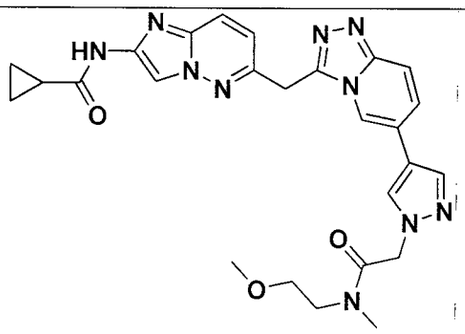
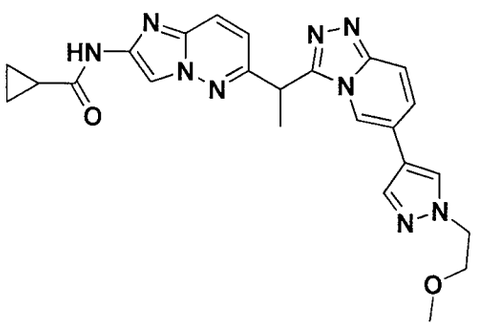
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 N-(6-((6-(1-(2-(dimetilamino)-2-oxoetil)-1H-pirazol-4-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 2-cloro-4-(1-((2-(ciclopropancarboxamido)imidazo[1,2-b]piridazin-6-il)metil)-1H-benzo[d][1,2,3]triazol-6-il)-N-metilbenzamida

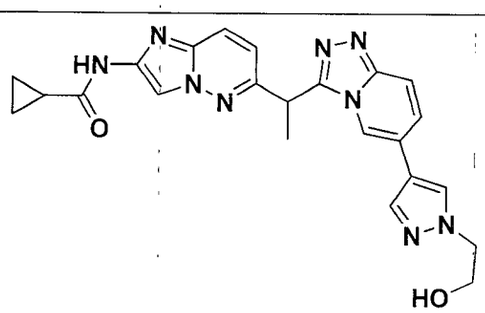
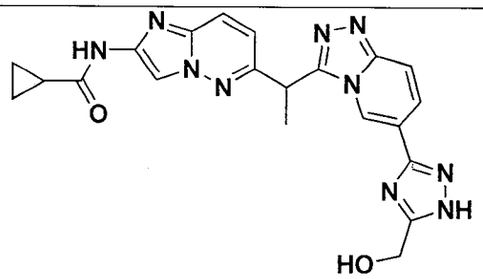
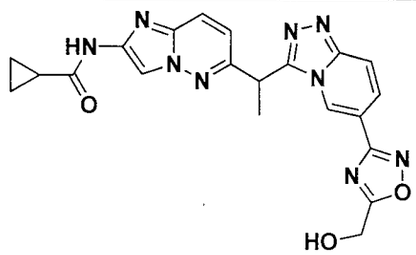
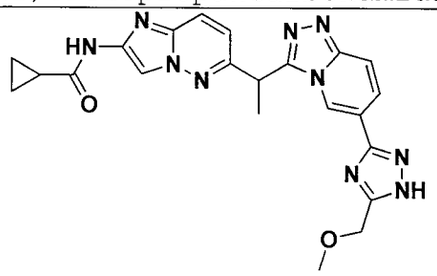
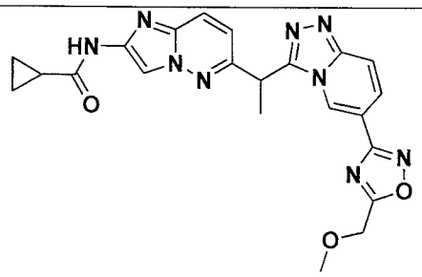
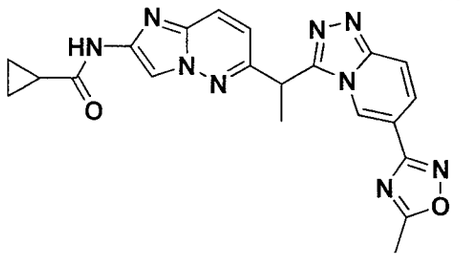
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 N-(6-((6-(prop-1-en-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-isopropil-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-((6-(2-hidroxipropan-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-(5-metil-1,2,4-oxadiazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

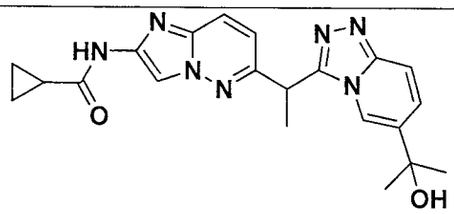
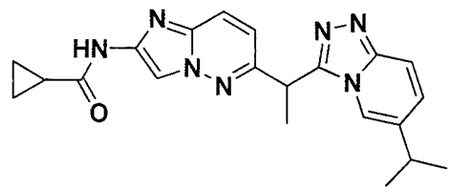
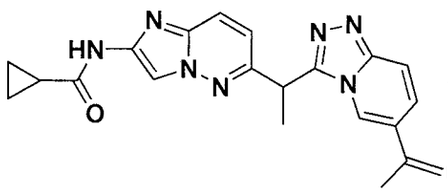
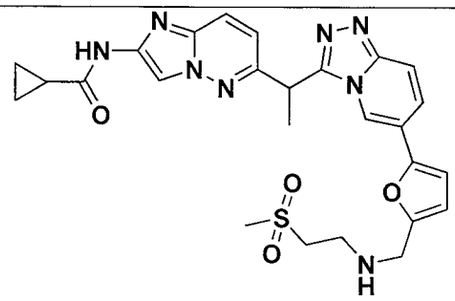
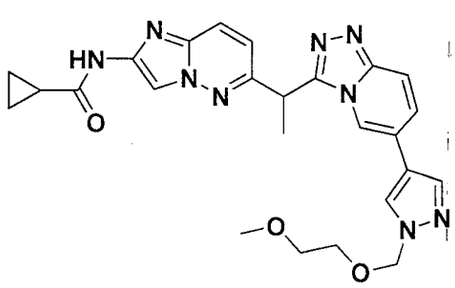
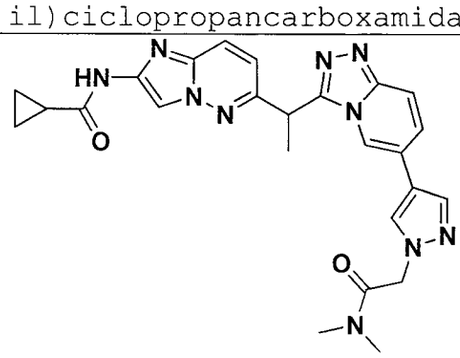
 N-(6-((6-(5-(hidroximetil)-1,2,4-oxadiazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-(5-(hidroximetil)-1H-1,2,4-triazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-((6-(5-(metoximetil)-1,2,4-oxadiazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-(5-(metoximetil)-1H-1,2,4-triazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-((6-(1-metil-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-(1-(2-hidroxietil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

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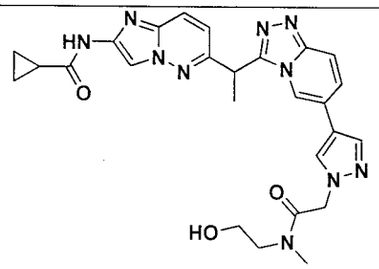
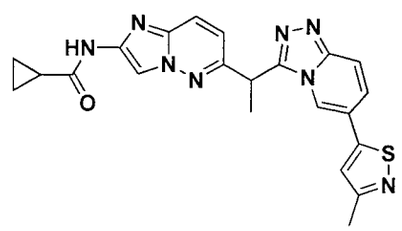
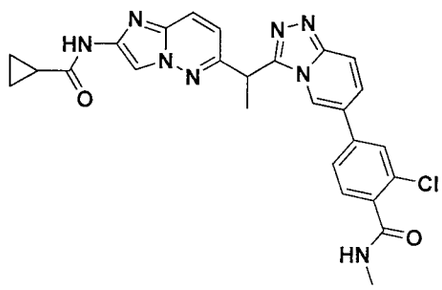
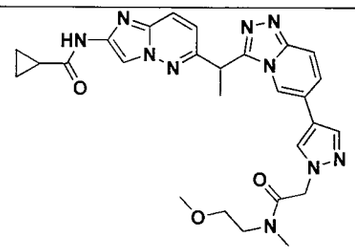
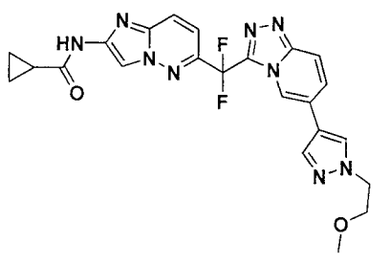
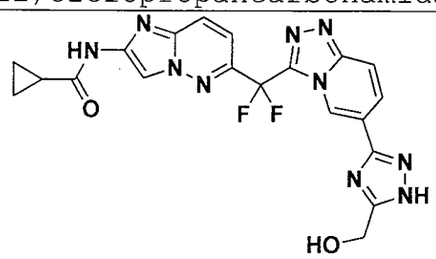
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 N-(6-((6-(1-(2-(dimetilamino)-2-oxoetil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 2-cloro-4-(3-((2-(ciclopropancarboxamido)imidazo[1,2-b]piridazin-6-il)metil)-[1,2,4]triazolo[4,3-a]piridin-6-il)-N-metilbenzamida

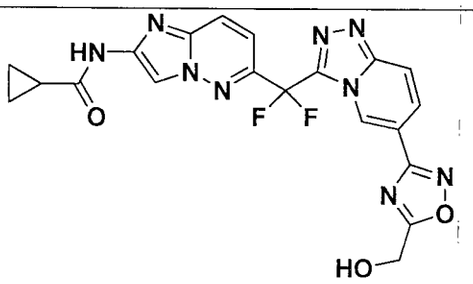
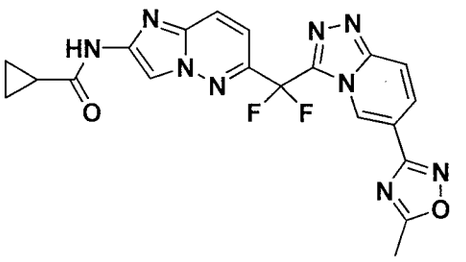
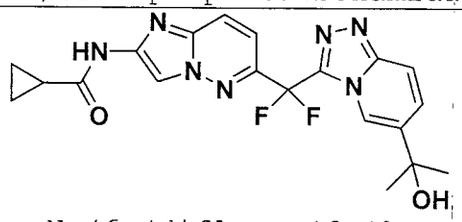
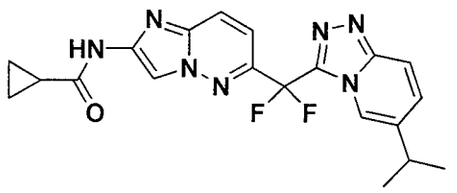
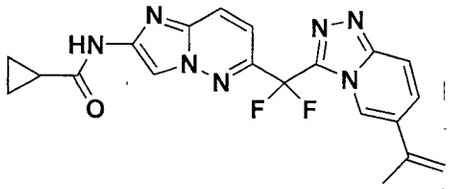
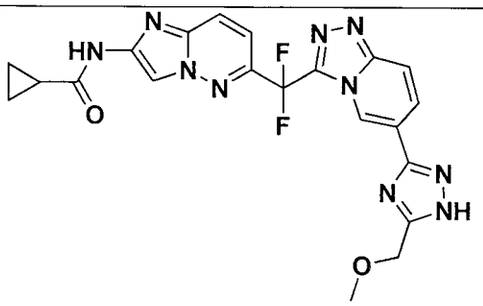
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 N-(6-((6-(1-(2-((2-metoxietil)(metil)amino)-2-oxoetil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(1-(6-(1-(2-metoxietil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

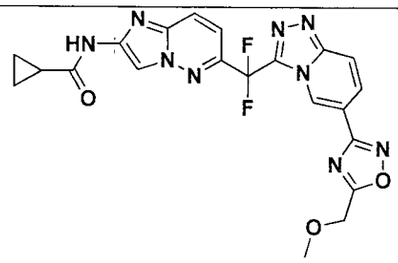
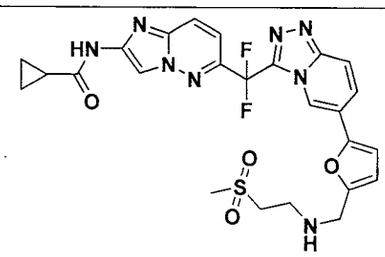
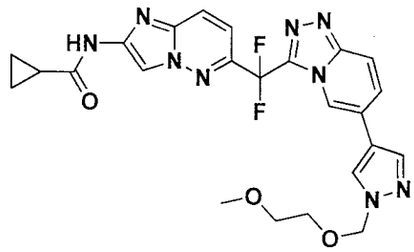
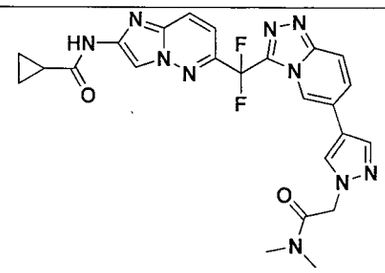
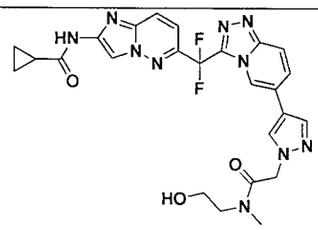
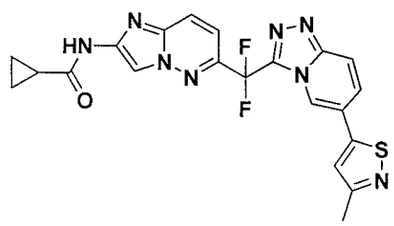
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 N-(6-(1-(6-(5-(hidroximetil)-1,2,4-oxadiazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(1-(6-(5-(metoximetil)-1H-1,2,4-triazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(1-(6-(5-(metoximetil)-1,2,4-oxadiazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(1-(6-(5-metil-1,2,4-oxadiazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

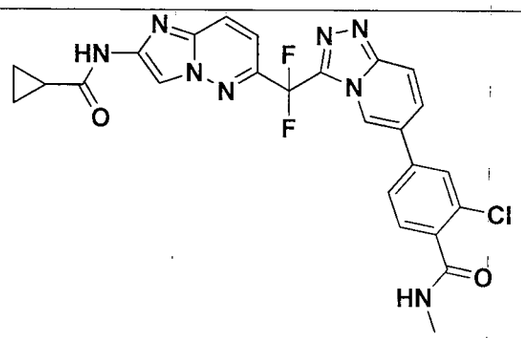
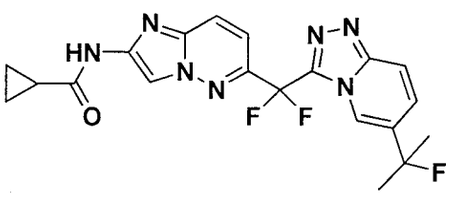
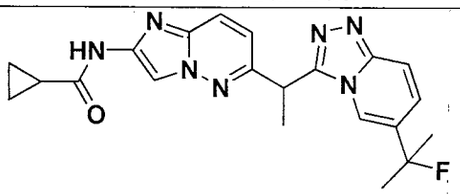
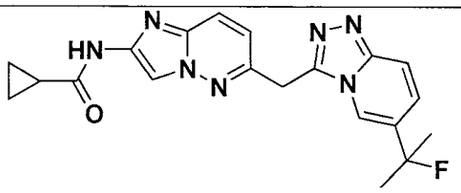
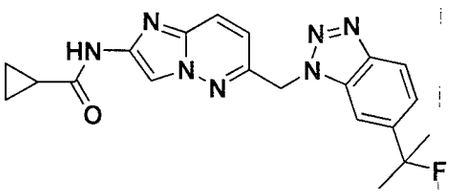
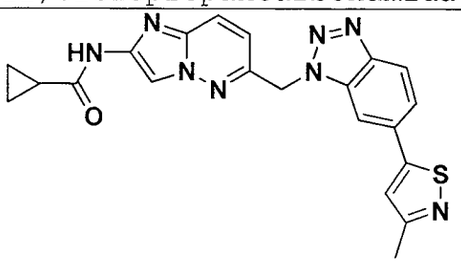
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 N-(6-(1-(6-(prop-1-en-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(1-(6-(5-((2-(metilsulfonil)etilamino)metil)furan-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(1-(6-(1-((2-metoxietoxi)metil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(1-(6-(1-(2-(dimetilamino)-2-oxoetil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

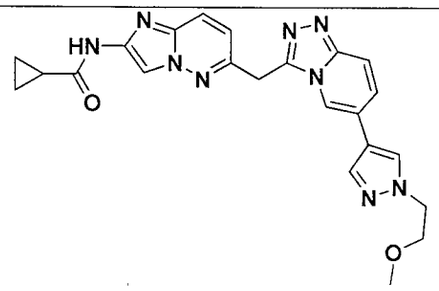
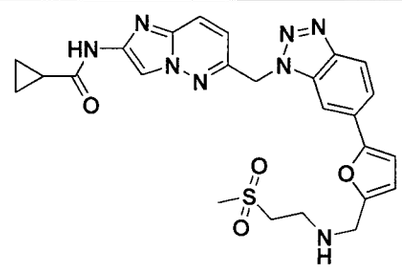
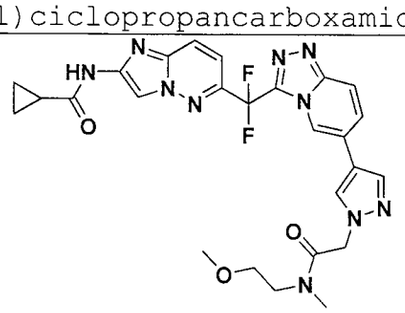
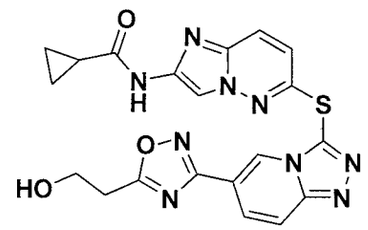
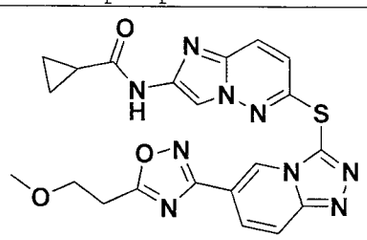
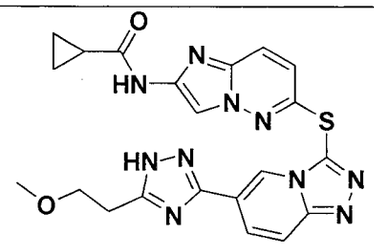
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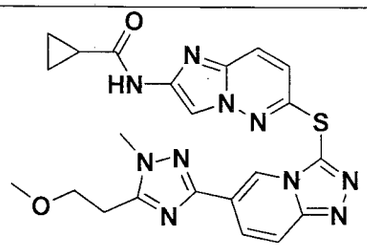
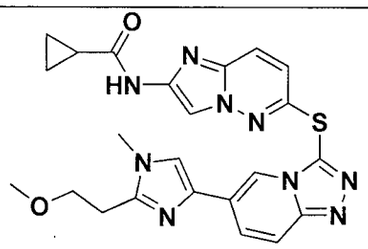
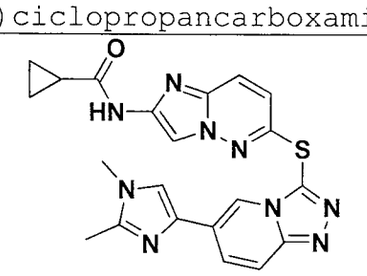
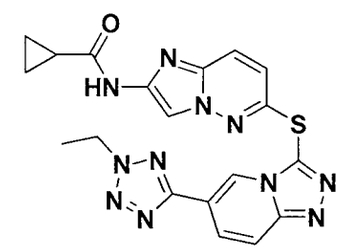
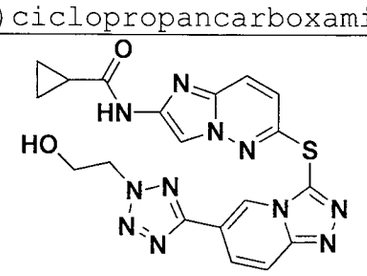
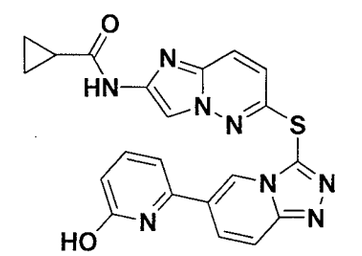
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 2-cloro-4-(3-(1-(2-(ciclopropancarboxamido)imidazo[1,2-b]piridazin-6-il)etil)-[1,2,4]triazolo[4,3-a]piridin-6-il)-N-metilbenzamida	 N-(6-(1-(6-(1-(2-((2-metoxietil)(metil)amino)-2-oxoetil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(difluoro(6-(1-(2-metoxietil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(difluoro(6-(5-(hidroximetil)-1H-1,2,4-triazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

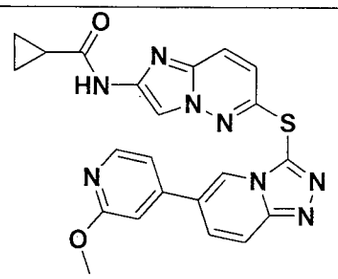
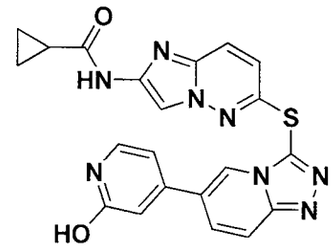
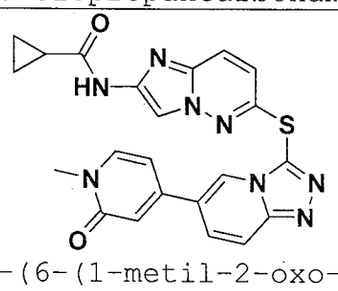
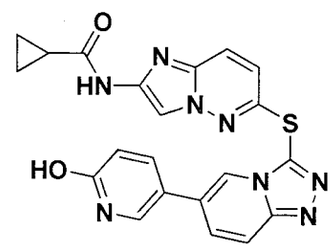
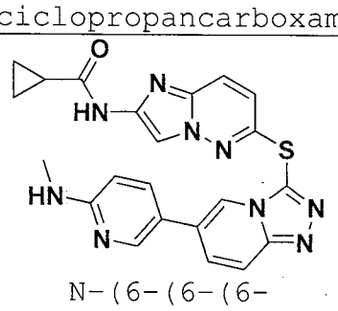
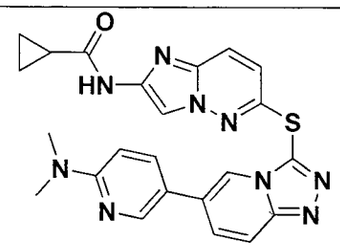
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 N-(6-(difluoro(6-(2-hidroxipropan-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(difluoro(6-isopropil-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(difluoro(6-(prop-1-en-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(difluoro(6-(5-(metoximetil)-1H-1,2,4-triazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

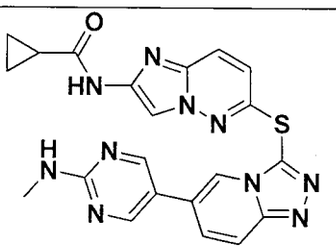
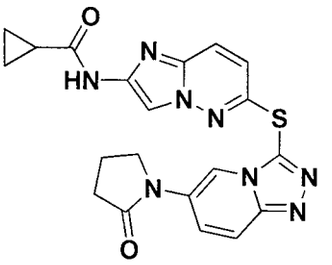
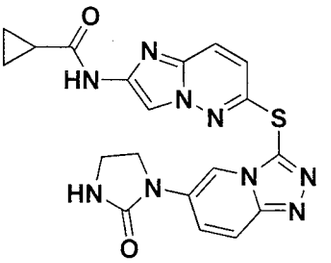
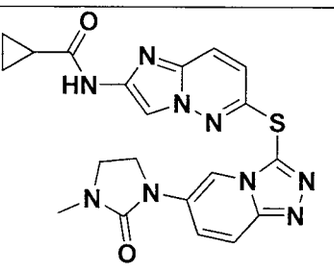
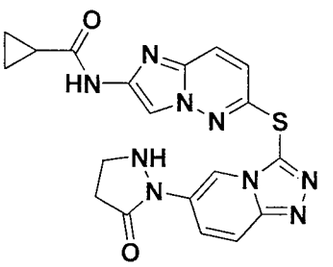
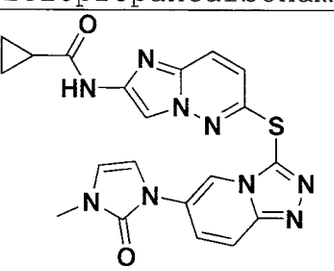
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 N-(6-(difluoro(6-(1-((2-metoxietoxi)metil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-(1-(2-(dimetilamino)-2-oxoetil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)difluorometil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(difluoro(6-(1-(2-((2-hidroxietil)(metil)amino)-2-oxoetil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(difluoro(6-(3-metilisotiazol-5-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

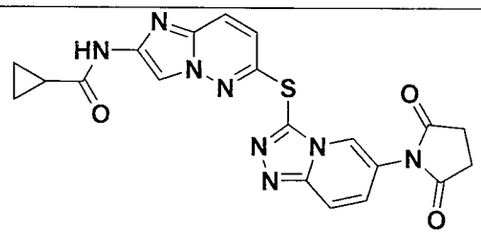
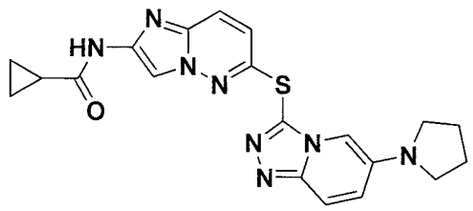
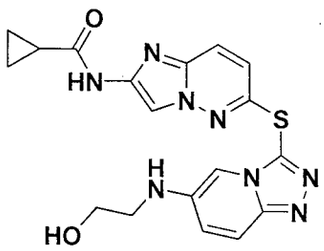
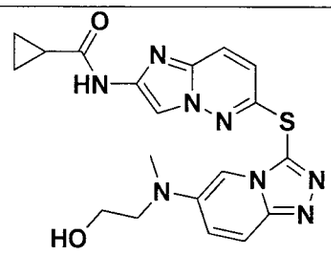
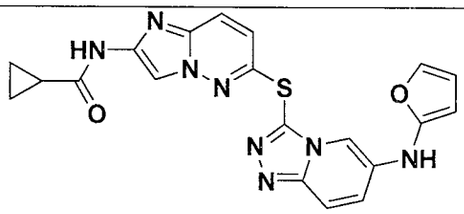
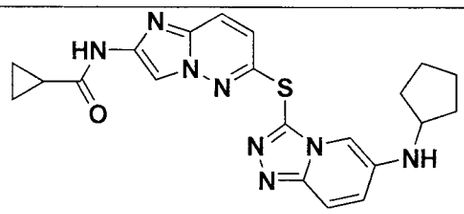
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 N-(6-(1-(6-(2-fluoropropan-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)etil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-(2-fluoropropan-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-((6-(2-fluoropropan-2-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-((6-(3-metilisotiazol-5-il)-1H-benzo[d][1,2,3]triazol-1-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

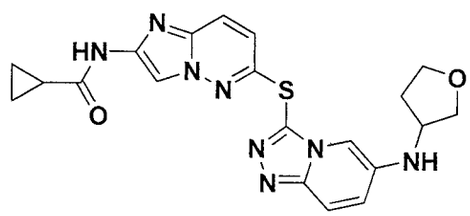
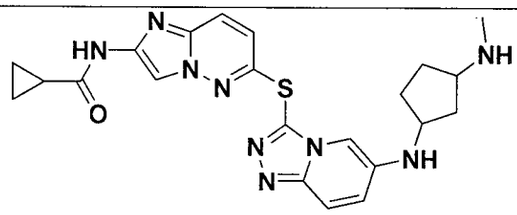
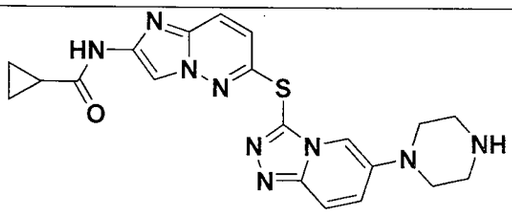
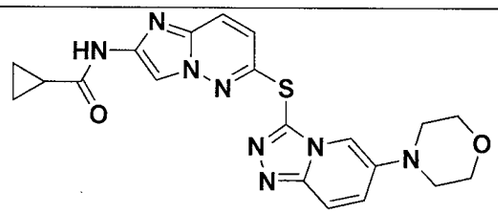
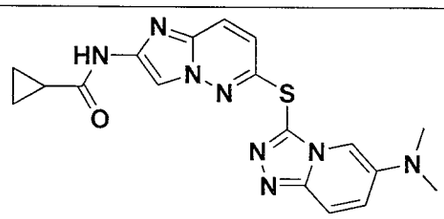
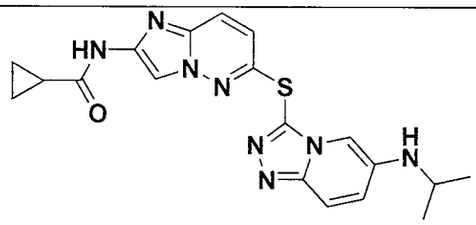
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 N-(6-(difluoro(6-(1-(2-((2-metoxietil)(metil)amino)-2-oxoetil)-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)metil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(5-(2-hidroxietil)-1,2,4-oxadiazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(5-(2-metoxietil)-1,2,4-oxadiazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(5-(2-metoxietil)-1H-1,2,4-triazol-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

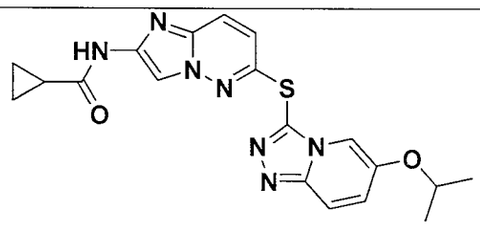
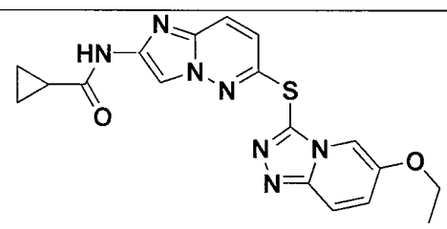
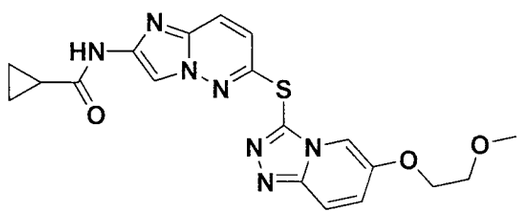
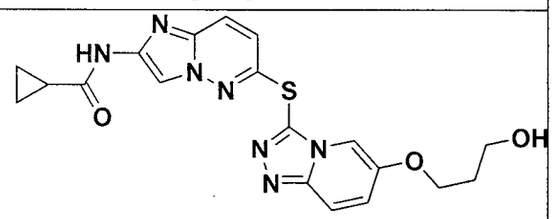
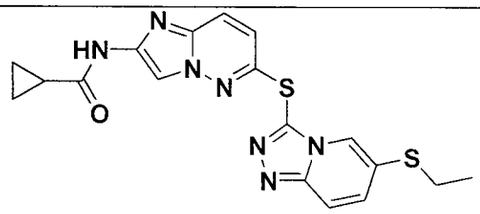
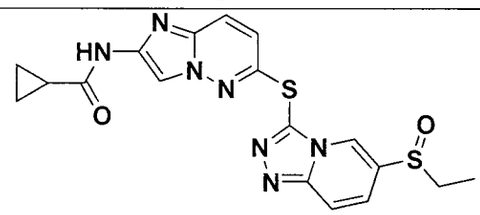
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 N-(6-(6-(1,2-dimetil-1H-imidazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(2-etil-2H-tetrazol-5-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(2-(2-hidroxietil)-2H-tetrazol-5-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(6-hidroxipiridin-2-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

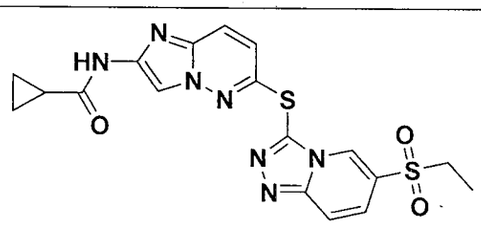
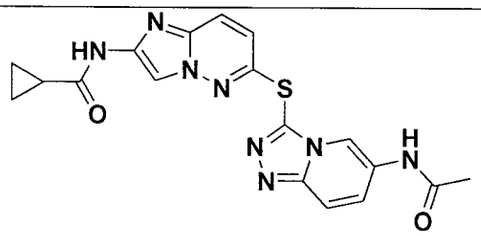
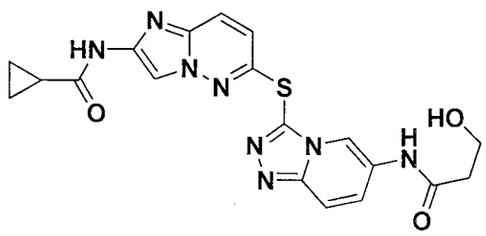
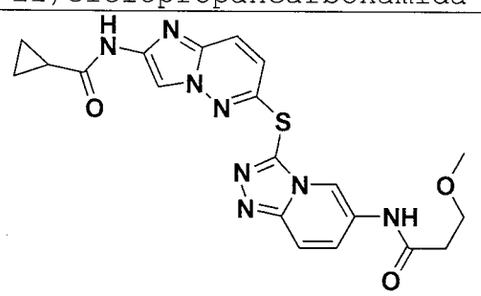
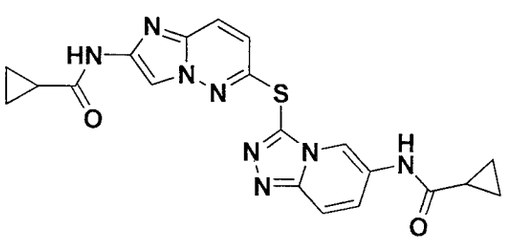
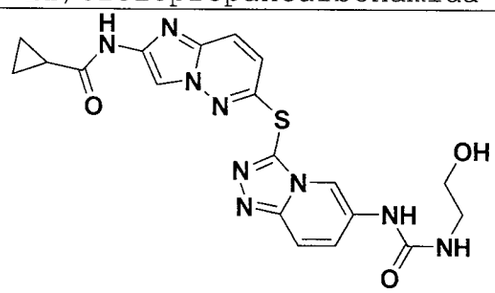
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 N-(6-(6-(1-metil-2-oxo-1,2-dihidropiridin-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(6-hidroxipiridin-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(6-(metilamino)piridin-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(6-(dimetilamino)piridin-3-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

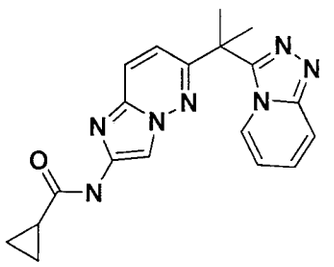
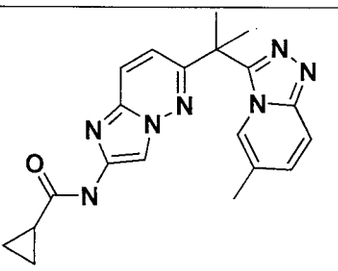
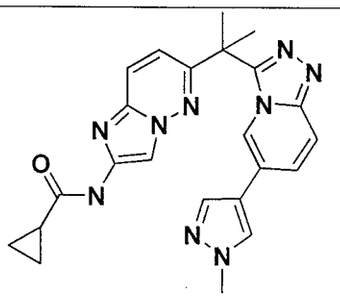
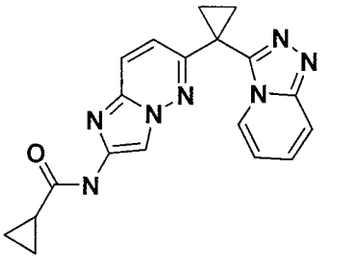
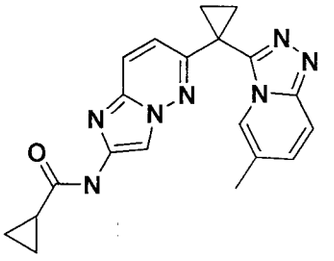
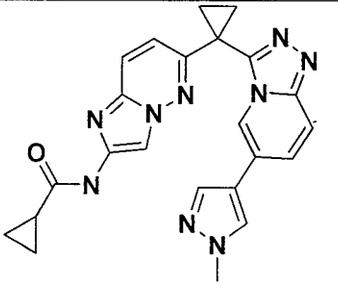
 N-(6-(6-(2-(metilamino)pirimidin-5-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(2-oxopirrolidin-1-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(2-oxoimidazolidin-1-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(3-metil-2-oxoimidazolidin-1-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(5-oxopirazolidin-1-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(3-metil-2-oxo-2,3-dihidro-1H-imidazol-1-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

 N-(6-(6-(2,5-dioxopirrolidin-1-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(pirrolidin-1-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(2-hidroxietilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-((2-hidroxietil)(metil)amino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(furan-2-ilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(ciclopentilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

 N-(6-(6-(tetrahidrofuran-3-ilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(3-(metilamino)ciclopentilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(piperazin-1-il)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-morfolino-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(dimetilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(isopropilamino)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

 N-(6-(6-isopropoxi-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-etoxi-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(2-metoxietoxi)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(3-hidroxipropoxi)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(etiltio)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(etilsulfinil)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

 N-(6-(6-(etilsulfonil)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-acetamido-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(3-hidroxipropanamido)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(3-metoxipropanamido)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(6-(ciclopropancarboxamido)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(6-(3-(2-hidroxietil)ureido)-[1,2,4]triazolo[4,3-a]piridin-3-iltio)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

 N-(6-(2-([1,2,4]triazolo[4,3-a]piridin-3-il)propan-2-il)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(2-(6-metil-[1,2,4]triazolo[4,3-a]piridin-3-il)propan-2-il)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(2-(6-(1-metil-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)propan-2-il)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(1-([1,2,4]triazolo[4,3-a]piridin-3-il)ciclopropil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida
 N-(6-(1-(6-metil-[1,2,4]triazolo[4,3-a]piridin-3-il)ciclopropil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida	 N-(6-(1-(6-(1-metil-1H-pirazol-4-il)-[1,2,4]triazolo[4,3-a]piridin-3-il)ciclopropil)imidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida

determinación de la cantidad de marca radiactiva unida. De modo alternativo, la unión del inhibidor se puede determinar por la corrida del experimento de competición donde los nuevos inhibidores se incuban con la proteína quinasa

unida a radioligandos conocidos.

A. Determinación de la Inhibición de cMET

Se determinó la propiedad inhibidora de un compuesto con respecto a la catálisis de cMET por el uso de electroforesis capilar con cuantificación de fluorescencia de un producto peptídico fosforilado para cMET. La enzima cMET (aminoácidos 1023–1360) teóricamente a 24 µM se mantuvo a –80 °C hasta el uso, en un amortiguador que contiene 25 mM de Tris–HCl pH 8.5, 150 mM de NaCl, 3 mM de DTT y 10% de glicerol. Se preparó la enzima a partir de las células Sf9 usando cromatografía de afinidad de níquel del dominio de quinasa de cMET marcado con histidina N–terminal. Después de la purificación, se eliminó la marca y se concentró la enzima. La enzima final estaba fosforilada parcialmente y catalíticamente activa en forma parcial. Para activar la enzima por completo, cMET congelado se descongeló rápidamente y se activó con la adición de amortiguador de ensayo (50 mM de HEPES pH 7.5, 10 mM de NaCl, 10 mM de $MgCl_2$, 0.01% de Brij®35), 1.25 mM de ATP, 5 mM de $MgCl_2$ y 5 mM de DTT a una concentración de cMET de 2.4 µM seguido por una incubación de 30 minutos a temperatura ambiente. Se prepararon soluciones de compuestos de ensayo en variadas concentraciones en DMSO y se diluyeron a una concentración final de DMSO de 2% en cóctel de ensayo que contiene amortiguador de ensayo, 0.5 mM de EDTA, y 2 µM del sustrato peptídico FL–2 (5–FAM–EAIYAAPFAKKK–CONH2 donde 5–FAM = 5–carboxifluoresceína). Después, se añadió enzima cMET (1.2 nM final) y el sistema se incubó a temperatura ambiente durante 20 minutos. La catálisis se inició por la adición de ATP (50 µM final). Los ensayos se incubaron a temperatura ambiente durante 2 horas luego se inactivó por la adición de EDTA. El producto peptídico fosforilado se cuantificó por monitoreo de fluorescencia durante la electroforesis capilar con Caliper LifeSciences LabChip 3000 bajo los siguientes ajustes: presión de base = –0.1 psi, presión de prueba = –1.2 psi, voltaje corriente abajo = –500 V, voltaje corriente arriba = –2300 V, tipo de chip = TC372. El amortiguador de elución fue idéntico al amortiguador de ensayo excepto por la ausencia de DTT, FL–2 y ATP y la adición de 0.1% de reactivo de recubrimiento (Caliper). En estas condiciones, el producto fosforilado eluyó a los 37 segundos y el sustrato no fosforilado eluyó a los 45 segundos. Se cuantificó la altura del pico y

se uso para determinar las velocidades de la enzima.

Se calcularon los valores de IC_{50} por ajuste de la curva de cuadrados mínimos no lineal de la ecuación estándar de IC_{50} para velocidad de cMET corregida por fondo versus concentración del compuesto. Como punto de referencia para este ensayo, estaurosporina exhibió una IC_{50} de ~150 nM. Los valores de IC_{50} para los compuestos de la invención seleccionados contra cMET se dan en la Tabla 1.

B. Determinación de inhibición de viabilidad celular

Las células se mantuvieron a 37 °C en una atmósfera humidificada que contiene 5%–8% de CO_2 siguiendo las instrucciones del proveedor (American Type Culture Collection (Rockville, MD)). La inhibición de viabilidad celular se determinó para un panel de líneas celulares tumorales (MKN45, EBC1 y A549), usando la sales de tetrazolio soluble, MTS (Promega, Madison, WI). Las células se sembraron a razón de 2.000–7.500 células/cavidad en placas de cultivo de tejido de 96 cavidades y se dejaron fijar durante aproximadamente 24 horas antes de la adición de compuestos o vehículo DMSO. Después de 96 horas de incubación con compuestos de ensayo, la conversión de MTS por células metabólicamente activas se determinó por la medición de la DO 490 nm con un lector de microplaca Spectamax (Molecular Devices, San Diego, CA). Las células se trataron por duplicado con los compuestos de ensayo. Los compuestos se diluyeron en forma seriada (1:2.5) a partir de la columna 1 a 11 y la columna 12 que contenía vehículo DMSO. Los compuestos se diluyeron en el medio de crecimiento celular luego se añadió solución del compuesto a las células. Se añadieron cantidades iguales de DMSO a las células (concentración final es 0.5%). Después de la corrección por fondo y la normalización frente a las células tratadas con DMSO, se calcularon los valores de EC_{50} usando ajuste de curva no lineal de la viabilidad celular en función de la concentración del compuesto. Las líneas celulares MKN45 y EBC1 contienen altos niveles de fosfo–Met y son dependientes de cMET para la proliferación, mientras que la línea A549 se usa como control negativo.

Los valores de EC_{50} se pueden calcular por ajuste de curva no lineal del las concentraciones de compuesto y las intensidades de fluorescencia en la ecuación de EC_{50} estándar. Los valores de EC_{50} para los compuestos de la invención seleccionados contra MKN45, EBC1 y A549 se dan en la Tabla 1.

TABLA 1

Compuesto	cMet IC_{50}, nm	MKN45 EC_{50}, nm	EBC1 EC_{50}, nm	A549 EC_{50}, nm
1	> 100	---	---	---
2	> 100	---	---	---
3 (Sal HCl)	> 100	250 - 630	100 - 199	8000 - 25000
3 (Sal TFA)	> 100	250 - 630	100 - 199	8000 - 25000
3 (base libre)	> 100	100 - 199	60 - 100	8000 - 25000
4	30 - 59	100 - 249	< 35	> 50000
5	< 30	< 100	< 35	> 50000
6	> 100	> 630	> 200	> 50000
9	60 - 100	250 - 630	100 - 199	8000 - 25000
12	> 100	> 630	> 200	> 50000
13 (Sal HCl)	30 - 59	100 - 249	< 35	8000 - 25000
13 (Sal TFA)	30 - 59	60 - 100	< 30	5000 - 8000
13 (base libre)	30 - 59	< 30	< 30	> 50000
14	30 - 59	250 - 630	100 - 199	600 - 1600
15	60 - 100	250 - 630	100 - 199	8000 - 25000
16	> 100	> 630	> 200	> 50000
17	60 - 100	< 100	< 35	> 19500
18	30 - 59	100 - 249	100 - 199	> 19500
19	60 - 100	250 - 630	100 - 199	> 19500
20	60 - 100	250 - 630	> 200	> 50000
21	> 100	> 630	> 200	> 50000
22	60 - 100	> 630	> 200	> 50000
23	30 - 59	250 - 630	100 - 199	> 50000
24	60 - 100	100 - 249	35 - 99	> 50000
25	< 30	< 100	< 35	8000 - 25000
26	< 30	< 100	< 35	> 19500

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Compuesto	cMet IC_{50}, nm	MKN45 EC_{50}, nm	EBC1 EC_{50}, nm	A549 EC_{50}, nm
27	< 30	< 100	35 - 99	> 50000
28	< 30	< 100	< 35	> 50000
29	60 - 100	< 100	35 - 99	> 50000
30	30 - 59	> 630	> 200	> 19500
31	30 - 59	< 100	< 35	> 50000
32	< 30	100 - 249	35 - 99	> 50000
33	> 100	> 630	> 200	> 50000
34	60 - 100	> 630	> 200	> 50000
35	> 100	> 630	100 - 199	> 19500
36	< 30	250 - 630	35 - 99	> 50000
37	30 - 59	250 - 630	100 - 199	> 50000
38	> 100	> 630	> 200	> 50000
39	60 - 100	100 - 249	35 - 99	600 - 1600
40	> 100	> 630	> 200	> 50000
41	60 - 100	100 - 249	35 - 99	8000 - 25000
42	60 - 100	100 - 249	35 - 99	> 50000
43	> 100	---	---	---
44	< 30	< 100	< 35	600 - 1600
45 (Sal HCl)	< 30	< 30	< 30	> 50000
45 (Sal TFA)	30 - 59	---	---	---
46	30 - 59	60 - 100	60 - 100	> 50000
47	< 30	< 30	< 30	> 50000
49 (Sal HCl)	< 30	30 - 59	< 30	8000 - 25000
49 (Sal TFA)	30 - 59	60 - 100	60 - 100	> 50000
49 (base libre)	< 30	60 - 100	< 30	> 50000
50	< 30	30 - 59	< 30	> 50000
51	> 100	> 100	> 100	> 50000
52	> 100	> 100	> 100	> 50000
53	250 - 630	250 - 630	250 - 630	> 50000
55	< 30	< 30	< 30	> 50000
56	< 30	< 30	< 30	> 50000
57	< 30	< 30	< 30	> 50000

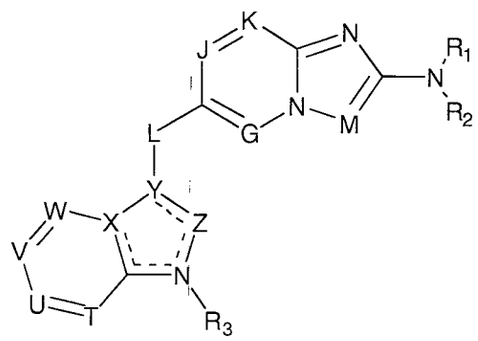
Compuesto	cMet IC_{50}, nm	MKN45 EC_{50}, nm	EBC1 EC_{50}, nm	A549 EC_{50}, nm
58	< 30	< 30	< 30	> 50000
59	< 30	100 - 249	60 - 100	> 50000
60	< 30	60 - 100	60 - 100	> 50000
61	< 30	< 30	< 30	> 50000
62	< 30	< 30	< 30	5000 - 8000
63	< 30	< 30	< 30	> 50000
64	< 30	100 - 249	100 - 249	> 50000
65	< 30	< 30	< 30	> 50000
66	< 30	100 - 249	100 - 249	> 50000
67	< 30	100 - 249	60 - 100	> 50000
68	< 30	30 - 59	30 - 59	> 50000
69	< 30	< 30	< 30	> 50000
70	< 30	< 30	< 30	> 50000
71	< 30	< 30	< 30	> 50000
72	< 30	< 30	< 30	> 50000
73	< 30	< 30	< 30	8000 - 25000
74	< 30	< 30	< 30	8000 - 25000
75	< 30	< 30	< 30	8000 - 25000
76	< 30	< 30	< 30	> 50000
77	< 30	< 30	< 30	> 50000
78	30 - 59	< 30	< 30	> 50000
79	60 - 100	< 30	< 30	> 50000
80	30 - 59	< 30	30 - 59	> 50000
81	< 30	< 30	< 30	> 50000
82	< 30	< 30	< 30	> 50000
83	< 30	< 30	< 30	> 50000
84	< 30	< 30	< 30	> 50000
85	< 30	< 30	< 30	> 50000
86	30 - 59	< 30	< 30	> 50000
87	100 - 249	30 - 59	30 - 59	> 50000
88	< 30	< 30	< 30	> 50000
89	< 30	-	-	-

Compuesto	cMet IC_{50}, nm	MKN45 EC_{50}, nm	EBC1 EC_{50}, nm	A549 EC_{50}, nm
90	< 30	< 30	< 30	> 50000
91	< 30	< 30	< 30	> 50000
92	< 30	< 30	< 30	> 50000
93	60 - 100	30 - 59	30 - 59	8000 - 25000
94	250 - 630	-	-	-
95	< 30	-	-	-
96	< 30	< 30	< 30	8000 - 25000
97	< 30	< 30	< 30	> 50000
98	< 30	< 30	< 30	> 50000
99	250 - 630	100 - 249	100 - 249	> 50000
101	< 30	100 - 249	30 - 59	> 50000
102	30 - 59	60 - 100	30 - 59	> 50000
103	< 30	30 - 59	< 30	> 50000
104	< 30	< 30	< 30	> 50000
105	< 30	250 - 630	100 - 249	> 50000
106	< 30	60 - 100	30 - 59	> 50000
107	< 30	100 - 249	60 - 100	> 50000
108	30 - 59	8000 - 25000	8000-25000	> 50000
109	250 - 630	8000 - 25000	8000-25000	8000 - 25000
110	30 - 59	100 - 249	30 - 59	> 50000
111	< 30	100 - 249	30 - 59	8000 - 25000
112	100 - 249	-	-	-
113	250 - 630	-	-	-
114	> 630	> 630	> 630	> 50000

modificaciones y variaciones de esta invención con la condición de que ellas estén dentro del alcance de las reivindicaciones adjuntas y sus equivalentes.

REIVINDICACIONES:

1. Un compuesto que tiene la fórmula:



o una de sus sales farmacéuticamente aceptables, caracterizado porque

G se selecciona del grupo que consiste en CR_4 y N;

J se selecciona del grupo que consiste en CR_5 y N;

K se selecciona del grupo que consiste en CR_6 y N;

M se selecciona del grupo que consiste en CR_7 y N;

L está ausente o un enlazante que provee 1, 2, 3, 4, 5 o 6 separación de átomos entre los anillos a los que L se une, en donde los átomos del enlazante que provee la separación se seleccionan del grupo que consiste en carbono, oxígeno, nitrógeno y azufre;

T se selecciona del grupo que consiste en CR_8 y N;

U se selecciona del grupo que consiste en CR_9 y N;

V se selecciona del grupo que consiste en CR_{10} y N;

W se selecciona del grupo que consiste en CR_{11} y N;

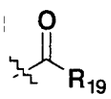
X se selecciona del grupo que consiste en CR_{12} y N;

Y se selecciona del grupo que consiste en CR_{13} y N;

Z se selecciona del grupo que consiste en $CR_{14}R_{15}$ y NR_{16};

R_1 se selecciona del grupo que consiste en hidrógeno, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, alquil carbonilo (C_{1-10}), cicloalquil(C_{3-12}) carbonilo (C_{1-5}), heterocicloalquil(C_{3-12}) carbonilo (C_{1-10}), arilcarbonilo (C_{1-10}), heteroaril(C_{1-10}) carbonilo (C_{1-5}), bicicloaril (C_{9-12})carbonilo (C_{1-5}), heterobicicloaril (C_{8-12})carbonilo (C_{1-5}), amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_1 tiene la fórmula



R_2 es hidrógeno o un sustituyente convertible *in vivo* a hidrógeno;

R_3 se selecciona del grupo que consiste en hidrógeno, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_3 está ausente cuando el nitrógeno al que está unido forma parte de un doble enlace;

R_4 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno

sustituido o no sustituido;

R_5 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_6 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_7 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}),

heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_8 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_9 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, amido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}), haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}), carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), aminoalquilo (C_{1-10}), amidoalquil (C_{1-10})aminoalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) carbonilarilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_{10} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, amido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}), haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}),

carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), aminoalquilo (C_{1-10}), amidoalquil (C_{1-10})aminoalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) carbonilarilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_{11} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;

R_{12} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_{12} está ausente cuando el carbono al que está unido

forma parte de un doble enlace;

R_{13} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_{13} está ausente cuando el carbono al que está unido forma parte de un doble enlace;

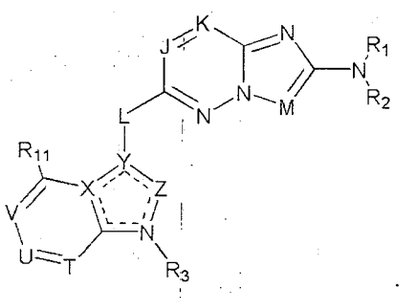
R_{14} y R_{15} se selecciona de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, imino, sulfonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_{15} está ausente cuando el carbono al que está unido forma parte de un doble enlace;

R_{16} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}),

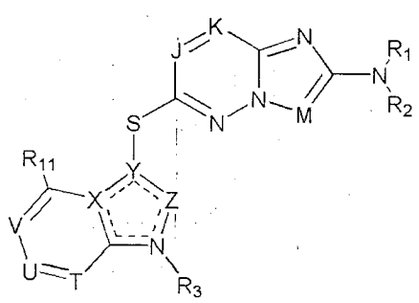
cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloaril (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_{16} está ausente cuando el nitrógeno al que está unido forma parte de un doble enlace, y

R_{19} se selecciona del grupo que consiste en hidrógeno, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

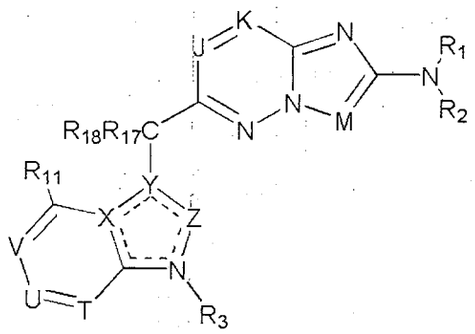
2. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:



3. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:

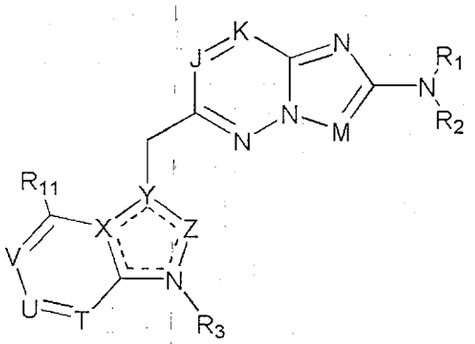


4. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:

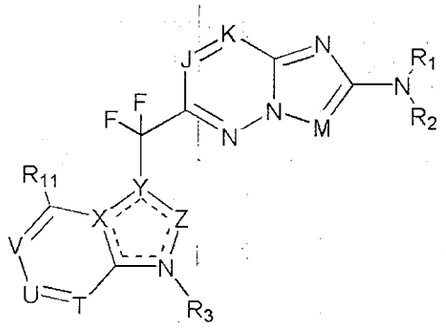


en donde R_{17} y R_{18} se seleccionan de modo independiente del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, amino, alquilamino (C_{1-10}), sulfonamido, imino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

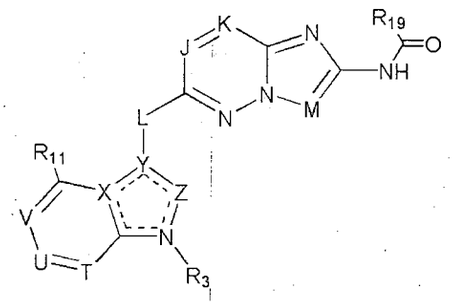
5. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:



6. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:

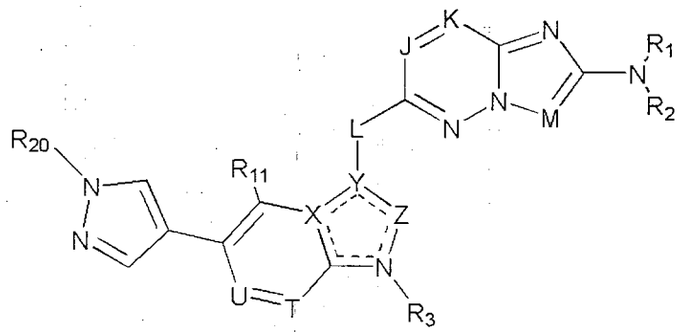


7. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:



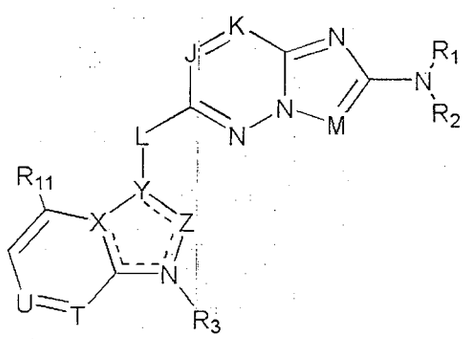
en donde R_{19} se selecciona del grupo que consiste en hidrógeno, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, amino, alquilamino (C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (C_{1-10}), haloalquilo (C_{1-10}), hidroxialquilo (C_{1-10}), carbonilalquilo (C_{1-10}), tiocarbonilalquilo (C_{1-10}), sulfonilalquilo (C_{1-10}), sulfinilalquilo (C_{1-10}), azaalquilo (C_{1-10}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

8. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:

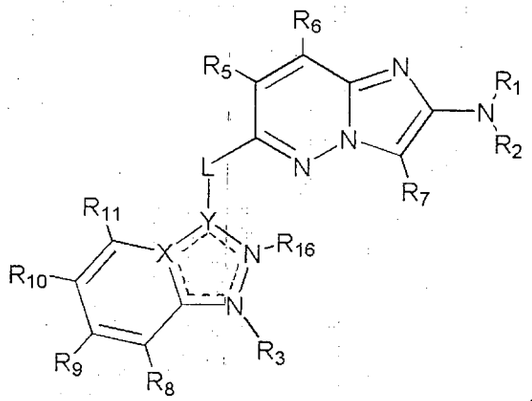


en donde R_{20} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, amino, alquilamino (C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo (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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

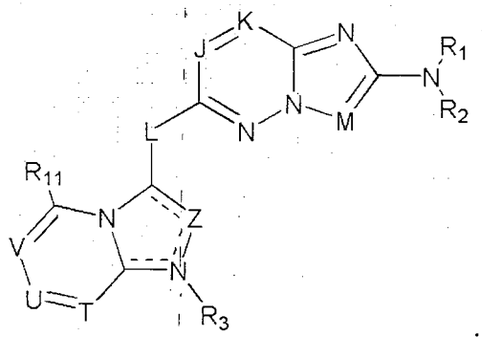
9. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:



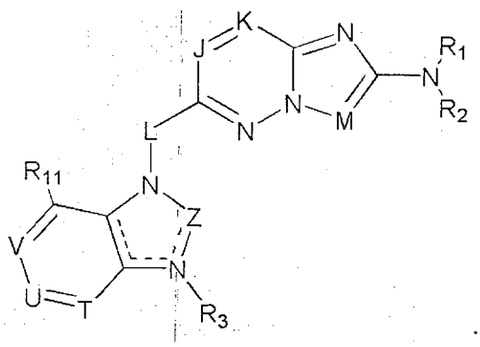
10. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:



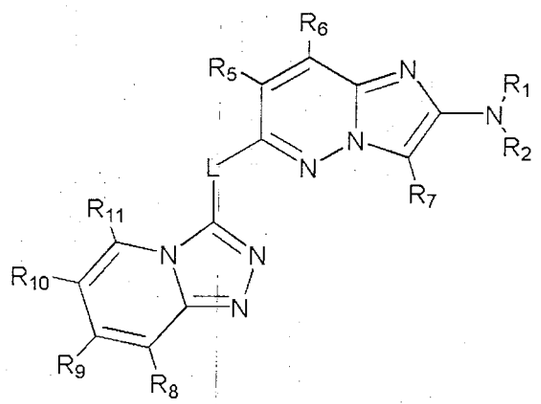
11. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:



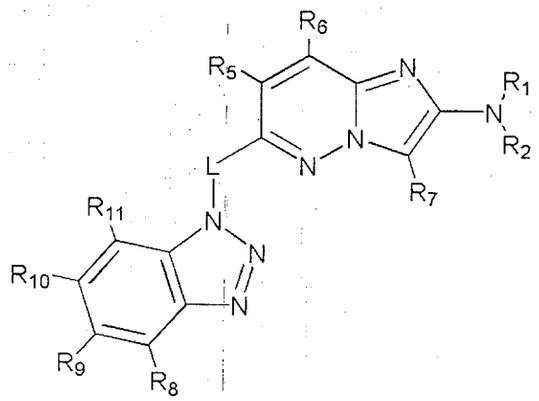
12. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:



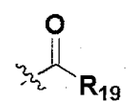
13. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:



14. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula:



15. El compuesto de conformidad con cualquiera de las reivindicaciones 1–6 y 8–14, caracterizado porque R_1 tiene la fórmula



en donde R_{19} se selecciona del grupo que consiste en hidrógeno, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

16. El compuesto de conformidad con cualquiera de las reivindicaciones 1–6 y 8–15, caracterizado porque R_2 es hidrógeno.

17. El compuesto de conformidad con cualquiera de las reivindicaciones 1–12, 15 y 16, caracterizado porque R_3 está ausente.

18. El compuesto de conformidad con cualquiera de las reivindicaciones 1 y 15–17, caracterizado porque R_4 se selecciona del grupo que consiste en hidrógeno, halo y un alquilo (C_{1-3}) sustituido o no sustituido.

19. El compuesto de conformidad con cualquiera de las reivindicaciones 1–18, caracterizado porque R_5 se selecciona del grupo que consiste en hidrógeno, halo y un alquilo (C_{1-3}) sustituido o no sustituido.

20. El compuesto de conformidad con cualquiera de las reivindicaciones 1–19, caracterizado porque R_6 se selecciona del grupo que consiste en hidrógeno, halo y un alquilo (C_{1-3}) sustituido o no sustituido.

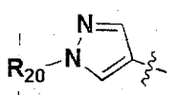
21. El compuesto de conformidad con cualquiera de las reivindicaciones 1–20, caracterizado porque R_7 se selecciona del grupo que consiste en hidrógeno, halo y un alquilo (C_{1-3}) sustituido o no sustituido.

22. El compuesto de conformidad con cualquiera de las reivindicaciones 1–21, caracterizado porque R_8 se selecciona del grupo que consiste en hidrógeno, halo y un alquilo (C_{1-3}) sustituido o no sustituido.

23. El compuesto de conformidad con cualquiera de las reivindicaciones 1–22, caracterizado porque R_9 se selecciona del grupo que consiste en hidrógeno, halo y

un alquilo (C_{1-3}) sustituido o no sustituido.

24. El compuesto de conformidad con cualquiera de las reivindicaciones 1–7 y 10–23, caracterizado porque R_{10} tiene la fórmula



en donde R_{20} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}) carbonilo, oxicarbonilo, aminocarbonilo, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (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}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquil (C_{3-12}), heterocicloalquil (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}), heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido.

25. El compuesto de conformidad con cualquiera de las reivindicaciones 1–24, caracterizado porque R_{11} se selecciona del grupo que consiste en hidrógeno, halo y un alquilo (C_{1-3}) sustituido o no sustituido.

26. El compuesto de conformidad con cualquiera de las reivindicaciones 1–10 y 15–25, caracterizado porque R_{12} está ausente.

27. El compuesto de conformidad con cualquiera de las reivindicaciones 1–10 y 15–26, caracterizado porque R_{13} está ausente.

28. El compuesto de conformidad con cualquiera de las reivindicaciones 1–9, 11, 12 y 15–27, caracterizado porque R_{14} se selecciona del grupo que consiste en hidrógeno, halo y un alquilo (C_{1-3}) sustituido o no sustituido.

29. El compuesto de conformidad con cualquiera de las reivindicaciones 1–9, 11, 12 y 15–28, caracterizado porque R_{15} está ausente.

30. El compuesto de conformidad con cualquiera de las reivindicaciones 1–12 y 15–29, caracterizado porque R_{16} está ausente.

31. El compuesto de conformidad con cualquiera de las reivindicaciones 4 y 15–30, caracterizado porque R_{17} se selecciona del grupo que consiste en hidrógeno, halo y un alquilo (C_{1-3}) sustituido o no sustituido.

32. El compuesto de conformidad con cualquiera de las reivindicaciones 4 y 15–31, caracterizado porque R_{18} se selecciona del grupo que consiste en hidrógeno, halo y un alquilo (C_{1-3}) sustituido o no sustituido.

33. El compuesto de conformidad con cualquiera de las reivindicaciones 1–32, caracterizado porque R_{19} es un alquilo (C_{1-5}) sustituido o no sustituido.

34. El compuesto de conformidad con cualquiera de las reivindicaciones 1–32, caracterizado porque R_{19} es un cicloalquilo (C_{3-6}) sustituido o no sustituido.

35. El compuesto de conformidad con cualquiera de las reivindicaciones 1–32, caracterizado porque R_{19} es un ciclopropilo sustituido o no sustituido.

36. El compuesto de conformidad con cualquiera de las reivindicaciones 8 y 15–35, caracterizado porque R_{20} se selecciona del grupo que consiste en hidrógeno, halo, un alquilo (C_{1-5}) sustituido o no sustituido, una arilo sustituido o no sustituido, un cicloalquilo (C_{3-12}) sustituido o no sustituido, un heteroarilo (C_{4-10}) sustituido o no sustituido, un hidroxialquilo (C_{1-6}) sustituido o no sustituido y un heterocicloalquil (C_{3-6})alquilo (C_{1-4}) sustituido o no sustituido.

37. El compuesto de conformidad con cualquiera de las reivindicaciones 8 y 15–35, caracterizado porque R_{20} es hidrógeno.

38. El compuesto de conformidad con cualquiera de las reivindicaciones 8 y 15–35, caracterizado porque R_{20} es metilo.

39. El compuesto de conformidad con cualquiera de las reivindicaciones 1–38, caracterizado porque el compuesto está en forma de una sal farmacéuticamente aceptable.

40. Una composición farmacéutica, caracterizada porque comprende un compuesto de conformidad con cualquiera de las reivindicaciones 1–39; y un excipiente farmacéuticamente aceptable.

41. Un kit, caracterizado porque comprende:
un compuesto de conformidad con cualquiera de las reivindicaciones 1–39; e
instrucciones que comprenden una o más formas de información seleccionado del grupo que consiste en indicación del estado de enfermedad para la que se administra el compuesto, información de almacenamiento del compuesto, información de dosis e instrucciones respecto de cómo administrar el compuesto.

42. Un artículo de manufactura, caracterizado porque comprende:
un compuesto de conformidad con cualquiera de las reivindicaciones 1–39; y
materiales de envase.

43. Un método terapéutico, caracterizado porque comprende administrar un compuesto de conformidad con cualquiera de las reivindicaciones 1–39 a un sujeto.

44. Un método para inhibir cMET, caracterizado porque comprende poner en contacto cMET con un compuesto de conformidad con cualquiera de las reivindicaciones 1–39.

45. Un método para inhibir cMET, caracterizado porque comprende causar que un compuesto de conformidad con cualquiera de las reivindicaciones 1–39 esté presente en un sujeto a fin de inhibir cMET *in vivo*.

46. Un método para inhibir cMET, caracterizado porque comprende administrar un primer compuesto a un sujeto que se convierte *in vivo* en un segundo compuesto en donde el segundo compuesto inhibe cMET *in vivo*, el segundo compuesto es un compuesto de conformidad con cualquiera de las reivindicaciones 1–39.

47. Un método para tratar un estado de enfermedad para el cual cMET posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, caracterizado porque el método comprende causar que un compuesto de conformidad con cualquiera de las reivindicaciones 1–39 esté presente en un sujeto en una cantidad terapéuticamente efectiva para el estado de enfermedad.

48. Un método para tratar un estado de enfermedad para el cual cMET posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, caracterizado porque el método comprende administrar un compuesto de conformidad con cualquiera de las reivindicaciones 1–39 a un sujeto, en donde el compuesto está presente en el sujeto en una cantidad terapéuticamente efectiva para el estado de enfermedad.

49. Un método para tratar un estado de enfermedad para el cual cMET posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, caracterizado porque el método comprende administrar un primer compuesto a un sujeto que se convierte *in vivo* a un segundo compuesto en donde el segundo compuesto inhibe cMET *in vivo*, el segundo compuesto es un compuesto de conformidad con cualquiera de las reivindicaciones 1–39.

50. El método de conformidad con cualquiera de las reivindicaciones 47–49, caracterizado porque el estado de enfermedad se selecciona del grupo que consiste en cáncer, ateroesclerosis y fibrosis del pulmón.

51. El método de conformidad con la reivindicación 50, caracterizado porque el cáncer se selecciona del grupo que consiste en cáncer gástrico, cáncer de

pulmón, cáncer de colon, cáncer de mama y otros tumores sólidos.

52. Un compuesto de conformidad con cualquiera de las reivindicaciones 1–39, caracterizado para uso como un medicamento.

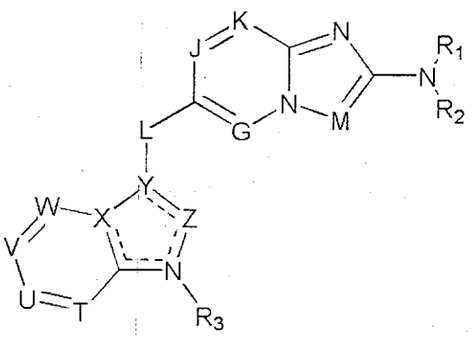
53. Uso de un compuesto de conformidad con cualquiera de las reivindicaciones 1–39, para inhibir cMET.

54. Uso de un compuesto de conformidad con cualquiera de las reivindicaciones 1–39, para tratar un estado de enfermedad para el que cMET posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad.

55. Uso de un compuesto de conformidad con cualquiera de las reivindicaciones 1–39, para tratar cáncer.

RESUMEN DE LA INVENCIÓN

Se proporcionan compuestos de la siguiente fórmula para uso con cMET:



en donde las variables son como se definieron en la presente. También se proporcionan composiciones farmacéuticas, kits y artículos de manufactura que comprenden dichos compuestos; métodos e intermediarios útiles para obtener los compuestos; y métodos para usar dichos compuestos.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT __X__ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

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(51) Clasificación Internacional :

(71)Solicitante(s) **TAKEDA PHARMACEUTICAL COMPANY**

(72) Inventor(es) **JEROME C. BRESSI, SHAOSONG CHU, PHILIP ERICKSON, MALLAREDDY KOMAMDLA, LILY KWOK, JOHN D. LAWSON, JEFFREY A. STAFFORD, MICHAEL B. WALLACE, ZHIYUAN ZHANG, SANJIB DAS**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

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(71)Solicitante(s) **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

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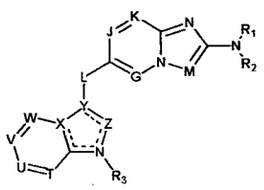
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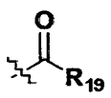
(54) Titulo: **INHIBIDORES DE CMET**

Reivindicación(es):

1. Un compuesto que tiene la fórmula:



o una de sus sales farmacéuticamente aceptables, caracterizado porque
G se selecciona del grupo que consiste en CR_4 y N;
J se selecciona del grupo que consiste en CR_5 y N;
K se selecciona del grupo que consiste en CR_6 y N;
M se selecciona del grupo que consiste en CR_7 y N;
L está ausente o un enlazante que provee 1, 2, 3, 4, 5 o 6 separación de átomos entre los anillos a los que L se une, en donde los átomos del enlazante que provee la separación se seleccionan del grupo que consiste en carbono, oxígeno, nitrógeno y azufre;
T se selecciona del grupo que consiste en CR_8 y N;
U se selecciona del grupo que consiste en CR_9 y N;
V se selecciona del grupo que consiste en CR_{10} y N;
W se selecciona del grupo que consiste en CR_{11} y N;
X se selecciona del grupo que consiste en CR_{12} y N;
Y se selecciona del grupo que consiste en CR_{13} y N;
Z se selecciona del grupo que consiste en $CR_{14}R_{15}$ y NR_{16};
R_1 se selecciona del grupo que consiste en hidrógeno, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, alquil carbonilo (C_{1-10}), cicloalquil(C_{3-12}) carbonilo (C_{1-5}), heterocicloalquil(C_{3-12}) carbonilo (C_{1-10}), arilcarbonilo (C_{1-10}), heteroaril(C_{1-10}) carbonilo (C_{1-5}), bicicloaril (C_{9-12})carbonilo (C_{1-5}), heterobicicloaril (C_{8-12})carbonilo (C_{1-5}), amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_1 tiene la fórmula



R_2 es hidrógeno o un sustituyente convertible *in vivo* a hidrógeno;
R_3 se selecciona del grupo que consiste en hidrógeno, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido, o R_3 está ausente cuando el nitrógeno al que está unido forma parte de un doble enlace;
R_4 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, 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}), oxaalquilo (C_{1-10}), oxoalquilo (C_{1-10}), iminoalquilo (C_{1-10}), cicloalquil (C_{3-12})alquilo (C_{1-5}), heterocicloalquil (C_{3-12})alquilo (C_{1-10}), arilalquilo (C_{1-10}), heteroaril (C_{1-10})alquilo (C_{1-5}), bicicloaril (C_{9-12})alquilo (C_{1-5}), heterobicicloaril (C_{8-12})alquilo (C_{1-5}), heteroalquilo (C_{1-10}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{3-12}), bicicloalquilo (C_{9-12}), heterobicicloalquilo (C_{3-12}), arilo (C_{4-12}) heteroarilo (C_{4-10}), bicicloarilo (C_{9-12}) y heterobicicloarilo (C_{4-12}), cada uno sustituido o no sustituido;
R_5 se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi (C_{1-10}), ariloxi (C_{4-12}), heteroariloxi (C_{1-10}), carbonilo, oxicarbonilo, aminocarbonilo, amino, alquil (C_{1-10})amino, sulfonamido, ...

569

Industria y Comercio
SUPERINTENDENCIA

ADMISION

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-030354- -00000-0000
Fecha: 2011-03-11 15:33:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 568

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
- [X] Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- [ ] Dibujos de ser estos pertinentes
- [X] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [X] Incompleta [ ]

DISEÑO INDUSTRIAL [ ] **(Art. 119 Decisión 486/00)**

- [ ] Indicación que se solicita diseño industrial
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño
- [ ] Comprobante de pago de las tasas establecidas

Completa [ ] Incompleta [ ]

ESQUEMA DE TRAZADO [ ] **(Art. 92 Decisión 486/00)**

- [ ] Indicación que se solicita un esquema de trazado
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Representación gráfica de un esquema de trazado
- [ ] Comprobante de pago de las tasas establecidas

Completa [ ] Incompleta [ ]

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
MARGARITA CASTELLANOS ABONDANO
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No.	11 030354
	Solicitud internacional	PCT/US2009/053913
	Fecha inicio fase nacional	14/03/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

07038

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. 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 consideraró 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 (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 29 ABR. 2011
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