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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-036512- -00000-0000

Fecha: 2012-03-01 16:12:28 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 411

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** INHIBIDORES DE JAK2 Y SU USO EN EL TRATAMIENTO DE ENFERMEDADES MIELOPROLIFERATIVAS Y CANCER

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** BRISTOL-MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS

74. **APODERADO** ALVARO CORREA

22. **BOGOTÁ, D. C.,** Marzo 1, 2012

(FORMA P-10)

115198-Imprenta Nacional de Colombia-2011

PETIT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FORMULARIO ÚNICO DE SOLICITUD DE

PCT

ENTRADA EN FASE NACIONAL

(1) **SOLICITUD DE :**

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**	Nombre: **BRISTOL-MYERS SQUIBB COMPANY** Dirección: Route 206 and Province Line Road Princeton, New Jersey 08543-4000, U.S.A. Nacionalidad o Domicilio: Estados Unidos de América Lugar de Constitución: Estados Unidos de América Teléfono: Fax: E-Mail	**IDENTIFICACION** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número _____
(3) **REPRESENTANTE O APODERADO**	Nombre: ALVARO CORREA ORDOÑEZ Dirección: Avenida 82 No. 10-62 Piso 6 Teléfono: 6341500 Fax: 3762211 E-Mail: office.bogota@bakermckenzie.com	**IDENTIFICACION** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número 79.143.366 Usaquén TP 20281
(4) **INVENTOR (ES) (72)**	Nombre: PURANDARE, Ashok V.; GREBINSKI, James W.; HART, Amy; INGHRIM, Jennifer; SCHROEDER, Gretchen; WAN, Honghe Dirección: c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US); c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US); c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US); c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US); c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US). Nacionalidad o Domicilio: Estados unidos de América(Respectivamente)	

(5) **PCT (85)**

Solicitud Internacional No.	PCT/US2010/047621	Fecha	02-09-2010
Publicación Internacional No.	WO 2011/028864	Fecha	10-03-2011

(6) **Título (54)** INHIBIDORES DE JAK2 Y SU USO EN EL TRATAMIENTO DE ENFERMEDADES MIELOPROLIFERATIVAS Y CANCER

(7) **Clasificación Internacional (51)** C07D 471/14; A61K 31/437; A61P 35/00

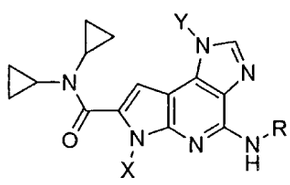
(8) **Prioridad**	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	03-09-2009	61/239,501

(9) **Comprobante de pago No.** 12-003781 – 12-008975 – 12-008927 **Fecha** 13-01-12 y 30-01-12

(10) **ANEXOS**

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

(11) **FIGURA CARATERISTICA**



(I)

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA: _____

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

2012/001

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

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RECIBO DE CAJA

No. 12 - 003781

Bogotá D.C., Enero 13 de 2012 - 16:51:56

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	411692610	12/01/2012	71.175.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	590.000.00	590.000.00
				$590.000.00

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORR

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-036512- -00000-0000

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2012/007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

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SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 008975

Bogotá D.C., Enero 30 de 2012 - 16:34:29

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	450325595	27/01/2012	83.977.500.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICACIONES N.CREACION CORRECCION A SOLICITUD EN TRAMITE / MODOFICA	120.000.00	120.000.00
				$120.000.00

SON: **CIENTO VEINTE MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-036512- -00000-0000

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2012/002

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 008927

Bogotá D.C., Enero 30 de 2012 - 16:34:29

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	450325595	27/01/2012	83.977.500.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	54 INFORMACION DETALLADA DE UN TRAMITE	30.000.00	30.000.00
				$30.000.00

SON: **TREINTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-036512- -00000-0000
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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT X MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional: C07D 471/14; A61K 31/437; A61P 35/00

(71) Solicitante(s): **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es): PURANDARE, Ashok V.; GREBINSKI, James W.; HART, Amy; INGHRIM, Jennifer; SCHROEDER, Gretchen; WAN, Honghe

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	61/239,501	03-09-2009	US

(85) Fecha inicio fase nacional: 03-04-2012

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 02-09-2010
No. de solicitud: PCT/US2010/047621

(87) Publicación internacional
Fecha: 10-03-2011
N° publicación: WO 2011/028864

(54) Titulo: INHIBIDORES DE JAK2 Y SU USO EN EL TRATAMIENTO DE ENFERMEDADES MIELOPROLIFERATIVAS Y CANCER

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

SUPERINTENDENCIA PATENTE DE INVENCION ____ PCT X MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

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(72) Inventor(es): PURANDARE, Ashok V.; GREBINSKI, James W.; HART, Amy; INGHRIM, Jennifer; SCHROEDER, Gretchen; WAN, Honghe

(74) Apoderado: ALVARO CORREA ORDOÑEZ

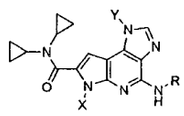
(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	61/239,501	03-09-2009	US

(85) Fecha límite inicio fase nacional: 03-04-2012
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud 02-09-2010
No. de solicitud: PCT/US2010/047621

(87) Publicación internacional:
Fecha: 10-03-2011
No. Publicación: WO 2011/028864

(54) Titulo: INHIBIDORES DE JAK2 Y SU USO EN EL TRATAMIENTO DE ENFERMEDADES MIELOPROLIFERATIVAS Y CANCER

(57)Resumen: La presente invención se refiere a compuestos de fórmula I



(I)

y sales farmacéuticamente aceptables de los mismos. Los compuestos de fórmula I inhiben la actividad tirosina cinasa de JAK2, lo que los hace útiles como agentes antiproliferativos en el tratamiento del cáncer y de otras enfermedades.

CONTINUA AL RESPALDO ...

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SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) ***No.*** 61/239,501 32) ***Fecha*** 03-09-2009 (33) ***País*** US

(51) Int Cl: C07D 471/14; A61K 31/437; A61P 35/00

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

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(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(85) Fecha limite inicio fase nacional: 03-04-2012

(86) Datos relativos a la presentación de la solicitud PCT

Fecha de presentación de la solicitud: 02-09-2010

No. de solicitud PCT/US2010/047621

(87) Publicación internacional

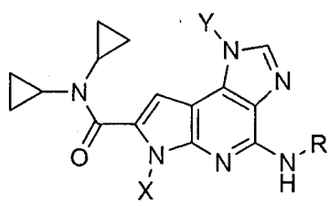
Fecha: 10-03-2011

N° publicación: WO 2011/028864

(54) Titulo: INHIBIDORES DE JAK2 Y SU USO EN EL TRATAMIENTO DE ENFERMEDADES MIELOPROLIFERATIVAS Y CANCER

RESUMEN:

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(I)

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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61/239,501 3 September 2009 (03.09.2009) US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PURANDARE, Ashok V.** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **GREBINSKI, James W.** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **HART, Amy** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **INGHRIM, Jennifer** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **SCHROEDER, Gretchen** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **WAN, Honghe** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US).

(74) Agents: **KORSEN, Elliott** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (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, TH, 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, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, 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, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

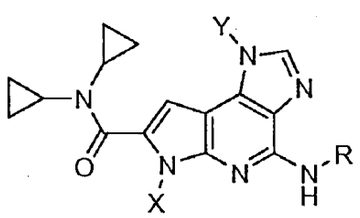
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: JAK2 INHIBITORS AND THEIR USE FOR THE TREATMENT OF MYELOPROLIFERATIVE DISEASES AND CANCER



(I)

(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof. The formula (I) compounds inhibit tyrosine kinase activity of JAK2, thereby making them useful as antiproliferative agents for the treatment of cancer and other diseases.

WO 2011/028864 A1

JAK2 INHIBITORS AND THEIR USE FOR THE TREATMENT OF MYELOPROLIFERATIVE DISEASES AND CANCER

FIELD OF THE INVENTION

[0001] This invention relates to novel compounds that are useful as anti-cancer/ antiproliferative agents. This invention also relates to a method of using the compounds in the treatment of proliferative diseases, such as cancer, and to pharmaceutical compositions containing the compounds.

BACKGROUND OF THE INVENTION

[0002] Efforts to identify new therapeutic approaches to *Ph(-)* myeloproliferative disease have been bolstered by the observations of constitutive activation of the JAK-Stat signaling pathway MPD patients. In particular, a single valine to phenyalanine mutation at residue 617 (JAK2-V617F) in JAK2 has been observed in the majority of PV (95%), ET (50-60%) and PMF (50-60%) patients (Table 2, Kralovics et al., 2005; Baxter et al., 2005; Tefferi et al., 2005). The V617F mutation resides in the region of the *JAK2* gene encoding the pseudokinase domain which is thought to function as an autoinhibitory domain to regulate JAK2 tyrosine kinase activity. Mutations in exon 12 of JAK2 which also result in constitutive JAK2 kinase activity are also observed with a lesser frequency (<5% in PV and ET) and are mutually exclusive with JAK2V617F lesions (Pardanari et al., 2007; Scott et al., 2007). JAK2 is a member of a non-receptor tyrosine kinase family that also includes JAK1, Tyk2 and JAK3 and function as mediators of cytokine receptor signaling (for review see Murray, 2007). Upon cytokine binding to its cognate receptor, receptor-bound JAK family members are activated and phosphorylate a STAT, a latent transcription factor, which upon JAK-mediated phosphorylation undergoes dimerization and translocation to the nucleus to regulate gene expression. Genetic and biochemical studies have established distinct combinations of engagement of a JAK family member with an individual cytokine receptor. For instance, erythropoietin (EPO), thrombopoietin (TPO) and granuolocyte colony stimulating factor (GM-CSF) receptor engagement results in the predominant activation of JAK2 to mediate downstream signaling. Consistent with the patho-physiology of MPD associated with the JAK2-V617F

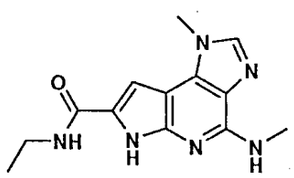
mutation, these cytokines promote the differentiation and expansion of the cell types underlying PV, ET and PMF, respectively. Unlike other genetic activation events, expression of JAK2-V617F is not sufficient to promote transformation in cell based model systems and has been shown to require the co-expression of the type I cytokine receptors, highlighting an important functional co-dependence of the JAK-cytokine receptor interaction (Lu et al., 2005). Interestingly, activating mutations in the TPO receptor (MPL, tryptophan to leucine substitution at residue 515) have been identified in MPD patients afflicted with JAK2-V617F *negative* PMF and ET (5% and 1%, respectively) resulting in constitutive JAK2-Stat activation (Pikman et al., 2006). These observations indicate that JAK-Stat signal transduction can be activated through mutation in MPD at multiple points in the pathway in a mutually exclusive manner and suggest the possible presence of additional pathway mutations in JAK2 – V617F and MPL-W515L negative MPD.

[0003] Important validation of JAK2 signaling as a driver of *Ph(-)* MPD emerged from rodent models where JAK2-V617F mutant signaling was reconstituted in the hematopoietic stem cell compartment. Several laboratories demonstrated that viral transduction of JAK2-V617F into mouse bone marrow and subsequent re-implantation into recipient mice reconstituted several aspects human MPD (Wernig et al. 2006, Lacout et al., 2006, Bumm et al., 2006, Zaeleskas et al., 2006). These features included elevated hematocrit, splenomegaly from extramedullary hematopoiesis, granulocytosis and bone marrow fibrosis all which are also manifested in polycythemia vera. Interestingly, unlike the human condition, thrombocytosis was not observed in these murine models and was suggested to be attributable to secondary genetic events that contribute to platelet expansion (Wernig et al., 2006). Similar reconstitution of the TPO receptor mutation (MPL-W515L) in rodent bone marrow resulted in a myeloproliferative disease with a more rapid onset than JAK2-V617F animals that was reminiscent of primary myelofribosis including splenomegaly, hepatomegaly, and reticulin fibrosis of bone marrow (Pikman et al., 2006). Also unlike the JAK2-V617F model, mice expressing MPL-W515L displayed dramatic thrombocytosis perhaps indicating a more dominant function of the receptor activation compared to JAK2-V617 in the expansion of this lineage. Nonetheless,

these observations collectively underscore the role of both MPL-W515L and JAK2-V617F as driver mutations underlying the progression of human MPD.

[0004] A key question to the genetic basis of MPD is the role of additional genetic events that contribute to disease progression beyond JAK2 and MPL. Several lines of evidence suggest additional genetic alterations in MPD disease progression. In fact, mitotic recombination occurs frequently in MPD patients to generate two JAK2-V617F alleles indicating a selection for cell clones homozygous for the mutated kinase (Levine et al., 2005). In this regard it will be important to develop conditional JAK2-V617F knock-in animals and to determine the phenotypic consequences of the homozygous versus heterozygous JAK2-V617F burden. Additionally, there is evidence for an inherited germline allele that precedes and predisposes patients to acquire JAK2-V617F (Goerttler et al., 2005; Levine et al., 2006) as well as loss of chromosomal region 20q in some MPD patients. Although MPD conversion AML is observed clinically at moderate levels and activating JAK chromosomal translocations are observed in leukemia, epidemiological data suggest that it is questionable that JAK2-V617F is a genetic driver in this context suggesting additional genetic alterations are required for full leukemic transformation (Theocharides et al., 2007). These observations notwithstanding, JAK2 inhibition with small molecule inhibitors is sufficient to modulate disease progression in pre-clinical animal models suggesting that JAK2 activation is sufficient for maintaining MPD (Paradani et al., 2007). It will be important to identify these additional genetic alterations and decipher how these genetic changes contribute to the disease progression of PV, ET and PMF in the context of JAK2-V617F and MPL-W515L. It will also be important to implement approaches to identify if other JAK2 pathway components are mutated in MPD patients not associated with the acquisition of JAK2-V617F, JAK2 exon12 or MPL-W515L mutations.

[0005] The patent publication WO2006/122137 discloses coumpounds which are useful as IKK inhibitors. Example No. A171 discloses the compound of the formula

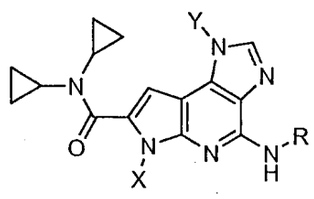


which was found to have weak activity against JAK2 in the assay described hereinbelow.

DETAILED DESCRIPTION OF THE INVENTION

[0006] The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

[0007] In accordance with the present invention, there are disclosed compounds of formula I



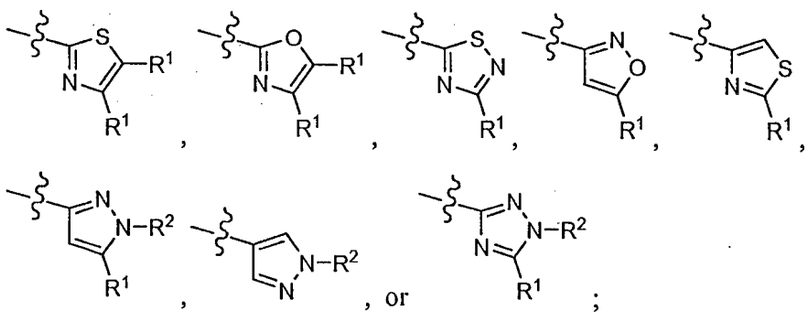
(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

Y is C_{1-4} alkyl;

X is C_{1-4} alkyl;

R is



any of which are optionally fused with a 5 or 6 membered carbocycle or heterocycle having one heteroatom selected from NR^3 or S, said fused carbocycle or heterocycle being optionally substituted with 0-3 R^1.

[0008] R^1 is H, halo, CN, C_{1-6} alkyl substituted with 0-3 R^c, CF_3, $CONR^aR^a$, NR^aR^a, $COOR^b$, SO_2-C_{1-4}alkyl, $C(O)R^d$, cycloalkyl substituted with 0-3 R^e, furanyl, tetrahydropyranyl, or pyridinyl;

R^2 is absent, H, C_{1-6} alkyl substituted with 0-3 R^c, $C(O)O-C_{1-4}$alkyl, SO_2-C_{1-4}alkyl, cycloalkyl substituted with 0-3 R^e, or tetrahydropyranyl;

R^3 is absent, H, or $C(O)O-C_{1-4}$alkyl;

R^a is H, C_{1-6} alkyl substituted with 0-3 R^e, C_{3-6} cycloalkyl substituted with 0-3 R^e, tetrahydropyranyl, or dioxotetrahydrothiophenyl;

R^b is H or C_{1-6} alkyl;

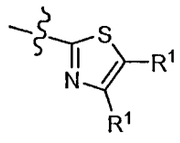
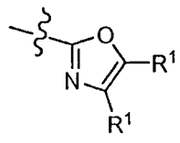
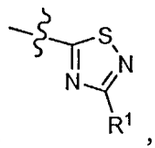
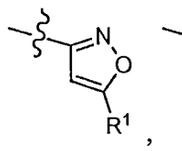
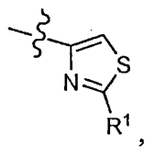
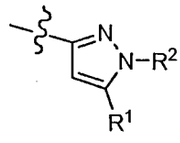
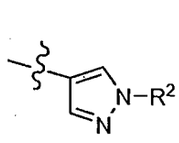
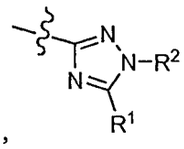
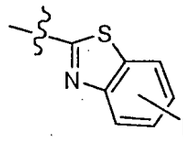
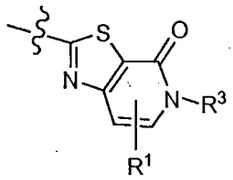
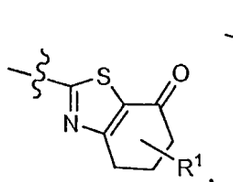
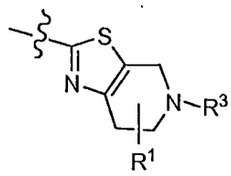
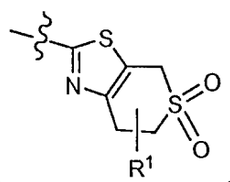
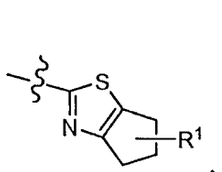
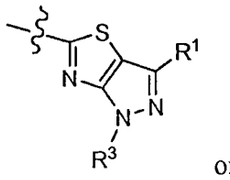
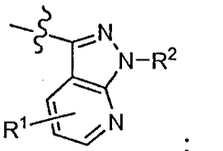
R^c is H, halo, CN, OH, $O-C_{1-4}$alkyl, $O-C_{1-4}$alkyl-$O-C_{1-4}$alkyl, NH_2, $N(C_{1-4}$ alkyl$)_2$, $C(O)N(C_{1-4}$alkyl$)_2$, SO_2-C_{1-4}alkyl, or morpholinyl or piperazinyl, either of which are optionally substituted with 0-1 C_{1-4}alkyl;

R^d is C_{1-6} alkyl, or azeridinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, dioxidothiomorpholinyl or tetrahydropyranyl, any of which are substituted with 0-2 R^e; and

R^e is H, halo, CN, C_{1-4} alkyl, OH, $O-C_{1-4}$alkyl, SO_2-C_{1-4}alkyl, $NHC(O)-C_{1-4}$alkyl, morpholinyl, $OC(O)-C_{1-4}$alkyl, $C(O)N(C_{1-4}$alkyl$)_2$, or $O-C_{1-4}$alkyl-$O-C_{1-4}$alkyl.

[0009] In another embodiment are compounds of Formula (I), wherein:

R is


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or

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any of which are optionally substituted with 0-3 R^1.

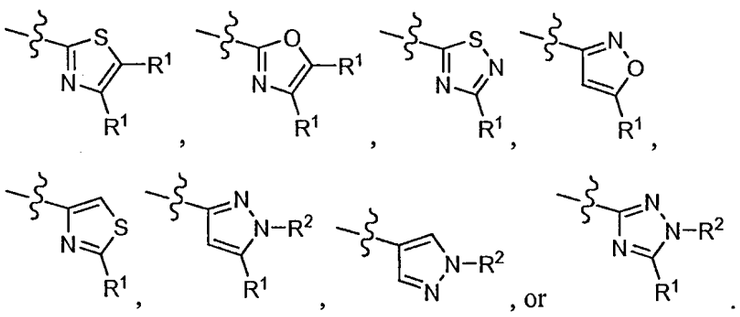
[0010] In another embodiment are compounds of Formula (I), wherein:

Y is methyl; and

X is ethyl.

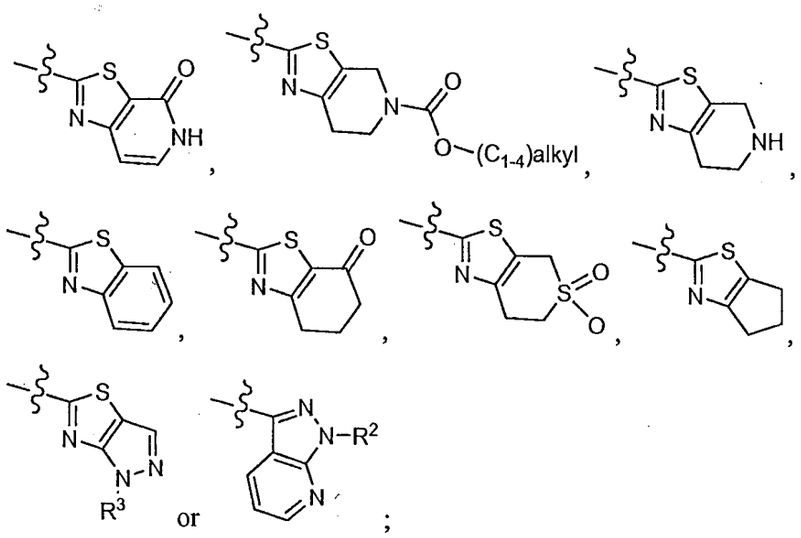
[0011] In another embodiment are compounds of Formula (I), wherein:

R is



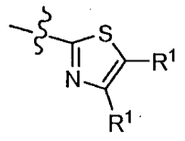
[0012] In another embodiment are compounds of Formula (I), wherein:

R is



any of which are optionally substituted with 0-2 R^1

[0013] In another embodiment are compounds of Formula (I), wherein

R is  ;

R^1 is H, halo, CN, C_{1-6} alkyl substituted with 0-3 R^c, CF_3, $CONR^aR^a$, $COOR^b$, SO_2-C_{1-4}alkyl, $C(O)R^d$, cycloalkyl substituted with 0-3 R^e, or pyridinyl;

R^a is H, C_{1-6} alkyl substituted with 0-3 R^e, C_{3-6} cycloalkyl substituted with 0-3 R^e, tetrahydropyranyl or dioxotetrahydrothiophenyl;

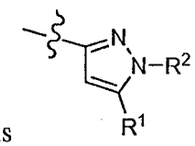
R^b is H or C_{1-6} alkyl;

R^c is H, halo, OH, O-C_{1-4}alkyl, SO_2-C_{1-4}alkyl or morpholinyl;

R^d is C_{1-6} alkyl, or azetidinyl, pyrrolidinyl, morpholinyl, piperazinyl or dioxidothiomorpholinyl, any of which are substituted with 0-2 R^e;

R^e is H, halo, CN, OH, O-C_{1-4}alkyl, SO_2-C_{1-4}alkyl, NHC(O)-C_{1-4}alkyl or morpholinyl.

[0014] In another embodiment are compounds of Formula (I), wherein:

R is  ;

R^1 is H, halo, C_{1-6} alkyl substituted with 0-3 R^c, CF_3, $CONR^aR^a$, $COOR^b$, $C(O)R^d$, cycloalkyl substituted with 0-3 R^e or furanyl;

R^2 is H, C_{1-6} alkyl substituted with 0-3 R^c, SO_2-C_{1-4}alkyl, cycloalkyl substituted with 0-3 R^e, or tetrahydropyranyl;

R^a is H, or C_{1-6} alkyl substituted with 0-3 R^e;

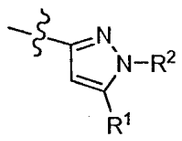
R^b is H or C_{1-6} alkyl;

R^c is H, halo, CN, OH, O-C_{1-4}alkyl, O-C_{1-4}alkyl-O-C_{1-4}alkyl, NH_2, N(C_{1-4} alkyl)$_2$, C(O)N(C_{1-4}alkyl)$_2$, SO_2-C_{1-4}alkyl, or morpholinyl or piperazinyl, either of which are optionally substituted with 0-1 C_{1-4}alkyl;

R^d is C_{1-6} alkyl, or morpholinyl, piperazinyl or dioxidothiomorpholinyl, any of which are substituted with 0-2 R^e; and

R^c is H, C_{1-4} alkyl, CN, OH, NHC(O)-C_{1-4}alkyl or morpholinyl.

[0015] In another embodiment are compounds of Formula (I), wherein:

R is  ;

R^1 is C_{1-6} alkyl substituted with 0-3 R^c; and

R^2 is C_{1-6} alkyl.

[0016] In another embodiment are compounds of Formula (I), wherein the compound of formula (I) is selected from the exemplified compounds.

[0017] In another embodiment the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and one or more of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0018] In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula I or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0019] In another embodiment, the present invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof.

[0020] In another embodiment, the present invention provides a method for treating proliferative disorders and/or cancer comprising administering to a patient in need of such treatment a therapeutically effective amount of one or more of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof, in combination with one or more other anti-cancer agent, or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof.

[0021] In another embodiment, the present invention provides a method for treating proliferative disorders and/or cancer comprising administering to a patient in need of such treatment a therapeutically effective amount of one or more of the compounds of the

present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof.

[0022] In another embodiment, the present invention provides a method of treating a patient in need of proliferative disorder and/or cancer treatment, comprising administering a compound of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug form thereof in an amount effective to treat the proliferative disorder and/or cancer.

[0023] In another embodiment, the present invention provides a method of treating myeloproliferative diseases, such as polycythemia vera, essential thrombocytopenia and primary myelofibrosis, solid tumors of the pancreas, prostate, lung, head and neck, breast, colon, ovary, gastric cancer as well as other tumor types including multiple myeloma, melanoma, neuroblastoma, glioblastoma, systemic mastocytosis,and hematological malignancies such as acute myelogenous leukemia (including refractory acute myeloid leukemia) and acute lymphoid leukemia.

[0024] In another embodiment, the present invention provides a novel method, comprising administering a compound of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug form thereof in an amount effective to treat a proliferative disorder and/or cancer.

[0025] In another embodiment, the present invention provides a method for treating proliferative disorders and/or cancer comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I) or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof, in combination with one or more other anti-cancer agent or antiproliferative agent and/or another agent, or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof.

[0026] In another embodiment, the present invention provides a method for treating proliferative disorders and/or cancer comprising administering to a patient in need of such treatment a therapeutically effective amount of one or more of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof, in combination with one or more other anti-cancer agent, or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof.

[0027] In another embodiment, the present invention provides a compound of the present invention for use in therapy.

[0028] In another embodiment, the present invention provides a compound of the present invention for use in therapy for treating a proliferative disorder and/or cancer.

[0029] In another embodiment, the present invention also provides the use of a compound of formula I of the present invention for the manufacture of a medicament for the treatment of a proliferative disorder and/or cancer.

[0030] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects and/or embodiments of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is its own independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

DEFINITIONS

[0031] The following are definitions of terms that may be used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

[0032] Compounds of this invention may have one or more asymmetric centers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms of compounds of the present invention are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and

diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

[0033] The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N).

[0034] When any variable (e.g., R^3) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^3, then said group may optionally be substituted with up to two R^3 groups and R^3 at each occurrence is selected independently from the definition of R^3. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0035] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0036] In cases wherein there are nitrogen atoms (e.g., amines) on compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

[0037] As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "$C_{1\text{-}10}$ alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl groups can be unsubstituted or

substituted so that one or more of its hydrogens are replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl), and the like.

[0038] "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more double carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

[0039] "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more triple carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

[0040] "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

[0041] The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. C_{3-10} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified,

are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and indanyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[0042] The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, biphenyl and diphenyl groups, each of which may be substituted.

[0043] The term "substituted aryl" refers to an aryl group substituted by, for example, one to four substituents such as alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by hydroxy, halo, alkyl, alkoxy, alkenyl, alkynyl, aryl or arylalkyl.

[0044] The term "heteroaryl" refers to an optionally substituted, aromatic group for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom and at least one carbon atom-containing ring, for example, pyridine, tetrazole, indazole.

[0045] As used herein, the term "heterocycle", "heterocyclyl", "heterocyclic system" or "heterocyclic group" is intended to mean a stable 5, 6, or 7- membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, 13, or 14-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or fully unsaturated, and which consists of carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., N→O and $S(O)_p$). The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The

heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

[0046] Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[0047] Preferred 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl,

oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

[0048] Preferred 5 to 6 membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[0049] In another embodiment, heterocycles include, but are not limited to, pyridyl, pyridinyl, isoxazyl, isoquinolinyl, thienyl, pyrazolyl, furanyl, pyrrolyl, thiazolyl, imidazolyl, pyrazinyl, thiadiazolyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, oxadiazolyl, indanonyl, piperazinyl, pyranyl, or pyrrolyl

[0050] Also included are smaller heterocycles, such as, epoxides and aziridines.

[0051] As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, benzodioxane, and the like. Heteroaryl groups can be substituted or unsubstituted. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., N→O and $S(O)_p$). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges

include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[0052] The term "carbocyclic ring" or "carbocycle" refers to stable, saturated, partially saturated or unsaturated, mono or bicyclic hydrocarbon rings that contain 3-12 atoms. Particularly, this includes a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, dihydroindenyl and tetrahydronaphthyl. The term "optionally substituted" as it refers to "carbocyclic ring" or "carbocycle" herein indicates that the carbocyclic ring may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups.

[0053] The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

[0054] The compounds of formula I may exist as a free form (with no ionization) or may form salts which are also within the scope of this invention. Pharmaceutically acceptable (i.e. non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolating or purifying the compounds of this invention.

[0055] The compounds of formula I may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, tributylamine, pyridine and amino acids such as arginine, lysine and the like. Such salts can be formed as known to those skilled in the art.

[0056] The compounds for formula I may form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrogen chloride, hydrogen

bromide, methanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, oxalic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others (e.g., nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates and the like). Such salts can be formed as known to those skilled in the art.

[0057] In addition, zwitterions ("inner salts") may be formed.

[0058] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

[0059] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include 13C and 14C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

[0060] Compounds of the formula I may also have prodrug forms. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent

compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

[0061] Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, Vol. 112, pp. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) *A Textbook of Drug Design and Development*, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991); and

c) H. Bundgaard, *Advanced Drug Delivery Reviews*, 8, 1-38 (1992).

[0062] It should further be understood that solvates (e.g., hydrates) of the compounds of formula I are also with the scope of the present invention. Methods of solvation are generally known in the art.

[0063] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that the presently recited compounds do not contain a N-halo, $S(O)_2H$, or S(O)H group.

[0064] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

[0065] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination. "Therapeutically effective amount" is also intended to include an amount of the combination of compounds which is effective for the treatment of disease.

[0066] The present invention further includes compositions comprising one or more compounds of the present invention and a pharmaceutically acceptable carrier.

[0067] A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference in its entirety.

UTILITY

[0068] The present invention is based on the discovery that certain compounds are inhibitors of protein kinases. More specifically, compounds such as those described in this invention inhibit the protein tyrosine kinase activity of members of the JAK family of receptors , These inhibitors will be useful in the treatment of proliferative diseases that are dependent on signaling by one or more of these receptors. Such diseases include myeloproliferative diseases, solid tumors of the pancreatic, prostate, lung, head and neck, breast, colon, ovary, as well as other tumor types including multiple myeloma, melanoma, neuroblastoma, glioblastoma and hematological malignancies such as acute myelogenous leukemia.

[0069] The invention also relates to a pharmaceutical composition of compound of formula I, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier in the treatment of hyperproliferative disorder in mammal. In particular, said

pharmaceutical composition is expected to inhibit the growth and/or metastasis of those primary and recurrent solid tumors which are associated with Flt-3 (Fms-like kinase-3), JAK2, JAK3, and JAK1, especially those tumors which are significantly dependent on JAK2, for their growth and spread, including for example, cancers of the blood, thyroid, breast, colon, pancreas, or a variety of tumor types including multiple myeloma, melanoma, neuroblastoma and glioblastoma. In addition to JAK2 activity, inhibitory activity against JAK3/JAK1 or TYK2 may be useful in the treatment of certain cancers having an inflammatory component.

[0070] Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiproliferative effect in a warm-blooded animal such as a human being.

[0071] According to a further feature of the invention there is provided a method for producing an antiproliferative effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined herein before.

[0072] By virtue of their ability to inhibit Flt-3, JAK2, and JAK3, kinases, compounds of the present invention can be used for the treatment of proliferative diseases, including cancer.

[0073] Thus, the present invention provides methods for the treatment of a variety of cancers, including, but not limited to, the following:

carcinoma including that of the bladder (including accelerated and metastatic bladder cancer), breast, colon (including colorectal cancer), kidney, liver, lung (including small and non-small cell lung cancer and lung adenocarcinoma), ovary, prostate, testes, genitourinary tract, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, cervix, thyroid, and skin (including squamous cell carcinoma);

hematopoietic tumors of lymphoid lineage including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, histiocytic lymphoma, and Burkett's lymphoma;

hematopoietic tumors of myeloid lineage including acute and chronic myelogenous leukemias, myelodysplastic syndrome, myeloid leukemia, and promyelocytic leukemia;

tumors of the central and peripheral nervous system including astrocytoma, neuroblastoma, glioma, and schwannomas;

tumors of mesenchymal origin including fibrosarcoma, rhabdomyoscarcoma, and osteosarcoma; and

other tumors including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer, and teratocarcinoma.

[0074] The present invention provides methods for the treatment of leukemia, myeloproliferative diseases such as polycythemia vera, essential thrombocytopenia and myelofibrosis, multiple myeloma, colon cancer, breast cancer, and gastric cancer.

[0075] The anti-proliferative treatment defined herein before may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. The compounds of this invention may also be useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formula I may be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate.

[0076] The term "anti-cancer" agent includes any known agent that is useful for the treatment of cancer including the following: 17α-ethinylestradiol, diethylstilbestrol, testosterone, prednisone, fluoxymesterone, dromostanolone propionate, testolactone, megestrolacetate, methylprednisolone, methyl-testosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, estramustine, medroxyprogesteroneacetate, leuprolide, flutamide, toremifene, Zoladex; matrix metalloproteinase inhibitors; VEGF inhibitors, such as anti-VEGF antibodies (Avastin®) and small molecules such as ZD6474 and SU6668; Vatalanib, BAY-43-9006, SU11248, CP-547632, and CEP-7055; HER 1 and HER 2 inhibitors including anti- HER2

antibodies (Herceptin); EGFR inhibitors including gefitinib, erlotinib, ABX-EGF, EMD72000, 11F8, and cetuximab; Eg5 inhibitors, such as SB-715992, SB-743921, and MKI-833; pan Her inhibitors, such as canertinib, EKB-569, CI-1033, AEE-788, XL-647, mAb 2C4, and GW-572016; kinase inhibitors, e.g. Gleevec® and dasatinib (Sprycel®); Casodex® (bicalutamide, Astra Zeneca), Tamoxifen; MEK-1 kinase inhibitors, MAPK kinase inhibitors, PI3 kinase inhibitors; PDGF inhibitors, such as imatinib; anti-angiogenic and antivascular agents which, by interrupting blood flow to solid tumors, render cancer cells quiescent by depriving them of nutrition; castration, which renders androgen dependent carcinomas non-proliferative; inhibitors of non-receptor and receptor tyrosine kinases; inhibitors of integrin signaling; tubulin acting agents such as vinblastine, vincristine, vinorelbine, vinflunine, paclitaxel , docetaxel, 7-O-methylthiomethylpaclitaxel, 4-desacetyl-4-methylcarbonatepaclitaxel, 3'-*tert*-butyl-3'-N-*tert*-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel, C-4 methyl carbonate paclitaxel, epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7-11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17 oxabicyclo [14.1.0]heptadecane-5,9-dione (ixabepilone), [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4-17-dioxabicyclo[14.1.0]-heptadecane-5,9-dione, and derivatives thereof; CDK inhibitors, antiproliferative cell cycle inhibitors, epidophyllotoxin, etoposide, VM-26; antineoplastic enzymes, e.g., topoisomerase I inhibitors, camptothecin, topotecan, SN-38; procarbazine; mitoxantrone; platinum coordination complexes such as cisplatin, carboplatin and oxaliplatin; biological response modifiers; growth inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; antimetabolites such as purine antagonists (e.g. 6-thioguanine and 6-mercaptopurine; glutamine antagonists, e.g. DON (AT-125; d-oxo-norleucine); ribonucleotide reductase inhibitors; mTOR inhibitors; and haematopoietic growth factors.

[0077] Additional cytotoxic agents include cyclophosphamide, doxorubicin, daunorubicin, mitoxanthrone, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, bicalutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins.

[0078] In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such treatment in addition to the antiproliferative treatment defined herein before may be surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example, linomide, inhibitors of integrin αvβ3 function, angiostatin, razoxane);

(ii) cytostatic agents such as antiestrogens (for example, tamoxifen, toremifene, raloxifene, droloxifene, iodoxifene), progestogens (for example, megestrol acetate), aromatase inhibitors (for example, anastrozole, letrozole, borazole, exemestane), antihormones, antiprogestogens, antiandrogens (for example, flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example, gosereline acetate, leuprolide), inhibitors of testosterone 5α-dihydroreductase (for example, finasteride), farnesyltransferase inhibitors, anti-invasion agents (for example, metalloproteinase inhibitors such as marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example, EGF, FGF, platelet derived growth factor and hepatocyte growth factor, such inhibitors include growth factor antibodies, growth factor receptor antibodies such as Avastin® (bevacizumab) and Erbitux® (cetuximab); tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example, antifolates such as methotrexate, fluoropyrimidines such as 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); Intercalating antitumour antibiotics (for example, anthracyclines such as doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example, cisplatin, carboplatin); alkylating agents (for example, nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide nitrosoureas, thiotepa; antimitotic agents (for example, vinca alkaloids like vincristine, vinorelbine, vinblastine and vinflunine) and taxoids such as Taxol® (paclitaxel), Taxotere® (docetaxel) and newer microtubule agents such as epothilone analogs (ixabepilone), discodermolide analogs, and eleutherobin analogs;

topoisomerase inhibitors (for example, epipodophyllotoxins such as etoposide and teniposide, amsacrine, topotecan, irinotecan); cell cycle inhibitors (for example, flavopyridols); biological response modifiers and proteasome inhibitors such as Velcade® (bortezomib).

[0079] As stated above, the formula I compounds of the present invention are of interest for their antiproliferative effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, psoriasis, and rheumatoid arthritis.

[0080] More specifically, the compounds of formula I are useful in the treatment of a variety of cancers, including (but not limited to) the following:

– carcinoma, including that of the prostate, pancreatic ductal adreno-carcinoma, breast, colon, lung, ovary, pancreas, and thyroid;

– tumors of the central and peripheral nervous system, including neuroblastoma, glioblastoma, and medullobalstoma;

– hematological malignancies such as acute myelogenous leukemia (AML), and

– other tumors, including melanoma and multiple myeloma.

[0081] Due to the key role of kinases in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation and inflammatory bowel disease.

[0082] The compounds of formula I are especially useful in treatment of tumors having a high incidence of tyrosine kinase activity, such as prostate, colon, brain, thyroid and pancreatic tumors. By the administration of a composition (or a combination) of the compounds of this invention, development of tumors in a mammalian host is reduced.

[0083] Compounds of formula I may also be useful in the treatment of other cancerous diseases (such as acute myelogenous leukemia).

[0084] The pharmaceutical compositions of the present invention containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches,

lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

[0085] When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

[0086] If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent or treatment within its approved dosage range. Compounds of formula I may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of formula I may be administered either prior to or after administration of the known anticancer or cytotoxic agent(s).

[0087] The compounds may be administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses.

DOSAGE AND FORMULATION

[0088] The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[0089] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,

and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to treat the cancer.

[0090] By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.001 to 100 mg/kg of body weight per day, and most preferably between about 0.001 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

[0091] Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[0092] The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

[0093] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium

chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

[0094] The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[0095] Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

[0096] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 1000 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.1-95% by weight based on the total weight of the composition.

[0097] Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[0098] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[0099] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols

are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

[00100] Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, a standard reference text in this field.

BIOLOGICAL ASSAYS

JAK2 Tyrosine Kinase Assay

[00101] The assays were performed in V-bottom 384-well plates. The final assay volume was 30 μL prepared from 15 μL additions of enzyme and substrates (fluoresceinated peptide and ATP) and test compounds in assay buffer (100 mM HEPES pH 7.4, 10 mM $MgCl_2$, 25 mM Beta-Glycerolphosphate, 0.015% Brij35 and 4 mM DTT). The reaction was initiated by the combination of JAK2 with substrates and test compounds. The reaction was incubated at room temperature for 60 min. and terminated by adding 45 μL of 35 mM EDTA to each sample. The reaction mixture was analyzed on the Caliper LabChip 3000 by electrophoretic separation of the fluorescent substrate and phosphorylated product. Inhibition data were calculated by comparison to no enzyme control reactions for 100% inhibition and vehicle-only reactions for 0% inhibition. The final concentration of reagents in the assays is ATP, 30 μM; JAK2 fluorescent peptide, 1.5 μM; JAK2, 1 nM; and DMSO, 1.6%. Dose response curves were generated to determine the concentration required inhibiting 50% of kinase activity (IC_{50}). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at eleven concentrations, each in duplicate. IC_{50} values were derived by non-linear regression analysis

JAK3 Tyrosine Kinase Assay

[00102] The assays were performed in V-bottom 384-well plates. The final assay volume was 30 μL prepared from 15 μL additions of enzyme and substrates (fluoresceinated peptide and ATP) and test compounds in assay buffer (100 mM HEPES pH 7.4, 10 mM $MgCl_2$, 25 mM Beta-Glycerolphosphate, 0.015% Brij35 and 4 mM DTT). The reaction was initiated by the combination of JAK3 with substrates and test compounds. The reaction was incubated at room temperature for 60 min. and terminated by adding 45 μL of 35 mM EDTA to each sample. The reaction mixture was analyzed on the Caliper LabChip 3000 by electrophoretic separation of the fluorescent substrate and phosphorylated product. Inhibition data were calculated by comparison to no enzyme control reactions for 100% inhibition and vehicle-only reactions for 0% inhibition. The final concentration of reagents in the assays is ATP, 8 μM; JAK3 fluorescent peptide, 1.5 μM; JAK3, 2.5 nM; and DMSO, 1.6%. Dose response curves were generated to determine the concentration required inhibiting 50% of kinase activity (IC_{50}). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at eleven concentrations, each in duplicate. IC_{50} values were derived by non-linear regression analysis.

Cell Proliferation Inhibition Assay

[00103] Compounds were evaluated for their ability to inhibit cell proliferation, using an assay that measures thymidine incorporation in the DNA of the dividing cell, which is directly correlated with cell numbers. SET-2 cells were plated at 10000 cells/well in 96-well plates and were cultured for 24 h in RPMI-1640 supplemented with 20% fetal bovine serum, before test compounds were added. Compounds were diluted in culture medium such that the final concentration of dimethyl sulfoxide never exceeded 0.1%. Following the addition of compounds, the cells were cultured for an additional 72 h before cell proliferation was determined by measuring DNA synthesis with 3H-thymidine incorporation.

[00104] Compounds described herein were tested in the JAK2 and Cell Proliferation Inhibition assay described above. The following results were obtained.

TABLE 1

Example#	JAK2 (IC50, uM)	SET-2 (IC50, uM)
3	1.50E-03	0.01
4	0.03	2.53
15	1.52E-03	0.49
29	0.01	10.00
33	6.37E-04	0.01
34	1.50E-03	0.24

Example#	JAK2 (IC50, uM)	SET-2 (IC50, uM)
35	5.36E-04	2.85
38	0.04	0.06
49	0.05	3.93
53	1.47E-03	0.10
55	7.48E-04	4.30E-03
61	7.51E-04	

Example#	JAK2 (IC50, uM)	SET-2 (IC50, uM)
70	7.33E-04	0.33
73	1.00E-03	0.06
81	0.01523	0.339
98	0.000695	0.007365
101	7.43E-04	10.00
109	1.52E-03	4.15

Example#	JAK2 (IC50, uM)	SET-2 (IC50, uM)
116	1.49E-03	0.17
125	0.05	1.27

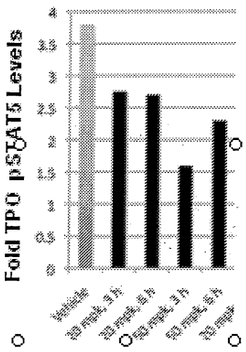
[00105] Compounds described herein have been tested in one or more of the above identified assays and have been found to be active.

C. *In vivo* assay

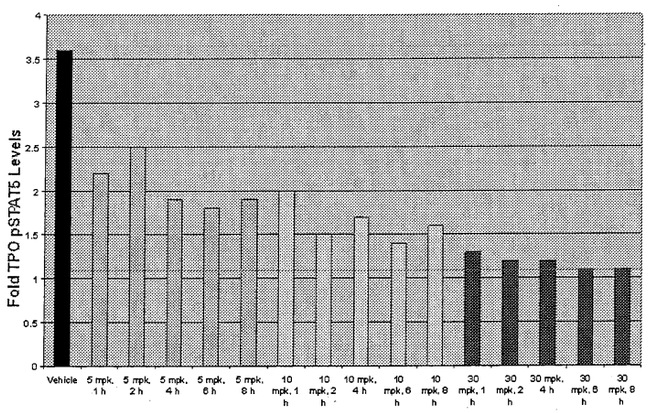
[00106] Compound formulated in appropriate vehicle was administered to mice either as an oral bolus or injected intraperitoneally or subcutaneously to Balb/C mice. Blood samples were collected through orbital bleeding or cardiac puncture at various time points post compound administration. Aliquots (90 μL) of the blood were placed in a 96 well plate. Diluted solution (5ul) of murine thrombopoietin (mTPO; Peprotech) (diluted 1:1000 in dPBS/BSA, 2 μL in 2ml dPBS/BSA was delivered to each well for pathway stimulation. The plates were incubated at 37°C in a water bath for 10 minutes. 1.5ml of fix/lyse solution (from BD Biosciences) was added to each well. The samples were then incubated at 37° C for 15 minutes to ensure lysis of red blood cells (RBCs). The plates were centrifuged at 2000 rpm for 5 minutes and aspirated using the V&P 96 well aspirator. The cells were washed with dPBS, re-centrifuged, re-suspended and transferred to a regular 96 well plate. The cells were washed twice with dPBS followed by addition of CD61 FITC (from eBiosciences) for surface receptor staining for 45 min in the dark at room temperature. The cells were then washed in dPBS and permeabilized for pSTAT5 staining as follows: 200 μL of

permeabilization buffer III (from BD Bioscience) was added and the samples were incubated on ice for 30 minutes and then samples were washed twice with dPBS/1%BSA and re-suspended in 100 µL of dPBS/BSA containing Stat5 (pY695) Alexa 647 antibodies. The samples were incubated at room temperature in the dark for 45 minutes, washed twice and re-suspended in 10 µL of the Stat5 (pY695) Alexa 647 antibodies used were added to the sample. The samples were re-suspended in 200 µL of dPBS/BSA and run on the FACSCanto on sample images were processed using Diva 6 and FlowJo 8.5.3 analysis software.

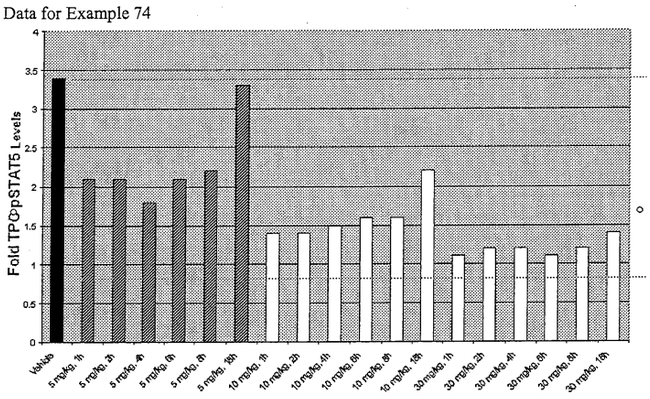
Data for Example 26



In vivo data for Example 73

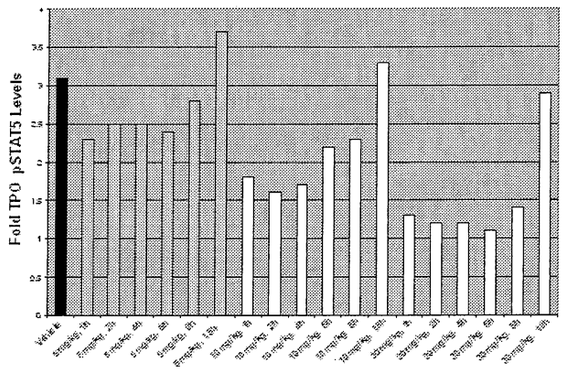


Data for Example 74



00064

Data for Example 76



000477

ABBREVIATIONS

[00107] The following abbreviations may be employed in the methods of preparation and Examples:

h = hours

DCM = dichloromethane

THF = tetrahydrofuran

HPLC = high performance liquid chromatography

DIEA = diisopropylethyl amine

i-PrOH = isopropyl alcohol

TFA = trifluoroacetic acid

min = minutes

DMF = dimethylformamide

EDC = N-(3-Dimethylaminopropyl)N'-ethylcarbodiimide

HOBt = hydroxybenzotriazole

NMP = N-methylpyrolidinone

EtOAc = ethyl acetate

AcOH = acetic acid

BOP reagent = benzotriazole-1-yl-oxy-tris-(dimethylamino)-phasphoniumhexafluorophosphate

brine = saturated aqueous sodium chloride solution

Et_3N = triethylamine

t_R = retention time

rt – room temperature

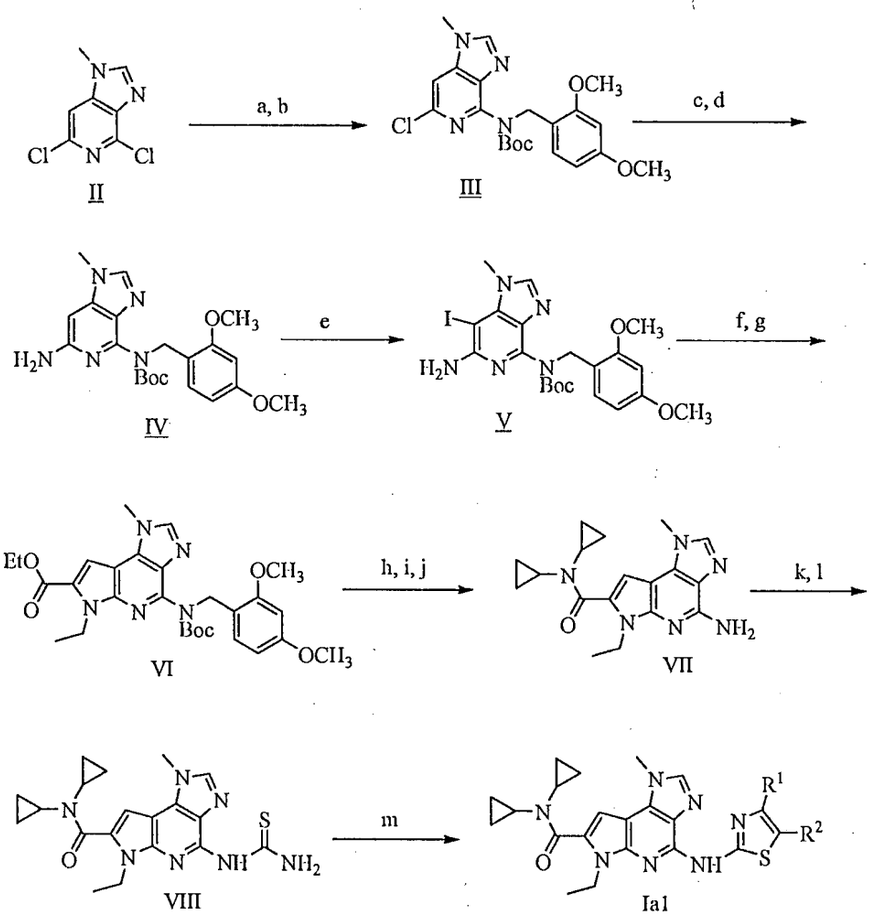
NCS = N-chlorosuccinamide

NBS = N-bromosuccinamide

NIS = N-iodosuccinamide

Methods of Preparation

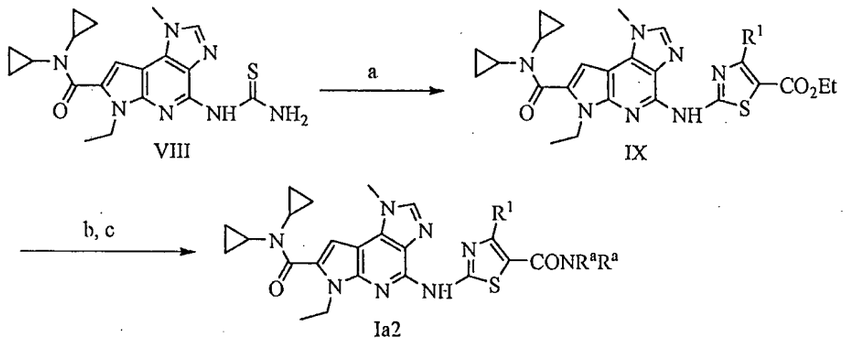
[00108] Compounds of general formula I in which the R group is thiazole (as in Ia1) and R^1 and R^2 groups are CF_3 or alkyl or cycloalkyl or combine to form a saturated carbocyclic or heterocyclic ring or where R2 group is $COOR^b$ could be prepared using the general method depicted in Scheme 1. Dichloro intermediate II (prepared using procedure reported in WO200612237) could be combined with a 2,4-dimethoxybenzyl and the resulting secondary amine is capped with suitable protective group (Boc) (III). The second chlorine atom could be converted into the corresponding amine (IV) through the benzophenone imine intermediate. The amino compound could be halogenated to intermediate V. V could be subjected to transition metal mediated indole ring formation and the resulting indole nitrogen is capped with ethyl iodide to afford VI. Ester hydrolysis followed by amide bond formation and cleavage of protective groups with acid treatment would yield amine VII. Amine VII could be converted into thiourea VIII by first coupling with benzoyl isothiocyanate followed treatment with aqueous base. Formation of thiazole could be achieved by condensation with an α-bromoketone derivative ($R^1CHBrCOR^2$).



a) 2,4-dimethoxybenzylamine, heat; b) NaHMDS, Boc_2O; c) $(Ph)_2$=NH; d) HCl; e) NIS; f) $Pd_2(dba)_3$, ethyl pyruvate; g) EtI, Cs_2CO_3; h) NaOH (aq); i) dicyclopropylamine HCl, HATU, DIPEA; j) TFA; k) Benzoyl isothiocyanate; l) NaOH (aq); m) $R^2CHBrCOR^1$

Scheme 1

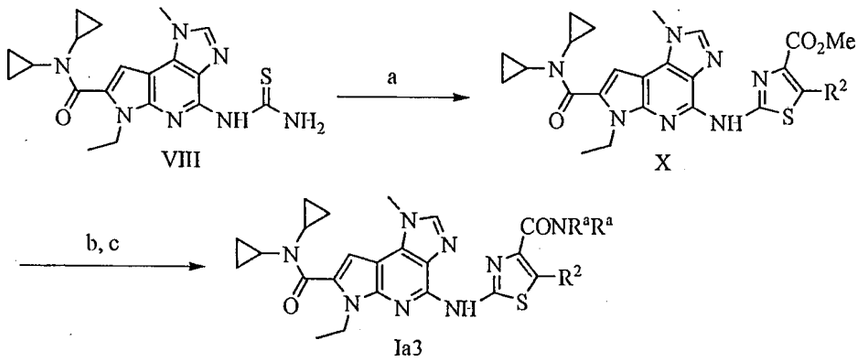
[00109] Compounds of general formula Ia2 in which the R^1 group is $CONR^aR^a$ could be made using Scheme 2. Thiourea intermediate (VIII) could be combined with $EtO_2CCHBrCOR^1$ to afford the thiazole ester (IX). The ester could be hydrolyzed and the acid could be coupled with amine to afford thiazole amide derivative (Ia)



a) $EtO_2CCHBrCOR^1$; b) NaOH (aq); c) HNR^aR^a, HATU, DIPEA

Scheme 2

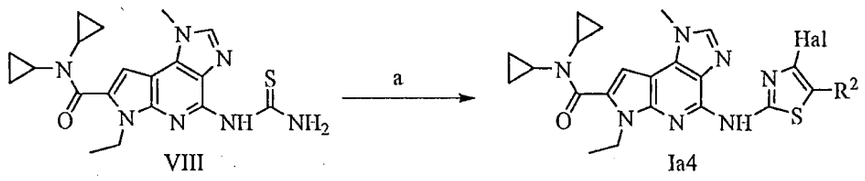
[00110] Similarly, compounds of general formula Ia3 in which the R^1 group is $CONR^aR^a$ could be prepared using the general protocol depicted in Scheme 3.



a) $R^2CHBrCOCO_2Me$; b) NaOH (aq); c) HNR^aR^a, HATU, DIPEA

Scheme 3

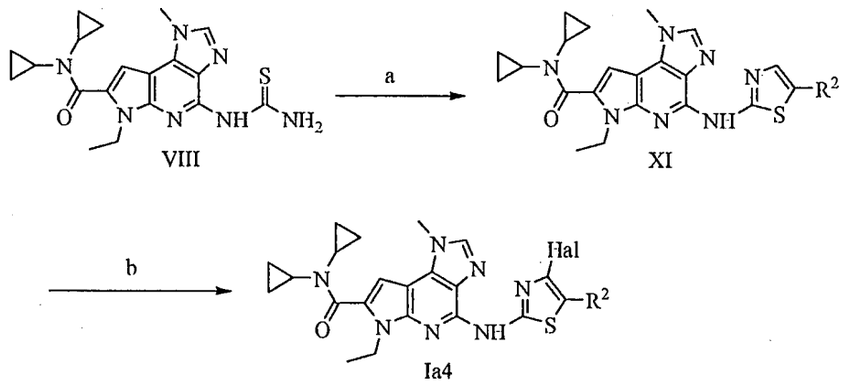
[00111] Compounds of general formula Ia in which R^1 is halogen (Cl, Br or I) could be prepared by condensing an a,a'-dihaloketone as depicted in Scheme 4.



a) $R^2COCH(Hal)_2$

Scheme 4

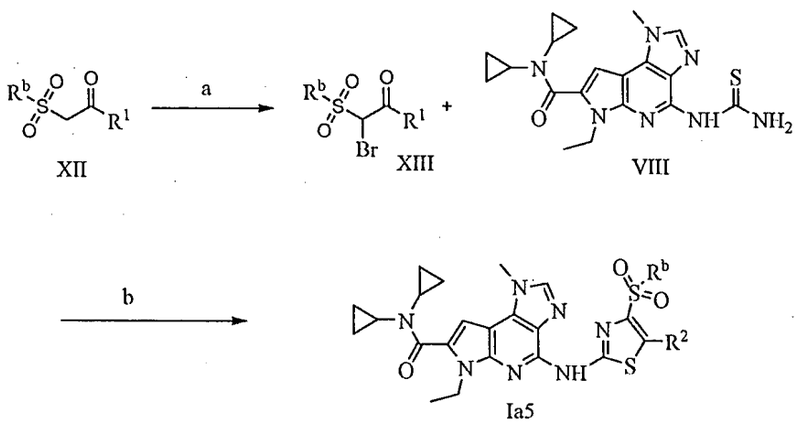
[00112] Alternatively, thiourea derivative VIII could be converted to room temperature into C-5 un-substituted thiazole XI and then directly halogenated using electrophilic halogen source or through metallation followed by quenching with an electrophilic halogenating agent (Scheme 5).



a) $BrCH_2COR^2$; b) Selectfluor or NCS or NBS or NIS or tBuLi followed Selectfluor or NBS or NCS

Scheme 5

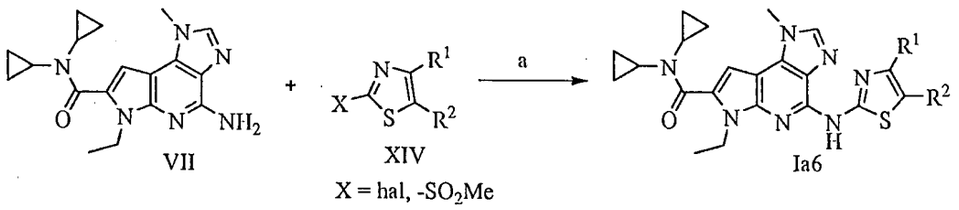
[00113] Compounds of general formula Ia5 in which R^1 is SO_2R^b could be synthesized using the general synthetic approach shown in Scheme 6



a) Br_2-acetic acid; b) EtOH, heat

Scheme 6

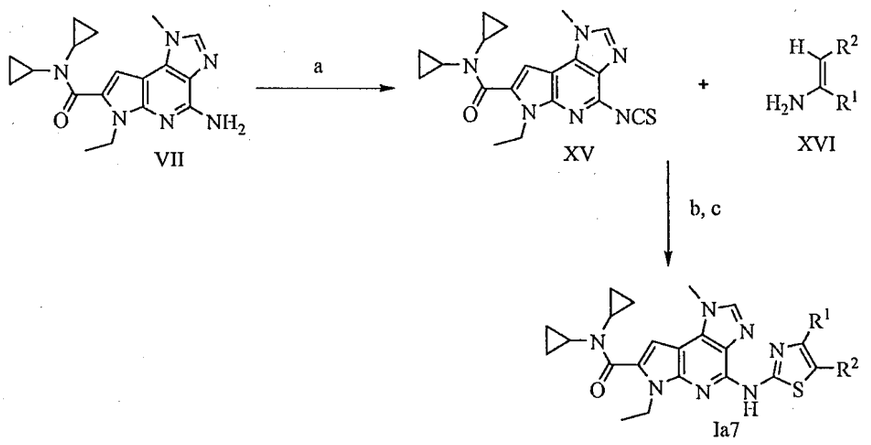
[00114] Compounds with general formula Ia in which R^1 and R^2 combine to form an aromatic or heteroaromatic ring could be prepared using Scheme 7.



a) Pd(0) catalyst, NaOtBu, phosphine ligand, heat

Scheme 7

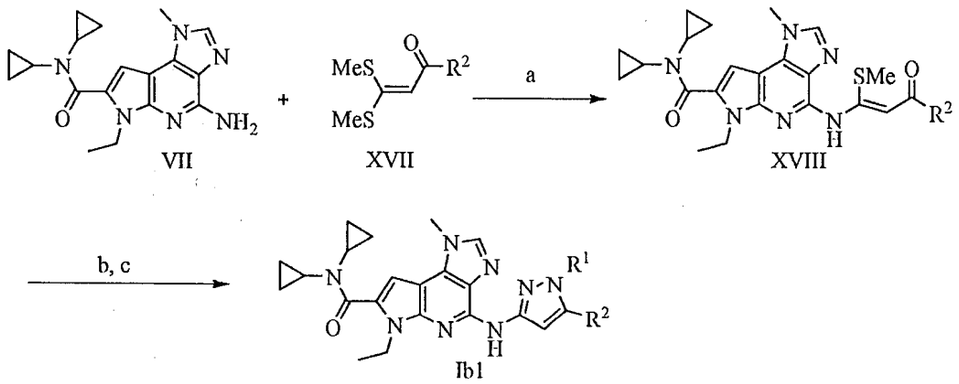
[00115] Alternatively, these compounds could be made by first coupling aniline or heteroaniline (XVI) with the isothiocyanate (XV) followed by oxidative cyclization (Scheme 8).



a) 1,1'-Thiocarbonyldi-2(1H)-pyridone; b) NaH; c) NIS

Scheme 8

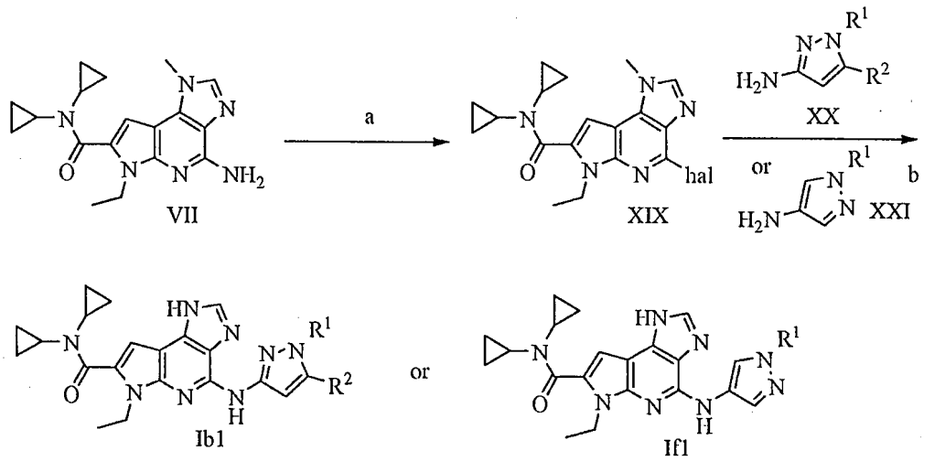
[00116] Compounds of general formula Ib1 could be prepared using the general synthetic approach depicted in Scheme 9. Aniline VII could be combined with γ-dithiomethylketone compound XVII, (prepared using the procedure reported at room temperature in *Synlett,* p 2331 (2008)) under basic condition to afford XVIII. Stepwise condensation of the Boc-protected hydrazine derivative would give the required pyrazole Ib1.



a) NaH, THF; b) $R^1N(Boc)NH_2$, AcOH, 35-40°C; c) HCO_2H or TFA, 60°C

Scheme 9

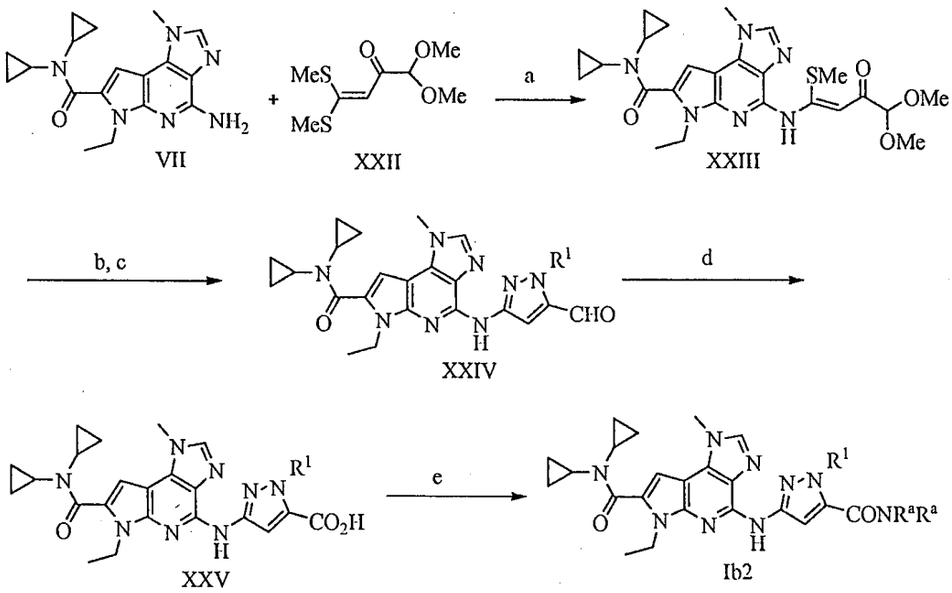
[00117] Compounds of general formula Ib1 or If1 and 1f could also be prepared by coupling C-4 halo derivative (XIX) with an appropriately substituted 2-aminopyrazole derivative (XX) using a transition metal catalyzed reaction (Scheme 10).



a) isoamyl nitrite, CH_2I_2 or isoamyl nitrite, CH_2Br_2; b) $Pd_2(dba)_3$, Xanphos, Cs_2CO_3

Scheme 10

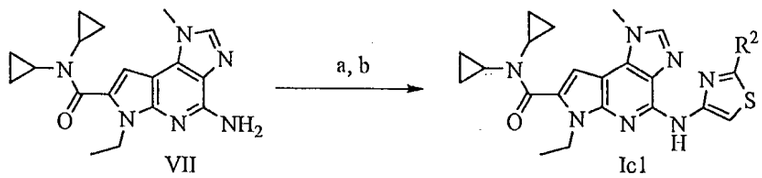
[00118] Compounds of general formula Ib2 in which R^2 group is $CONR^aR^a$ could be synthesized using Scheme 11. Aniline VII could be combined with γ-dithiomethylketone derivative XXII, (prepared using the procedure from *Tetrahedron*, p 2631 (2003)) to afford intermediate XXIII. Stepwise condensation of Boc-protected hydrazine derivative would give the required pyrazole aldehyde XXIV. Aldehyde could be oxidized using oxone or sodium hypochlorite to furnish carboxylic acid XXV. Coupling of acid XXV with amine would give pyrazole amide Ib2.



a) NaH, THF, heat; b) $R^1N(Boc)NH2$, AcOH; c) TFA; d) oxone or sodium hypochlorite; e) HNR^aR^a, HATU, DIPEA

Scheme 11

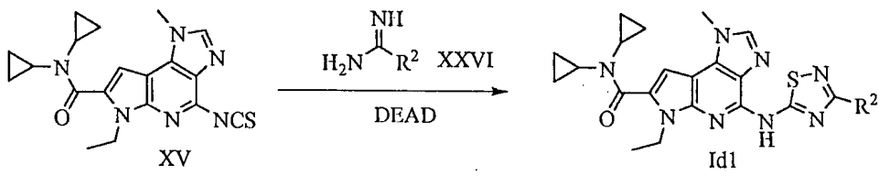
[00119] Compounds of general formula Ic1 could be prepared using the general protocol as shown in Scheme 12. Aniline VII could be coupled with chloroacetyl chloride and the resulting amide could be treated with thioamide (R^2CSNH_2) to furnish thiazole Ic1.



a) chloroacetyl chloride, base; b) R^2CSNH_2

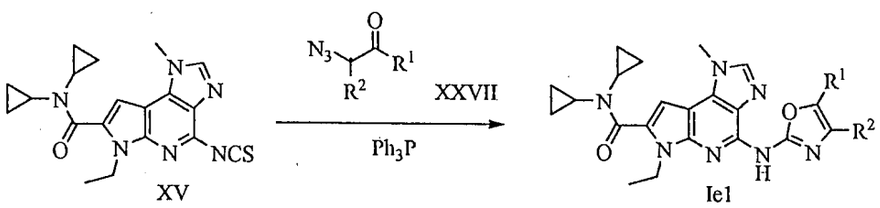
Scheme 12

[00120] Compounds of general formula Id1 could be made as per Scheme 13. Previously described isothiocyanate derivative XV could be combined with amidine XXV under dehydrating reaction conditions to give 1,2,4-thiadiazole (Id1).



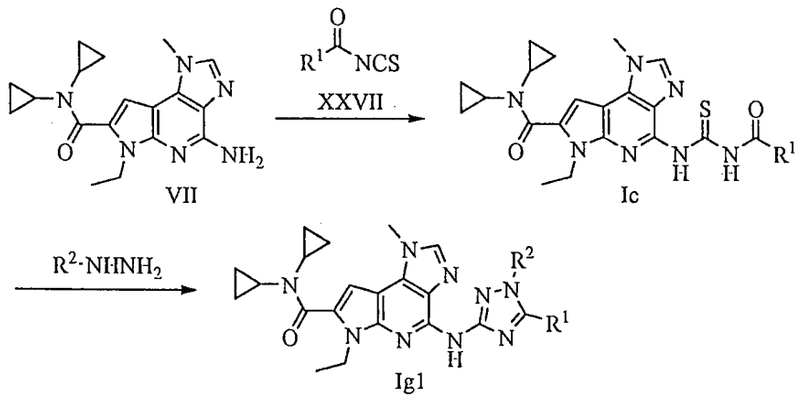
Scheme 13

[00121] Compounds of general formula Ie1 could be prepared using a synthetic approach as shown in Scheme 14. Isothiocyanate XV could be combined with azide XXVI in the presence of phosphine to yield 1,3-oxazole Ie1.



Scheme 14

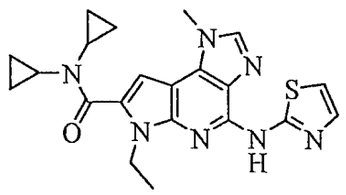
[00122] Compounds of general formula Ig1 could be prepared using a synthetic approach as shown in Scheme 15. Amine VII could be combined with acyl isothiocyanate XXVII. The acylthioureaido could be condensed with hydrazine derivative to yield the 1,2,4-triazol derivative Ig1.



Scheme 15

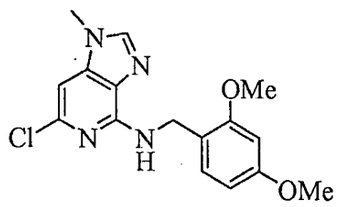
EXAMPLES

Example 1



N,N-dicyclopropyl-6-ethyl-1-methyl-4-(thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

1A Preparation of 6-chloro-*N*-(2,4-dimethoxybenzyl)-1-methyl-1*H*-imidazo[4,5-c] pyridin-4-amine



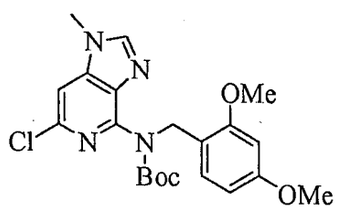
[00123] In a 200 mL round bottom flask, 4,6-dichloro-1-methyl-1*H*-imidazo[4,5-*c*]pyridine (15 g, 74.2 mmol) (prepared as per WO2006122137 example **A1.5**) was dissolved in 2,4-dimethoxybenzylamine (25 mL, 166 mmol). The reaction mixture

was heated to 110 °C for 3 h and cooled to room temperature. Water was added and a tan colored solid precipitated out. Vacuum filtration yielded a tan solid. The solid was washed with ethyl acetate and hexane to yield 6-chloro-*N*-(2,4-dimethoxybenzyl)-1-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (23.459 g, 95 % yield) as a cream colored solid.

[00124] MS (ESI) m/z 333.0 (M+H)

[00125] 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.05 (s, 1 H), 7.17 (t, 1 H, J=6.19 Hz), 7.06 (d, 1 H, J=8.25 Hz), 6.87 (s, 1 H), 6.55 (d, 1 H, J=2.47 Hz), 6.42 (dd, 1 H, J=8.52, 2.47 Hz), 4.54 (d, 2 H, J=5.77 Hz), 3.82 (s, 3 H), 3.74 (s, 3 H), 3.72 (s, 3 H)

1B Preparation of *tert*-butyl 6-chloro-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate

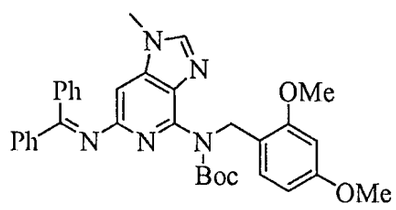


[00126] To a solution of 6-chloro-*N*-(2,4-dimethoxybenzyl)-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-amine (example **1A,** 0.63 g, 1.893 mmol) in tetrahydrofuran (38 mL) cooled to -78 °C, was added NaHMDS (1.0 M THF, 2.366 mL, 2.366 mmol) slowly. After stirring at -78 °C for 30 min, BOC_2O (0.483 mL, 2.082 mmol) was added. The cold bath was removed and the reaction was allowed to warm to rt ON. By HPLC, ~50% conversion was observed. The solution was re-cooled to -78 °C. NaHMDS (1.0 M THF, 2.366 mL, 2.366 mmol) was added and the mixture was stirred 30 min before the addition of BOC_2O (0.483 mL, 2.082 mmol). The cold bath was removed and the reaction warmed to room temperature 5 h. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was washed twice with water, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography using an Isco 40g column eluting with 50 - 100% ethyl acetate/hexane to yield *tert*-butyl 6-chloro-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl(2,4-dimethoxybenzyl) carbamate (0.638 g, 78 % yield) as a foamy white solid.

[00127] MS (ESI) m/z 433.0 (M+H)

[00128] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.91 (s, 1 H), 7.47 (d, 1 H, J=8.31 Hz), 7.19 (s, 1 H), 6.38 (dd, 1 H, J=8.31, 2.52 Hz), 6.32 (d, 1 H, J=2.52 Hz), 5.13 (s, 2 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.59 (s, 3 H), 1.40 (s, 9 H)

1C Preparation of *tert*-butyl 2,4-dimethoxybenzyl(6-(diphenylmethyleneamino)-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl)carbamate

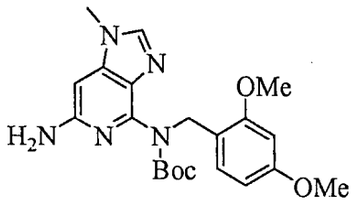


[00129] Anhydrous dioxane (4 mL) was added to a mixture of *tert*-butyl 6-chloro-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate (example **1B,** 0.638 g, 1.474 mmol), benzophenone imine (0.297 mL, 1.769 mmol), $Pd_2(dba)_3$ (0.270 g, 0.295 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.256 g, 0.442 mmol), and cesium carbonate (0.672 g, 2.063 mmol). The reaction mixture was heated to 90 °C overnight. After cooling to rt, solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was washed twice with water, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography using an Isco 40g column eluting with 50-100% ethyl acetate/hexane to provide *tert*-butyl 2,4-dimethoxybenzyl(6-(diphenylmethyleneamino)-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl)carbamate (0.757 g, 89 % yield) as a light yellow solid.

[00130] MS (ESI) m/z 414.0 ($M-CPh_2+2H$)

[00131] 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.16 (s, 1 H), 7.67 (dd, 2 H, J=8.56, 1.51 Hz), 7.44 - 7.60 (m, 3 H), 7.25 (d, 1 H, J=8.31 Hz), 6.96 - 7.11 (m, 4 H), 6.87 (s, 1 H), 6.46 (d, 1 H, J=2.52 Hz), 6.33 (dd, 1 H, J=8.56, 2.27 Hz), 4.52 (s, 2 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 1.25 (s, 9 H)

1D Preparation of *tert*-butyl 6-amino-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate

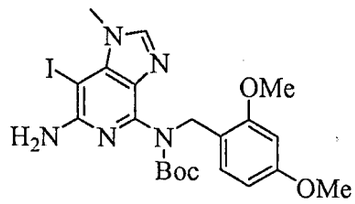


[00132] In a 1000 mL round bottom flask, *tert*-butyl 2,4-dimethoxybenzyl(6-(diphenylmethyleneamino)-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl)carbamate (example **1C,** 9.2 g, 15.93 mmol) was stirred in THF (50 mL). 1 N HCl (33 mL) was added. After 2 min, the reaction was quenched with 1 N NaOH (65 mL) and ethyl acetate (100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was dried under vacuum for 1h and triturated with ether (4x). Isolated *tert*-butyl 6-amino-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl(2,4-dimethoxybenzyl) carbamate (6.587 g, 15.93 mmol, 100 % yield) as a cream solid. Material carried forward with no further purification.

[00133] MS (ESI) m/z 413.0 (M+H)

[00134] 1H NMR (400 MHz, DMSO-d_6) δ ppm 7.93 (s,1 H), 7.44 (d, 1 H, J=8.31 Hz), 6.44 (d, 1 H, J=2.27 Hz), 6.35 (dd, 1 H, J=8.56, 2.27 Hz), 6.25 (s, 1 H), 5.58 (s, 2 H), 4.87 (s, 2 H), 3.67 (s, 6 H), 3.63 (s, 3 H), 1.30 (s, 9 H)

1E Preparation of *tert*-butyl 6-amino-7-iodo-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate



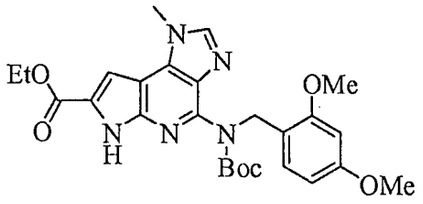
[00135] In a round bottom flask, *tert*-butyl 6-amino-1-methyl-1*H*-imidazo[4,5-c]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate (example **1D,** 7.887 g, 19.08 mmol) was dissolved in MeCN (200 mL) and cooled to 0 °C. *N*-Iodosuccinimide (4.51 g, 20.03 mmol) was dissolved in the remaining MeCN (50 mL) and added dropwise to the reaction mixture over 40 min. The reaction mixture was stirred at 0 °C for an

additional 10 min and was quenched with 2 M sodium hydrogensulfite (125 mL). Stirring and temperature were maintained for 50 min. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography using an Isco 120g column eluting with 20-100% ethyl acetate/CH_2Cl_2 to provide *tert*-butyl 6-amino-7-iodo-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate (8.436 g, 82 % yield) as a pale yellow solid.

[00136] MS (ESI) m/z 539.0 (M)

[00137] 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (s, 1 H), 7.40 (d, 1 H, J=8.06 Hz), 6.43 (d, 1 H, J=2.52 Hz), 6.31 - 6.39 (m, 1 H), 5.73 (s, 2 H), 4.86 (s, 2 H), 3.95 (s, 3 H), 3.67 (s, 3 H), 3.64 (s, 3 H), 1.30 (s, 9 H)

1F Preparation of ethyl 4-(*tert*-butoxycarbonyl(2,4-dimethoxybenzyl)amino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxylate



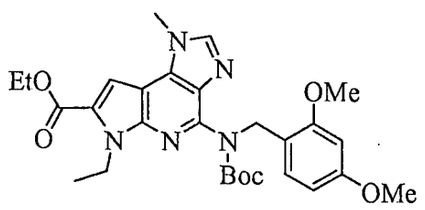
[00138] To a flask charged with *tert*-butyl 6-amino-7-iodo-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate (example **1E**, 3.49 g, 6.47 mmol) in DMA (43.1 mL) was added $Pd_2(dba)_3$ (0.474 g, 0.518 mmol), ethyl pyruvate (7.22 mL, 64.7 mmol), and *N*-methyldicyclohexylamine (2.77 mL, 12.94 mmol). The reaction mixture was sparged with argon for 10 min and heated at 60 °C 6 h. The reaction was complete by LCMS. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and saturated aqueous $NaHCO_3$. The resultant emulsion was vacuum filtered through a pad of Celite and transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with 10% aqueous LiCl solution (2 x). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The brown

residue was purified by flash chromatography using an Isco 120g column eluting with 40-80% ethyl acetate/hexane to yield ethyl 4-(*tert*-butoxycarbonyl(2,4-dimethoxybenzyl)amino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxylate (2.830 g, 86 % yield)

[00139] MS (ESI) m/z 510.0 (M+H)

[00140] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.83 (s, 1 H), 7.57 (d, 1 H, J=8.31 Hz), 7.39 (d, 1 H, J=2.27 Hz), 6.40 (dd, 1 H, J=8.44, 2.39 Hz), 6.32 (d, 1 H, J=2.52 Hz), 5.16 (s, 2 H), 4.43 (q, 2 H, J=7.05 Hz), 4.09 (s, 3 H), 3.74 (s, 3 H), 3.56 (s, 3 H), 1.43 (t, 3 H, J=7.18 Hz), 1.40 (s, 9 H)

1G Preparation of ethyl 4-(*tert*-butoxycarbonyl(2,4-dimethoxybenzyl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxylate

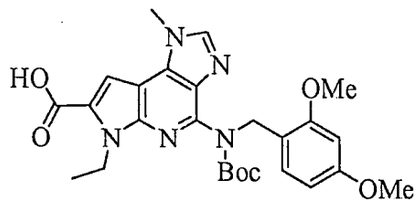


[00141] To a solution of ethyl 4-(*tert*-butoxycarbonyl(2,4-dimethoxybenzyl)amino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxylate (example **1F**, 5.046 g, 9.90 mmol) in DMF (49.5 mL) was added ethyl iodide (1.601 mL, 19.81 mmol) and cesium carbonate (6.45 g, 19.81 mmol). The reaction mixture was heated at 60 °C 60 min and cooled to room temperature. The reaction mixture was diluted with ethyl acetate and vacuum filtered to remove cesium carbonate. Saturated aqueous sodium bicarbonate was added and the aqueous layer was extracted with ethyl acetate (2 x). The combined organic layers were washed with 10% lithium chloride (3 x), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Crude product was carried forward.

[00142] MS (ESI) m/z 538.1 (M+H)

[00143] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.79 (s, 1 H), 7.62 (d, 1 H J=8.28 Hz), 7.43 (s, 1 H), 6.39 (dd, 1 H, J=8.41, 2.38 Hz), 6.32 (d, 1 H, J=2.26 Hz), 5.20 (s, 2 H), 4.79 (q, 2 H, J=7.03 Hz), 4.41 (q, 2 H, J=7.28 Hz), 4.07 (s, 3 H), 3.74 (s, 3 H), 3.61 (s, 3 H), 1.44 (t, 3 H, J=7.15 Hz), 1.41 (s, 9 H), 1.37 (t, 3 H, J=7.03 Hz)

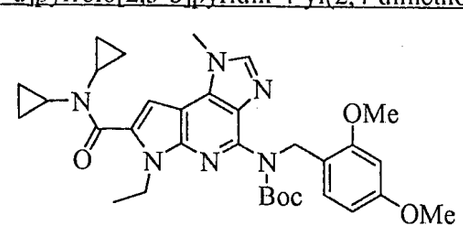
1H Preparation of 4-(*tert*-butoxycarbonyl(2,4-dimethoxybenzyl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxylic acid



[00144] To a solution of ethyl 4-(*tert*-butoxycarbonyl(2,4-dimethoxybenzyl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxylate (example **1G**, 5.32 g, 9.9 mmol) in ethanol (49.5 mL) was added 1 N NaOH aqueous solution (49.5 mL). The reaction mixture was heated at 60 °C 3 h and cooled to rt. Ethanol was removed by concentration *in vacuo*. The residue was acidified with 1 N HCl and the product was collected by vacuum filtration. 4-(*tert*-Butoxycarbonyl(2,4-dimethoxybenzyl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxylic acid (4.3 g, 8.44 mmol, 85 % yield over two steps) was isolated as a white solid after drying on the vacuum.

[00145] MS (ESI) m/z 510.0 (M+H)

1I Preparation of *tert*-butyl 7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate



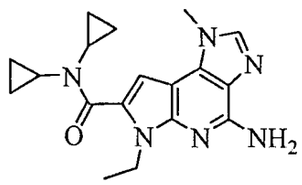
[00146] To a mixture of 4-(*tert*-butoxycarbonyl(2,4-dimethoxybenzyl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxylic acid (example **1H**, 0.89 g, 1.747 mmol) in acetonitrile (17.47 mL) was added dicyclopropylamine hydrochloride (0.303 g, 2.271 mmol), *N*-methylmorpholine (0.499 mL, 4.54 mmol), DMAP (0.021 g, 0.175 mmol), and HATU (0.797 g, 2.096 mmol). The reaction mixture was stirred at rt 5 h and heated to 50 °C for 45 min.

The reaction was cooled to room temperature. Acetonitrile was removed *in vacuo* and the residue was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude solid was purified by flash chromatography using an Isco 80 g column eluting with 1 - 4% MeOH/CH_2Cl_2 to yield *tert*-butyl 7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate (0.8 g, 78 % yield) as an off-white solid.

[00147] MS (ESI) m/z 589.0 (M+H)

[00148] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.78 (s, 1 H), 7.67 (d, 1 H, J=8.28 Hz), 6.85 (s, 1 H), 6.40 (dd, 1 H, J=8.41, 2.38 Hz), 6.33 (d, 1 H, J=2.51 Hz), 5.20 (s, 2 H), 4.58 (q, 2 H, J=7.03 Hz), 4.02 (s, 3 H), 3.74 (s, 3 H), 3.62 (s, 3 H), 2.77 - 2.85 (m, 2 H), 1.42 (s, 9 H), 1.39 (t, 3 H, J=7.40 Hz), 0.80 - 0.89 (m, 4 H), 0.72 - 0.78 (m, 4 H)

1J Preparation of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00149] To a solution of *tert*-butyl 7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-yl(2,4-dimethoxybenzyl)carbamate (example **1I**, 2.66 g, 4.51 mmol) in dichloromethane (33.8 mL) was added TFA (11.28 mL). The reaction mixture was stirred at rt 45 min and was concentrated *in vacuo*. The crude residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (2 x) and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude solid was purfied by flash chromatography using an Isco 40 g column eluting with 4 - 10% MeOH/CH_2Cl_2 to yield 4-amino-*N,N*-

dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (1.2 g, 3.55 mmol, 79 % yield) as a pale yellow solid.

[00150] MS (ESI) m/z 339.2 (M+H)

[00151] 1H NMR (400 MHz, MeOD) δ ppm 7.95 (s, 1 H), 7.15 (s, 1 H), 4.51 (q, 2 H J=7.13 Hz), 4.04 (s, 3 H), 2.89 - 2.98 (m, 2 H), 1.35 (t, 3 H), 0.82 - 0.91 (m, 4 H), 0.70 - 0.81 (m, 4 H)

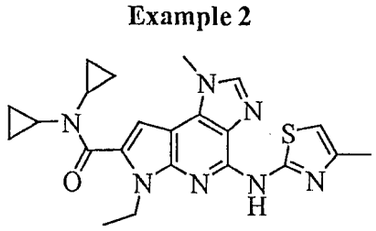
1 Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00152] To a mixture of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J**, 30 mg, 0.089 mmol), 2-bromothiazole (11.98 µL, 0.133 mmol), $Pd_2(dba)_3$ (12.18 mg, 0.013 mmol), BINAP (24.84 mg, 0.040 mmol) and sodium *tert*-butoxide (13.63 mg, 0.142 mmol) was added PhMe (887 µL). The mixture was sparged with argon gas for 5 min and heated to 85 °C for 5.5 h. The reaction mixture was filtered through a plug of Celite and concentrated. The crude residue was purified by preparative HPLC to provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (4 mg, 10.49 % yield) along with some recovered starting material.

[00153] MS (ESI) m/z 423.0 (M+H)

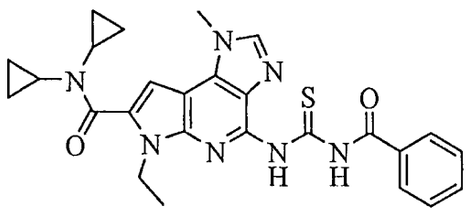
[00154] 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.14 (s, 1H), 7.47 (d, 1H, J = 3.57 Hz), 7.24 (s, 1H), 7.14 (d, 1H, J = 3.57 Hz), 4.63 (q, 2H, J = 6.87 Hz), 4.05 (s, 3H), 2.88 – 2.99 (m, 2H), 1.39 (t, 3H, J = 7.01 Hz), 0.73 – 0.81 (m, 4H), 0.64 – 0.70 (m, 4H)

Example 2



***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-methylthiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

2A Preparation of 4-(3-benzoylthioureido)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

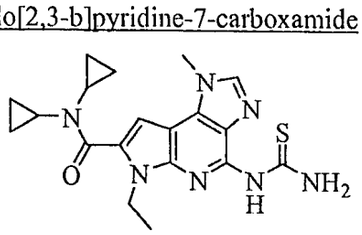


[00155] A solution of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J,** 234 mg, 0.69 mmol) and benzoyl isothiocyanate (0.1 ml, 0.83 mmol) in acetone (3 ml) was stirred at room temperature for 3h. The reaction mixture was cooled to 0°C and water was added. The resulting brown solid was collected by filtration and air-dried to give 4-(3-benzoylthioureido)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (306 mg, 88% yield)

[00156] MS (ESI) rt = 1.86 min, m/z 502 (M+H).

[00157] 1H NMR (400 MHz, DMSO-d6) δ ppm 8.44 (br. s., 1 H) 7.99 - 8.07 (m, 2 H) 7.64 - 7.74 (m, 1 H) 7.58 (t, *J*=7.65 Hz, 2 H) 7.34 (s, 1 H) 4.47 (br. s., 2 H) 4.11 (s, 3 H) 2.90 - 2.99 (m, 2 H) 2.08 (s, 1 H) 1.28 (br. s., 3 H) 0.64 - 0.81 (m, 8 H).

2B Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00158] 4-(3-Benzoylthioureido)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **2A,** 306 mg, 0.61 mmol) and 1N NaOH (10 ml, 10.00 mmol) in 10 ml EtOH were heated at 60°C for 1h. The reaction was cooled to room temperature and concentrated. The remaining aqueous solution was extracted (3x) with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel

chromatography (dichloromethane/methanol 0-4%) gave *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide as a yellow solid (199 mg ,82% yield).

[00159] MS (ESI) m/z 398 (M+H).

[00160] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 11.02 (br. s., 1 H) 9.27 (s, 2 H) 7.75 (s, 1 H) 6.89 (s, 1 H) 4.52 (q, *J*=7.12 Hz, 2 H) 4.06 (s, 3 H) 2.77 - 2.90 (m, 2 H) 1.45 (t, *J*=7.15 Hz, 3 H) 0.73 - 0.97 (m, 8 H).

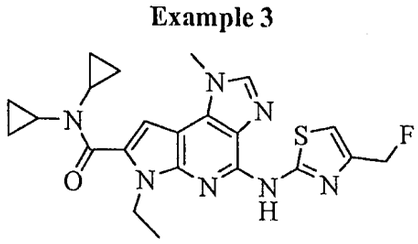
2 Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-methylthiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide-

[00161] *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **2B**, 40 mg, 0.10 mmol) and chloroacetone (62.4 mg, 0.40 mmol) in EtOH (2 ml) were heated at 80°C for 20 min. The reaction was cooled to room temperature and the solvent removed *in vacuo*. Saturated $NaHCO_3$ solution was added and the aqueous layer extracted (3x) with dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (dichloromethane/methanol 0-7%) to provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-methylthiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (9 mg, 12 % yield) as a white solid.

[00162] MS (CI) m/z 436.1 (M+H)

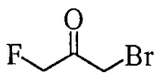
[00163] 1H NMR (400 MHz, DMSO-d_6) δ ppm 10.70 (br s, 1H), 8.12 (s, 1H), 7.23 (s, 1H), 6.69 (s, 1H), 4.61 (q, 2H, *J* = 7.19 Hz), 4.04 (s, 3H), 2.88 – 2.98 (m, 2H), 2.29 (s, 3H), 1.38 (t, 3H, *J* = 7.15 Hz), 0.72 – 0.81 (m, 4H), 0.62 – 0.70 (m, 4H)

Example 3



N,N-dicyclopropyl-6-ethyl-4-(4-(fluoromethyl)thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

3A Preparation of 1-bromo-3-fluoropropan-2-one



[00164] Bromine (0.36 ml, 7.02 mmol) was added dropwise to a solution of 1-fluoropropan-2-one (0.51 ml, 7.02 mmol) in carbon tetrachloride (25 ml). The solution was heated at 45°C for 3h. The reaction was cooled to room temperature and quenched with water. Upon extraction with dichloromethane (3x), the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (0-20% EtOAc/Hexanes) gave 1-bromo-3-fluoropropan-2-one as a yellow oil (118 mg, 65%).

[00165] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 5.14 (s, 1 H) 5.02 (s, 1 H) 4.10 (d, *J*=2.86 Hz, 2 H).

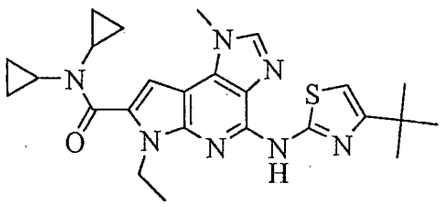
3 Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(4-(fluoromethyl)thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00166] Prepared from *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **2B**) and 1-bromo-3-fluoropropan-2-one (example **3A**) using the same procedure for **2**.

[00167] MS (ESI) rt = 1.94 min, m/z 454 (M+H).

[00168] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.34 (br. s., 1 H) 7.75 (s, 1 H) 6.96 (d, *J*=3.52 Hz, 1 H) 6.90 (s, 1 H) 5.27 - 5.53 (m, 2 H) 4.75 (q, *J*=7.12 Hz, 2 H) 3.98 - 4.11 (m, 3 H) 2.76 - 2.91 (m, 2 H) 1.54 (t, *J*=7.04 Hz, 3 H) 0.70 - 0.94 (m, 8 H).

Example 4



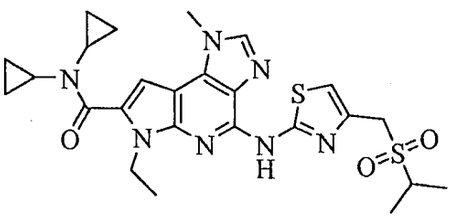
4-(4-*tert*-butylthiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00169] Prepared from *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **2B**) and 1-chloro-3,3-dimethylbutan-2-one using the same procedure as reported for **2** .

[00170] MS (ESI) rt = 1.99 min, m/z 478 (M+H).

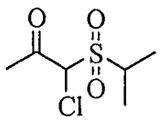
[00171] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.74 (s, 1 H) 6.90 (s, 1 H) 6.48 (s, 1 H) 4.74 (q, J=7.03 Hz, 1 H) 4.04 (s, 3 H) 2.77 - 2.90 (m, 2 H) 1.53 (t, *J*=7.03 Hz, 3 H) 1.37 (s, 9 H) 0.70 - 0.96 (m, 8 H).

Example 5



***N,N*-dicyclopropyl-6-ethyl-4-(4-(isopropylsulfonylmethyl)thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

5A Preparation of 1-chloro-1-(isopropylsulfonyl)propan-2-one



[00172] Sulfuryl chloride (0.248 mL, 3.05 mmol) was added dropwise to a solution of 1-(isopropylsulfonyl)propan-2-one (418 mg, 2.55 mmol) in 1:1 AcOH/DCM (16

ml) at 0°C. The reaction was stirred at rt for 4h. The solvent was removed *in vacuo*, then diluted with dichloromethane. The organic layer was washed (2x) with saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated to leave 800 mg of a colorless oil. The material was used without further purification.

[00173] 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 5.19 (s, 1 H) 3.65 (dt, *J*=13.66, 6.90 Hz, 1 H) 2.56 (s, 3 H) 1.45 (dd, *J*=6.94, 3.05 Hz, 6 H).

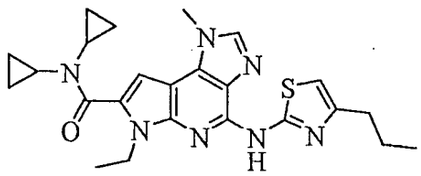
5 Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(4-(isopropylsulfonylmethyl)thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00174] Prepared from *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example 2B) and 1-chloro-1-(isopropylsulfonyl)propan-2-one (example 5[a]) using same procedure as reported for **2**.

[00175] MS (ESI) rt = 1.84 min, m/z 542 (M+H).

[00176] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.82 (s, 1 H) 7.01 (s, 1 H) 6.90 (s, 1 H) 4.73 (q, *J*=7.04 Hz, 2 H) 4.35 (s, 2 H) 4.06 (s, 3 H) 3.36 (quin, *J*=6.88 Hz, 1 H) 2.79 - 2.91 (m, 2 H) 1.53 (t, *J*=7.04 Hz, 3 H) 1.43 (d, *J*=6.82 Hz, 6 H) 0.74 - 0.92 (m, 8 H).

Example 6



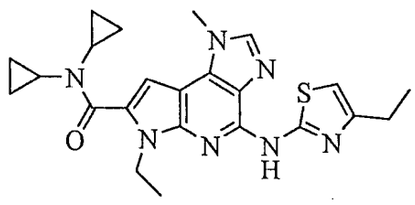
***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-propylthiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00177] Prepared from *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example 2B) and 1-bromopentan-2-one using the same procedure as reported for **2**.

[00178] MS (ESI) rt = 1.94 min, m/z 464 (M+H).

[00179] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.43 - 9.78 (m, 1 H) 7.71 (s, 1 H) 6.89 (s, 1 H) 6.48 (s, 1 H) 4.75 (q, *J*=7.04 Hz, 2 H) 4.04 (s, 3 H) 2.76 - 2.92 (m, 2 H) 2.68 (t, *J*=7.37 Hz, 2 H) 1.76 (dq, *J*=14.94, 7.42 Hz, 2 H) 1.53 (t, *J*=7.04 Hz, 3 H) 1.01 (t, *J*=7.26 Hz, 3 H) 0.69 - 0.94 (m, 8 H).

Example 7



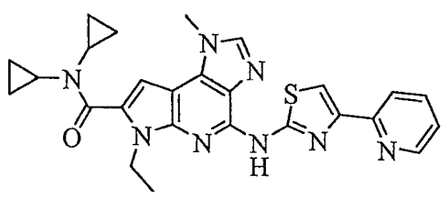
***N,N*-dicyclopropyl-6-ethyl-4-(4-ethylthiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00180] Prepared from *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **2B**) and 1-bromobutan-2-one using the same procedure as reported for **2**.

[00181] MS (ESI) m/z 450 (M+H).

[00182] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.71 (s, 1 H) 6.89 (s, 1 H) 6.49 (s, 1 H) 4.75 (q, *J*=7.03 Hz, 2 H) 4.04 (s, 3 H) 2.80 - 2.88 (m, 2 H) 2.75 (q, *J*=7.45 Hz, 1 H) 1.54 (t, *J*=7.15 Hz, 2 H) 1.33 (t, *J*=7.40 Hz, 2 H) 0.82 (br. s., 8 H).

Example 8



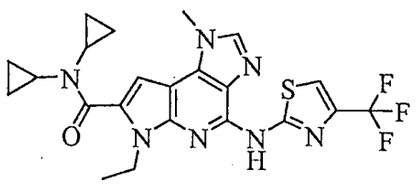
***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-(pyridin-2-yl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00183] A solution of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J**, 70 mg, 0.21 mmol) and benzoyl isothiocyanate (36 µl, 0.27 mmol) in acetone (1 ml) was stirred at room temperature for 1.5h. The solvent was removed *in vacuo*, the residue was taken up in EtOH (1.5 ml), and K_2CO_3 (40 mg, 0.290 mmol) was added. The reaction was heated at 60°C for 3h. Upon cooling to room temperature, 2-bromo-1-(pyridin-2-yl)ethanone, hydrobromide (139.4 mg, 0.50 mmol) was added and the reaction heated at 80°C for 24h. The reaction mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography (0-7% MeOH/dichloromethane). Re-purification by preparative HPLC provided 10.2 mg (10% yield) of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-(pyridin-2-yl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide as a brown solid.

[00184] MS (ESI) rt = 1.78 min, m/z 499 (M+H).

[00185] 1H NMR (DMSO-d6) δ ppm 10.9 (s, 1 H), 8.2 (bs, 1 H), 7.81 (d, 1 H), 7.75 (s, 1H), 3.92 (m, 4H), 3.77 (q, 2H, *J* = 7.8 Hz), 2.52-2.81 (m, 7H).

Example 9



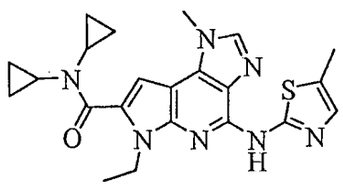
Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-(trifluoromethyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00186] This compound was prepared according to example **2** using 3-bromo-1,1,1-trifluoroacetone to provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-(trifluoromethyl) thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide.

[00187] MS (ESI) m/z 490.0 (M+H)

[00188] 1H NMR (500 MHz, DMSO-d_6) δ ppm 11.71 (s, 1H), 8.16 (s, 1H), 7.86 (s, 1H), 7.27 (s, 1H), 4.63 (q, 2H), 4.05 (s, 3H), 2.89 – 2.98 (m, 2H), 1.40 (t, 3H, J = 6.87 Hz), 0.74 – 0.80 (m, 4H), 0.64 – 0.71 (m, 4H)

Example 10



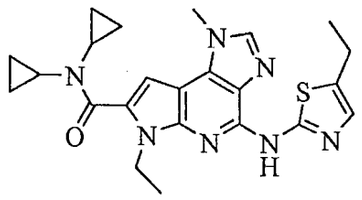
Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methylthiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00189] 4-Amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J**, 86.3 mg, 0.255 mmol) was dissolved in acetone and benzoyl isothiocyanate (37.8 μL, 0.281 mmol) was added. The reaction was stirred at room temperature for 2h. The solvent was removed *in vacuo*. The residue was taken up in ethanol (1500 μL) and K_2CO_3 (49.3 mg, 0.357 mmol) was added. The reaction mixture was warmed to 60 °C for 3 h. 2-Bromopropanal (45.4 mg, 0.332 mmol) was added. After 3 h, additional 2-bromopropanal (~100 mg) was added. Stirred at 60 °C for 16h. Additional 2-bromopropanal was added and the reaction mixture was stirred at 60 °C 3 h. The ethanol was removed by concentration *in vacuo*. The crude residue was purified by flash chromatography using an Isco 12 g column eluting with 2 - 10% MeOH/CH_2Cl_2). Additional purification was accomplished via preparative HPLC. *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methylthiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (20 mg, 17.47 % yield) was isolated as a white solid.

[00190] MS (ESI) m/z 436.0 (M+H)

[00191] 1H NMR (500 MHz, DMSO-d_6) δ ppm 10.56 (br s, 1H), 8.12 (s, 1H), 7.23 (s, 1H), 7.12 (s, 1H), 4.62 (q, 2H, J = 6.78 Hz), 4.04 (s, 3H), 2.87 – 2.99 (m, 2H), 2.39 (s, 3H), 1.35 – 1.46 (m, 3H), 0.72 – 0.81 (m, 4H), 0.59 – 0.71 (m, 4H)

Example 11



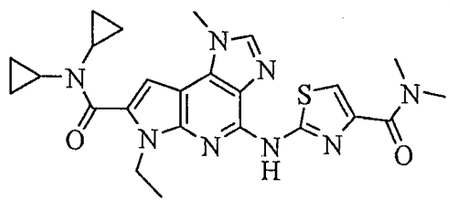
***N,N*-dicyclopropyl-6-ethyl-4-(5-ethylthiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00192] Prepared from 2-bromobutanal and 4-Amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example 1J) using the same procedure as that of example **8**.

[00193] MS (ESI) rt = 1.86 min, m/z 450 (M+H).

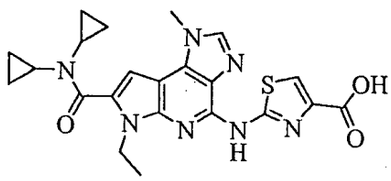
[00194] 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.91 - 9.22 (m, 1 H) 7.71 (s, 1 H) 7.14 (s, 1 H) 6.89 (s, 1 H) 4.75 (q, *J*=6.94 Hz, 2 H) 4.05 (s, 3 H) 2.80 - 2.89 (m, 4 H) 1.55 (t, *J*=5.00 Hz, 3 H) 1.37 (t, *J*=7.49 Hz, 3 H) 0.73 - 0.92 (m, 8 H).

Example 12



2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N,N*-dimethylthiazole-4-carboxamide

12A Preparation of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydro imidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-4-carboxylic acid

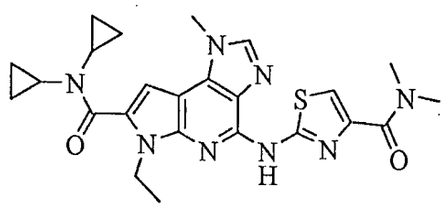


[00195] 4-Amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (**1J**, 300 mg, 0.89 mmol) and benzoyl isothiocyanate (0.16 ml, 1.15 mmol) in acetone (4 ml) were stirred at rt for 1.5h. The solvent was removed *in vacuo* and the residue taken up in EtOH (6 ml). K_2CO_3 (172 mg, 1.241 mmol) was added and the reaction heated at 60°C for 3h. The reaction was cooled to rt and ethyl 3-bromo-2-oxopropanoate (692 mg, 3.55 mmol) was added. The reaction was heated at 70°C overnight. Upon completion of the cyclization step, 1N NaOH (6.3 ml, 6.30 mmol) was added to the reaction mixture and heated at 60°C for 4h. The reaction was cooled to room temperature and the solvent removed *in vacuo*. The remaining aqueous solution was acidified to pH 1 and the precipitate removed by vacuum filtration, washing with water, EtOAc, and then dichloromethane to afford 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-4-ylamino)thiazole-4-carboxylic acid (325 mg ,79% yield) as brown solid.

[00196] MS (ESI) rt = 1.85 min, m/z 466 (M+H).

[00197] 1H NMR (400 MHz, DMSO-d6) δ ppm 8.16 (s, 1 H) 7.94 (s, 1 H) 7.26 (s, 1 H) 4.63 (q, *J*=6.94 Hz, 2 H) 4.05 (s, 3 H) 3.36 (br. S., 1 H) 2.89 – 2.99 (m, 2 H) 1.40 (t, *J*=7.03 Hz, 3 H) 0.61 – 0.83 (m, 8 H).

12 Preparation of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N,N*-dimethylthiazole-4-carboxamide



[00198] To 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d] pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-4-carboxylic acid (example **12A**, 44 mg, 0.095 mmol) in DMF (2 ml) was added HATU (108 mg, 0.284 mmol), DIPEA (0.066 mL, 0.378 mmol), and dimethylamine (0.013 mL, 0.189 mmol). The reaction was stirred at rt for 3h, then the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give 2-(7-

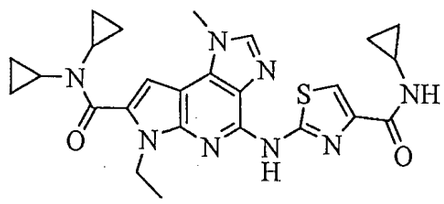
(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo [2,3-b]pyridine-4-ylamino)-*N,N*-dimethylthiazole-4-carboxamide (10 mg , 21% yield) as a brown solid.

[00199] MS (ESI) m/z 493 (M+H)

[00200] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.45 (br. S., 1 H) 7.81 (s, 1 H) 7.43 (s, 1 H) 6.90 (s, 1 H) 4.74 (q, *J*=7.03 Hz, 2 H) 4.05 (s, 3 H) 3.31 (br. S., 3 H) 3.13 (br. S., 3 H) 2.75 – 2.90 (m, 2 H) 1.54 (t, *J*=7.15 Hz, 3 H) 0.65 – 0.96 (m, 8 H).

Examples **13-17** were prepared using the procedure as described for example **12**

Example 13

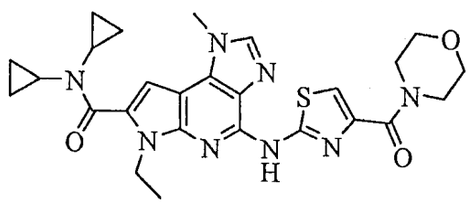


***N*-cyclopropyl-2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-4-carboxamide**

[00201] MS (ESI) rt = 1.99 min, m/z 505 (M+H).

[00202] 1H NMR (400 MHz, MeOD) δ ppm 8.07 (s, 1 H) 7.74 (s, 1 H) 7.26 (s, 1 H) 4.73 (q, J=7.03 Hz, 1 H) 4.13 (s, 3 H) 2.94 - 3.04 (m, 2 H) 2.85 - 2.93 (m, 1 H) 1.51 (t, *J*=7.03 Hz, 2 H) 0.67 - 0.95 (m, 12 H).

Example 14

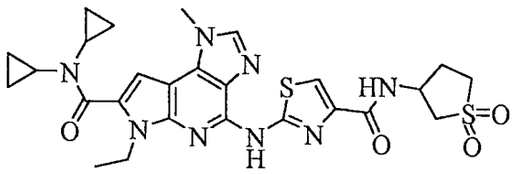


N,N-dicyclopropyl-6-ethyl-1-methyl-4-(4-(morpholine-4-carbonyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00203] MS (ESI) rt = 1.87 min, m/z 535 (M+H).

[00204] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.21 (br. s., 1 H) 7.76 (s, 1 H) 7.56 (s, 1 H) 6.81 - 6.94 (m, 1 H) 4.74 (q, *J*=7.11 Hz, 2 H) 4.07 (s, 3 H) 3.79 (br. s., 4 H) 3.50 (d, *J*=4.52 Hz, 2 H) 2.74 - 2.90 (m, 2 H) 1.60 (s, 2 H) 1.54 (t, *J*=7.03 Hz, 3 H) 0.70 - 0.94 (m, 8 H).

Example 15

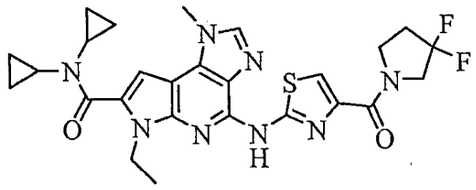


N,N-dicyclopropyl-4-((4-((1,1-dioxidotetrahydro-3-thiophenyl)carbamoyl)-1,3-thiazol-2-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00205] MS (ESI) rt = 1.88 min, m/z 583 (M+H).

[00206] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.31 (br. s., 1 H) 7.77 (s, 1 H) 7.69 - 7.75 (m, 1 H) 6.91 (s, 1 H) 4.85 - 4.99 (m, 1 H) 4.64 - 4.81 (m, 2 H) 4.07 (s, 3 H) 3.45 - 3.61 (m, 2 H) 3.35 (br. s., 1 H) 3.19 (dt, *J*=13.36, 8.12 Hz, 2 H) 2.75 - 2.91 (m, 2 H) 2.57 - 2.72 (m, 1 H) 2.42 (ddd, *J*=14.49, 7.53, 7.34 Hz, 1 H) 1.54 (t, *J*=6.90 Hz, 3 H) 0.69 - 0.94 (m, 8 H)

Example 16

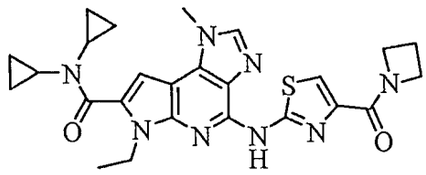


N,N-dicyclopropyl-4-(4-(3,3-difluoropyrrolidine-1-carbonyl)thiazol-2-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00207] MS (ESI) rt = 2.05 min, m/z 555 (M+H).

[00208] 1H NMR (400 MHz, MeOD) δ ppm 8.00 (s, 1 H) 7.73 (s, 1 H) 7.70 (s, 1 H) 7.19 (s, 1 H) 4.68 (q, J=7.03 Hz, 2 H) 4.51 (t, *J*=12.80 Hz, 1 H) 4.34 (t, *J*=7.40 Hz, 1 H) 4.06 (s, 3 H) 3.96 (t, *J*=13.18 Hz, 1 H) 3.86 (t, *J*=7.65 Hz, 1 H) 2.87 - 3.02 (m, 2 H) 2.34 - 2.59 (m, 2 H) 1.45 (t, *J*=6.90 Hz, 3 H) 0.72 - 0.95 (m, 8 H).

Example 17

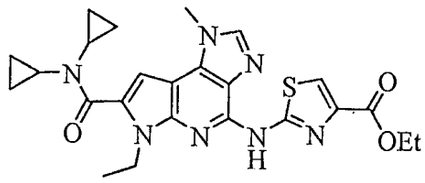


(4-(azetidine-1-carbonyl)thiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00209] MS (ESI) rt = 1.95 min, m/z 505 (M+H).

[00210] 1H NMR (400 MHz, MeOD) δ ppm 8.03 (s, 1 H) 7.70 (s, 1 H) 7.21 (s, 1 H) 4.78 (t, J=7.53 Hz, 2 H) 4.69 (q, *J*=7.03 Hz, 2 H) 4.19 (t, *J*=7.78 Hz, 2 H) 4.08 (s, 3 H) 2.95 (ddd, *J*=7.22, 3.45, 3.14 Hz, 2 H) 2.27 - 2.48 (m, 2 H) 1.47 (t, *J*=7.03 Hz, 3 H) 0.69 - 0.93 (m, 8 H).

Example 18



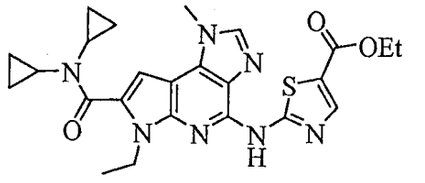
Ethyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-4-carboxylate

[00211] This compound was prepared according to example **2** using ethyl bromopyruvate and *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **2B**) to yield ethyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-4-carboxylate as yellow solid.

[00212] MS (ESI) m/z 494.1 (M+H)

[00213] 1H NMR (500 MHz, DMSO-d_6) δ ppm 11.42 (br s, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.25 (s, 1H), 4.62 (q, 2H), 4.30 (q, 2H, J = 7.15 Hz), 4.05 (s, 3H), 2.89 – 2.97 (m, 2H), 1.39 (t, 3H, J = 7.01 Hz), 1.32 (t, 3H, J = 7.15 Hz), 0.74 – 0.80 (m, 4H), 0.64 – 0.70 (m, 4H)

Example 19



Ethyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxylate

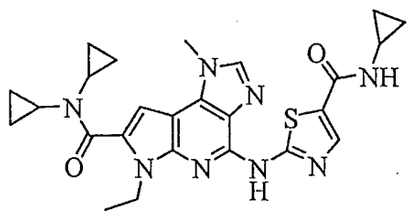
[00214] This compound was prepared according to example **2** using ethyl 2-chloro-2-formylacetate and *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo [4,5-d]pyrrolo [2,3-b]pyridine-7-carboxamide (example **2B**) to provide ethyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-

dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxylate (18.5 mg, 17 % yield) as a pale yellow solid.

[00215] MS (ESI) m/z 494.0 (M+H)

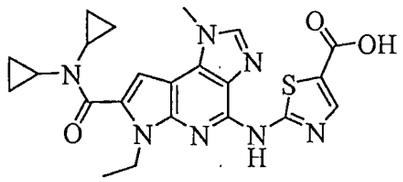
[00216] 1H NMR (400 MHz, DMSO-d_6) δ ppm 11.95 (s, 1H), 8.20 (s, 1H), 8.14 (s, 1H), 7.28 (s, 1H), 4.63 (q, 2H, J = 7.19 Hz), 4.28 (q, 2H, J = 7.19 Hz), 4.06 (s, 3H), 2.88 – 3.00 (m, 2H), 1.44 (t, 3H, J = 7.03 Hz), 1.32 (t, 3H, J = 7.15 Hz), 0.73 – 0.81 (m, 4H), 0.63 – 0.70 (m, 4H)

Example 20



***N*-cyclopropyl-2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxamide**

20A Preparation of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxylic acid



[00217] To a solution of ethyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxylate (**example 19,** 14.6 mg, 0.030 mmol) in EtOH (296 μL) was added 1 N NaOH aqueous solution (296 μL). The reaction mixture was stirred at rt 3 h and stirred at 50 °C 18 h. After cooling to room temperature, ethanol was removed by concentration *in vacuo*. The residue was acidified with 1 N HCl and the solid product was collected by filtration. 2-(7-(Dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxylic acid was isolated as a pale yellow solid which was used crude in the next reaction.

[00218] MS (ESI) m/z 465.9 (M+H)

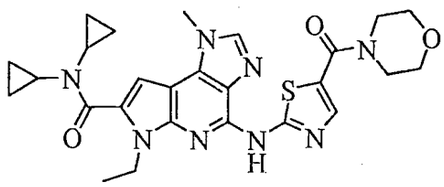
20 Preparation of *N*-cyclopropyl-2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxamide

[00219] To a mixture of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxylic acid (example **20A,** 13.97 mg, 0.030 mmol) in DMF (300 µL) was added cyclopropylamine (4.16 µL, 0.060 mmol), HATU (14.83 mg, 0.039 mmol), and Hünig'sBase (15.72 µL, 0.090 mmol). The reaction mxiture was stirred at rt 1 h and concentrated *in vacuo*. The residue was taken up in MeOH and purified by preparative HPLC. *N*-Cyclopropyl-2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroi midazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxamide (3 mg, 19.82 % yield) was isolated as a white solid.

[00220] MS (ESI) m/z 505.0 (M+H)

[00221] 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.36 (br s, 1H), 8.15 (s, 1H), 8.02 (s, 1H), 7.25 (s, 1H), 4.63 (q, 2H, J = 7.11 Hz), 4.05 (s, 3H), 2.89 – 3.00 (m, 2H), 2.76 (tq, 1H, J = 7.25, 3.70 Hz), 1.41 (t, 3H, J = 7.03 Hz), 0.74 – 0.81 (m, 4H), 0.64 – 0.72 (m, 6H), 0.51 – 0.59 (m, 2H)

Example 21



***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-(morpholine-4-carbonyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

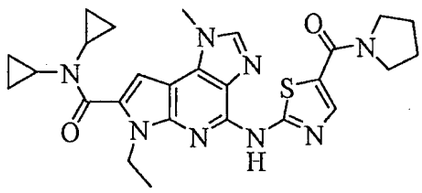
[00222] This compound was prepared according to Example **20** using morpholine and 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxylic acid (example **20A**) to

provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-(morpholine-4-carbonyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide as a white solid.

[00223] MS (ESI) m/z 535.1 (M+H)

[00224] 1H NMR (400 MHz, MeOD) δ ppm 8.08 (s, 1H), 7.79 – 7.93 (m, 1H), 7.26 (s, 1H), 4.74 (q, 2H, *J* = 7.28 Hz), 4.12 (s, 3H), 3.81 – 3.88 (m, 2H), 3.72 – 3.80 (m, 2H), 2.91 – 3.02 (m, 2H), 1.52 (t, 3H, *J* = 7.15 Hz), 0.83 – 0.93 (m, 4H), 0.72 – 0.84 (m, 4H)

Example 22



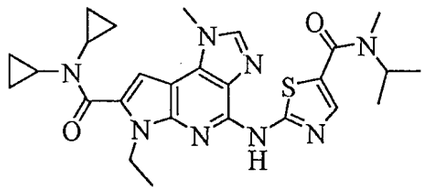
***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-(pyrrolidine-1-carbonyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00225] This compound was prepared according to Example **20** using pyrrolidine and 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)thiazole-5-carboxylic acid (example **20A**) to provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-(pyrrolidine-1-carbonyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00226] MS (ESI) m/z 519.1 (M+H).

[00227] ^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.58 (s, 1H), 7.97 (s, 1H), 7.28 (s, 1H), 4.71 (q, J = 6.7 Hz, 2H), 4.20 (s, 3H), 3.87 (t, J = 6.5 Hz, 2H), 3.67 (t, J = 6.7 Hz, 2H), 2.97 - 3.05 (m, 2H), 2.10 - 2.19 (m, 2H), 1.98 - 2.07 (m, 2H), 1.51 (t, J = 7.2 Hz, 3H), 0.88 - 0.95 (m, 4H), 0.80 - 0.86 (m, 4H)

Example 23



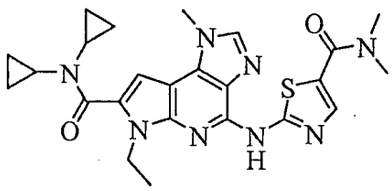
2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*-isopropyl-*N*-methylthiazole-5-carboxamide

[00228] This compound was prepared according to Example **20** using *N*-methylpropan-2-amine and 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo [2,3-b]pyridin-4-ylamino)thiazole-5-carboxylic acid (example **20A)** to provide 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*-isopropyl-*N*-methylthiazole-5-carboxamide

[00229] MS (ESI) m/z 521.1 (M+H).

[00230] ^{1}H NMR (400 MHz, METHANOL-d_4) δ: 8.68 (s, 1H), 7.87 (s., 1H), 7.32 (s, 1H), 4.74 (q, J = 7.0 Hz, 2H), 4.24 (s, 3H), 3.18 (br. s., 3H), 2.99 - 3.06 (m, 2H), 1.53 (t, J = 7.0 Hz, 3H), 1.35 (d, J = 6.8 Hz, 6H), 0.89 - 0.96 (m, 4H), 0.81 - 0.88 (m, 4H)

Example 24



2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*,*N*-dimethylthiazole-5-carboxamide

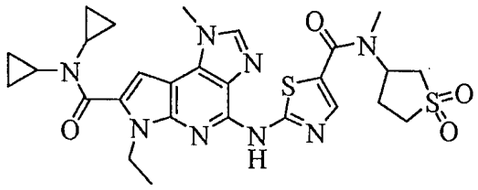
[00231] This compound was prepared according to Example **20** using *N*,*N*-dimethylamine and 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo [2,3-b]pyridin-4-ylamino)thiazole-5-carboxylic acid (example **20A)** to give 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-

dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N,N*-dimethylthiazole-5-carboxamide.

[00232] MS (ESI) m/z 493.1 (M+H).

[00233] ^{1}H NMR (400 MHz, METHANOL-d_4) δ: 8.56 (s, 1H), 7.91 (s, 1H), 7.31 (s, 1H), 4.72 (q, J = 7.0 Hz, 1H), 4.22 (s, 3H), 3.15 – 3.45 (br. S, 6 H), 2.97 - 3.05 (m, 2H), 2.91 (s, 1H), 1.54 (t, J = 7.0 Hz, 3H), 0.88 - 0.95 (m, 4H), 0.80 - 0.86 (m, 4H)

Example 25



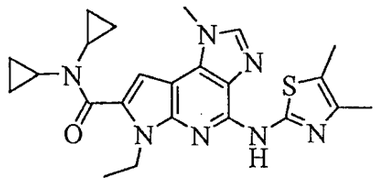
2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*-(1,1-Dioxo-tetrahydrothiophen-3-yl) -N-methylthiazole-5-carboxamide

[00234] This compound was prepared according to example **20**

[00235] MS (ESI) m/z 597.0 (M+H).

[00236] ^{1}H NMR (400 MHz, METHANOL-d_4) δ: 8.74 (s, 1H), 7.99 (s, 1H), 7.37 (s, 1H), 5.34 - 5.45 (m, 1H), 4.78 (q, J = 6.9 Hz, 2H), 4.28 (s, 3H), 4.05 (s, 3H), 3.49 - 3.59 (m, 1H), 3.22 – 3.33 (m, 1H), 3.00 - 3.10 (m, 2H), 2.94 (s, 1H), 2.47 - 2.66 (m, 2H), 1.57 (t, J = 6.9 Hz, 3H), 1.34 – 1.45 (M, 1H), 0.91 - 0.99 (m, J = 6.5 Hz, 4H), 0.83 - 0.90 (m, 4H)

Example 26



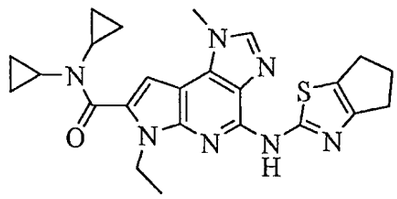
N,N-dicyclopropyl-4-(4,5-dimethylthiazol-2-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00237] This compound was prepared according to example **2** using 3-bromo-2-butanone (0.034 mL, 0.323 mmol) to provide *N,N*-dicyclopropyl-4-(4,5-dimethylthiazol-2-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (59.17 mg, 44.3 % yield) as a pale yellow solid.

[00238] MS (ESI) m/z 450.1 (M+H)

[00239] 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.15 (s, 1H), 7.23 (s, 1H), 4.61 (q, 2H, *J* = 7.03 Hz), 4.04 (s, 3H), 2.88 – 2.98 (m, 2H), 2.29 (s, 3H), 2.19 (s, 3H), 1.38 (t, 3H, *J* = 7.03 Hz), 0.73 – 0.80 (m, 4H), 0.62 – 0.71 (m, 4H)

Example 27



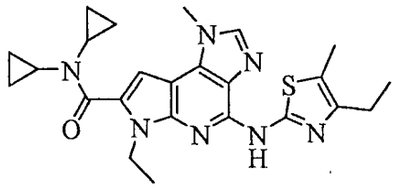
N,N-dicyclopropyl-4-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00240] Prepared using similar procedure as that of example **2**

[00241] MS (ESI) rt = 1.95 min, m/z 462 (M+H).

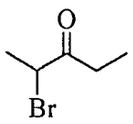
[00242] 1H NMR (500 MHz, MeOD) δ ppm 8.12 (s, 1 H) 7.22 (s, 1 H) 4.68 (q, *J*=7.12 Hz, 2 H) 4.10 (s, 3 H) 2.86 - 3.02 (m, 4 H) 2.80 (t, *J*=7.07 Hz, 2 H) 2.43 - 2.61 (m, 2 H) 1.46 (t, *J*=7.07 Hz, 3 H) 0.70 - 0.90 (m, 8 H).

Example 28



N,N-dicyclopropyl-6-ethyl-4-(4-ethyl-5-methylthiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

28A Preparation of 2-bromopentan-3-one



[00243] Prepared according to the procedure described in *Chem. Comm.* **2004**, 470-471.

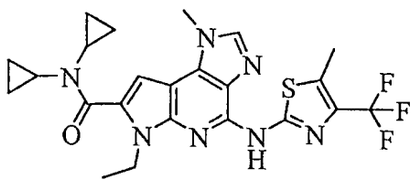
28 Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(4-ethyl-5-methylthiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00244] Prepared from example **26A** using similar procedure as that of example **2**

[00245] MS (ESI) m/z 464 (M+H).

[00246] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.81 – 9.19 (m, 1 H) 7.69 (s, 1 H) 6.89 (s, 1 H) 4.75 (q, *J*=7.12 Hz, 2 H) 4.03 (s, 3 H) 2.78 – 2.93 (m, 2 H) 2.63 (q, *J*=7.48 Hz, 2 H) 2.37 (s, 3 H) 1.53 (t, *J*=7.04 Hz, 3 H) 1.26 (t, *J*=7.48 Hz, 3 H) 0.73 – 0.95 (m, 8 H).

Example 29



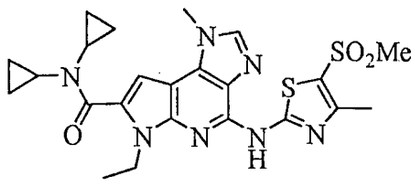
Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methyl-4-(trifluoromethyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00247] This compound was prepared according to example **2** using 3-bromo-1,1,1-trifluorobutan-2-one to provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methyl-4-(trifluoromethyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide as a white solid.

[00248] MS (ESI) m/z 504.0 (M+H)

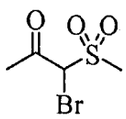
[00249] 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.14 (s, 1H), 7.25 (s, 1H), 4.62 (q, 2H, J = 6.97 Hz), 4.04 (s, 3H), 2.89 – 2.98 (m, 2H), 1.40 (t, 3H, J = 6.87 Hz), 0.73 – 0.80 (m, 4H), 0.65 – 0.71 (m, 4H)

Example 30



Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-methyl-5-(methylsulfonyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

30A Preparation of 1-bromo-1-(methylsulfonyl)propan-2-one



[00250] To a solution of methanesulphonylacetone (0.5 g, 3.67 mmol) in AcOH (7.34 mL) and dichloromethane (11.02 mL) in a round bottom flask was added bromine (0.189 mL, 3.67 mmol) dropwise. The reaction mixture was stirred at rt 90 min. Solvent was removed *in vacuo*. The residue was taken up in ether and washed with saturated aqueous sodium bicarbonate (2 x). The organics were concentrated *in vacuo*. 1-Bromo-1-(methylsulfonyl)propan-2-one (0.332 g, 42% yield) was isolated as an oil.

[00251] MS (CI) m/z 215.0 (M+H)

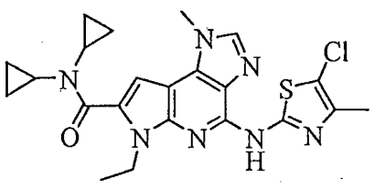
30 Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-methyl-5-(methylsulfonyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00252] This compound was prepared according to example **1** using 1-bromo-1-(methylsulfonyl)propan-2-one (**28A**, 32.5 mg, 0.151 mmol) to provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-methyl-5-(methylsulfonyl)thiazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (12.5 mg, 0.023 mmol, 30.6 % yield) as an off-white solid.

[00253] MS (ESI) m/z 514.1 (M+H)

[00254] 1H NMR (400 MHz, DMSO-d_6) δ ppm 12.00 (br s, 1H), 8.18 (s, 1H), 7.27 (s, 1H), 4.59 (q, 2H, J = 6.78 Hz), 4.06 (s, 3H), 3.29 (s, 3H), 2.88 – 2.98 (m, 2H), 2.53 (s, 3H), 1.41 (t, 3H, J = 6.90 Hz), 0.72 – 0.81 (m, 4H), 0.62 – 0.71 (m, 4H)

Example 31



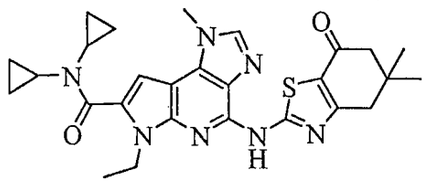
Preparation of 4-(5-chloro-4-methylthiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00255] This compound was prepared according to example **2** using 1,1-dichloropropan-2-one (14.26 μL, 0.147 mmol) to provide 4-(5-chloro-4-methylthiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (4.35 mg, 18.9% yield) as a pale green solid.

[00256] MS (ESI) m/z 470.1 (M+H)

[00257] 1H NMR (400 MHz, DMSO-d_6) δ ppm 11.34 (s, 1H), 8.14 (s, 1H), 7.25 (s, 1H), 4.58 (q, 2H, J = 7.28 Hz), 4.04 (s, 3H), 2.88 – 2.98 (m, 2H), 2.25 (s, 3H), 1.40 (t, 3H, J = 6.90 Hz), 0.73 – 0.81 (m, 4H), 0.63 – 0.70 (m, 4H)

Example 32



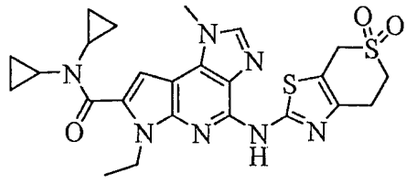
Preparation of *N,N*-dicyclopropyl-4-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00258] This compound was prepared according to example **2** using 2-chloro-5,5-dimethylcyclohexane-1,3-dione (34.9 mg, 0.200 mmol) to provide *N,N*-dicyclopropyl-4-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (11.24 mg, 21.7% yield) as a pale yellow solid.

[00259] MS (ESI) m/z 518.2 (M+H)

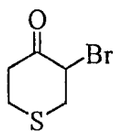
[00260] 1H NMR (400 MHz, DMSO-d_6) δ ppm 11.93 (s, 1H), 8.19 (s, 1H), 7.28 (s, 1H), 4.62 (q, 2H), 4.06 (s, 3H), 2.89 – 2.98 (m, 2H), 2.80 (s, 2H), 2.40 (s, 2H), 1.41 (t, 3H, J = 7.03 Hz), 1.09 (s, 6H), 0.73 – 0.80 (m, 4H), 0.63 – 0.71 (m, 4H)

Example 33



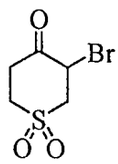
Preparation of 4-(5,5-dioxo-4,5,6,7-tetrahydro-5λ^6-thiopyrano[4,3-d]thiazol-2-ylamino)-6-ethyl-1-methyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-7-carboxylic acid dicyclopropylamide

33A Preparation of 3-bromodihydro-2*H*-thiopyran-4(3*H*)-one



[00261] To a mixture of tetrahydrothiopyran-4-one (0.5 g, 4.30 mmol) in dichloromethane (51.2 mL) and methanol (20.49 mL) was added tetra-n-butylammonium tribromide (2.283 g, 4.73 mmol). The reaction mixture was stirred at rt 2.5 h. Solvent was removed *in vacuo*. The crude solid was triturated with ether (3 x). The combined ether layers were dried over anydrous magnesium sulfate, filtered and concentrated *in vacuo*. The product was isolated as a pale orange oil. Material was used immediately in the next reaction.

33B Preparation of 3-bromo-1,1-dioxo-tetrahydro-1λ^6-thiopyran-4-one



[00262] To a cooled (0 °C) of 3-bromodihydro-2*H*-thiopyran-4(3*H*)-one (example **33A,** 0.791 g, 4.05 mmol) in dichloromethane (20.27 mL) was added mCPBA (1.749 g, 10.14 mmol) slowly. The reaction mixture was allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (2 x). The combined organics were dried over anhydrous magenesium sulfate, filtered and concentrated *in vacuo* to afford 3-bromo-1,1-dioxo-tetrahydro-1λ^6-thiopyran-4-one as a white solid which was used immediately in the next reaction.

33 Preparation of 4-(5,5-dioxo-4,5,6,7-tetrahydro-5λ^6-thiopyrano[4,3-d]thiazol-2-ylamino)-6-ethyl-1-methyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-7-carboxylic acid dicyclopropylamide

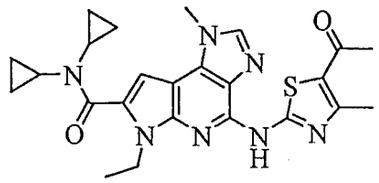
[00263] This compound was prepared according to example **1** using 3-bromo-1,1-dioxo-tetrahydro-1λ^6-thiopyran-4-one (example **33B,** 32.5 mg, 0.151 mmol) to provide 4-(5,5-dioxo-4,5,6,7-tetrahydro-5λ^6-thiopyrano[4,3-d]thiazol-2-ylamino)-6-

ethyl-1-methyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-7-carboxylic acid dicyclopropylamide (9 mg, 17.56 % yield) as a pale tan solid.

[00264] MS (ESI) m/z 526.2 (M+H)

[00265] 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.16 (s, 1H), 7.25 (s, 1H), 4.61 (q, 2H, J = 6.78 Hz), 4.54 (s, 2H), 4.04 (s, 3H), 3.49, (7, 2H, J = 6.02 Hz), 3.16 (t, 2H, J = 8.16 Hz), 2.89 – 2.97 (m, 2H), 1.38 (t, 3H, J = 7.03 Hz), 0.73 – 0.79 (m, 4H), 0.61 – 0.70 (m, 4H)

Example 34



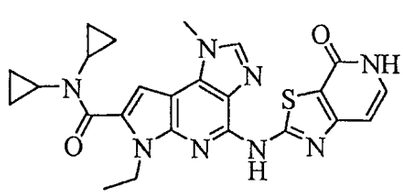
Preparation of 4-(5-acetyl-4-methylthiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00266] This compound was prepared according to example **2** using 3-chloro-2,4-pentanedione (36.0 μL, 0.302 mmol) to provide 4-(5-acetyl-4-methylthiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (76 mg, 100 % yield) as a pale yellow solid.

[00267] MS (ESI) m/z 478.2 (M+H)

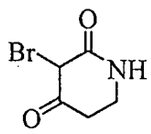
[00268] 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.31 (s, 1H), 7.28 (s, 1H), 4.62 (q, 2H, J = 6.94 Hz), 4.08 (s, 3H), 2.89 – 2.99 (m, 2H), 2.61 (s, 3H), 1.44 (t, 3H, J = 7.03 Hz), 0.72 – 0.81 (m, 4H), 0.64 – 0.72 (m, 4H)

Example 35



Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-oxo-4,5-dihydrothiazolo[5,4-c]pyridin-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

35A Preparation of 3-bromopiperidine-2,4-dione



To a mixture of piperidine-2,4-dione (0.072 g, 0.637 mmol) in acetic acid (1.591 mL) was added bromine (0.033 mL, 0.637 mmol) dropwise. The reaction mixture was stirred at rt 70 min. Dichloromethane was added and the cloudy mixture was concentrated *in vacuo*. The residual solution was treated with ethyl ether. A white solid crashed out and the AcOH/ether was decanted. The white solid, presumed to be product was carried forward. The white solid started liquifying and turning red rapidly upon exposure to light and standing.

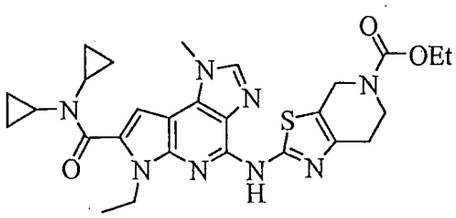
35 Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-oxo-4,5-dihydrothiazolo[5,4-c]pyridin-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00269] This compound was prepared according to example **2** using 3-bromopiperidine-2,4-dione (example **35A**) to provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-oxo-4,5-dihydrothiazolo[5,4-c]pyridin-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (4.51 mg, 12.3% yield) as a white solid containing 10% *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-oxo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide.

[00270] MS (ESI) m/z 489.1 (M+H)

[00271] 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.20 (s, 1H), 7.32 – 7.47 (m, 1H), 7.29 (s, 1H), 6.62 (d, 1H, J = 7.03 Hz), 4.66 (q, 2H, J = 7.19 Hz), 4.07 (s, 3H), 2.88 – 3.06 (m, 2H), 1.44 (t, 3H, J = 7.03 Hz), 0.72 – 0.85 (m, 4H), 0.60 – 0.72 (m, 4H)

Example 36



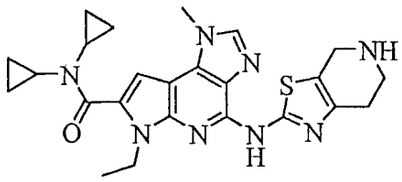
Preparation of ethyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4*H*)-carboxylate

[00272] This compound was prepared according to example **2** using 3-bromo-4-oxo-piperidine-1-carboxylic acid ethyl ester to provide ethyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4*H*)-carboxylate (5 mg, 15.36 % yield) as a white solid.

[00273] MS (ESI) m/z 549.2 (M+H)

[00274] 1H NMR (400 MHz, DMSO-d_6) δ ppm 10.83 (br s, 1H), 8.12 (s, 1H), 7.23 (s, 1H), 4.56 – 4.67 (m, 4H), 4.10 (q, 2H, J = 7.19 Hz), 4.04 (s, 3H), 3.72 (t, 2H, J = 5.52 Hz), 2.87 – 2.98 (m, 2H), 2.64 – 2.73 (m, 2H), 1.38 (t, 3H, J = 7.03 Hz), 1.22 (t, 3H, J = 7.15 Hz), 0.71 – 0.81 (m, 4H), 0.60 – 0.71 (m, 4H)

Example 37



Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

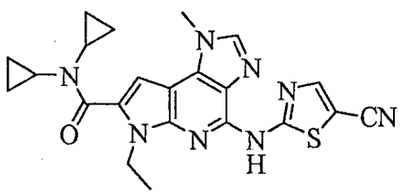
[00275] This compound was prepared according to example **2** using 3-bromopiperidin-4-one, hydrobromide (33.8 mg, 0.130 mmol) to provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (30 mg, 60 % yield) as a pale yellow solid.

[00276] MS (ESI) m/z 477.3 (M+H)

[00277] 1H NMR (400 MHz, DMSO-d_6) δ ppm 9.08 (br s, 2H), 8.25 (s, 1H), 7.27 (s, 1H), 4.63 (q, 2H, J = 6.78 Hz), 4.38 (br s, 2H), 4.06 (s, 3H), 2.85 – 2.98 (m, 4H), 1.38 (t, 3H, J = 7.03 Hz), 0.73 – 0.81 (m, 4H), 0.62 – 0.71 (m, 4H)

Example 38



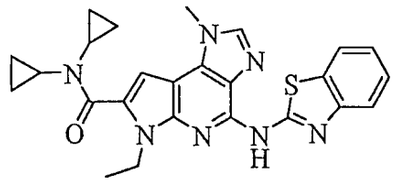
4-(5-cyanothiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00278] To a mixture of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J**, 60 mg, 0.177 mmol), 2-chlorothiazole-5-carbonitrile (38.5 mg, 0.266 mmol), Pd2(dba)3 (24.4 mg, 0.027 mmol), BINAP (49.7 mg, 0.080 mmol) and sodium *tert*-butoxide (27.3 mg, 0.284 mmol) was added DME (1 ml). The mixture was purged with argon gas for 5 min and heated to 85 °C for 3 h. The reaction mixture showed ~60% conversion by HPLC and was filtered through a plug of Celite and concentrated. The crude product was purified by preparative HPLC to afford 4-(5-cyanothiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide as a off-white solid.

[00279] MS (ESI) m/z 447.2 (M+H).

[00280] ^{1}H NMR (500 MHz, CD_3OD-$CDCl_3$) δ: 8.60 (s, 1H), 8.04 (s, 1H), 7.56 (s, 4H), 7.13 (s, 1H), 4.71 (q, J = 7.1 Hz, 2H), 4.20 (s, 3H), 2.84 - 2.91 (m, 2H), 1.52 (t, J = 7.1 Hz, 3H), 0.83 - 0.90 (m, 5H), 0.74 - 0.80 (m, 4H).

Example 39



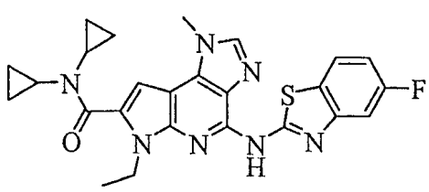
4-(benzo[d]thiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00281] To a solution of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J**, 21.2 mg, 0.063 mmol) in DMF (626 µL) was added sodium hydride (10.02 mg, 0.251 mmol) in one portion. After 20 min, 2-bromo-1,3-benzothiazole (53.6 mg, 0.251 mmol) was added. The reaction mixture was stirred at room temperature for 16h. The reaction mixture was quenched with water and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organics were washed with 10% LiCl, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography using an Isco 4 g column eluting with 0 - 5% MeOH/CH_2Cl_2 to yield 4-(benzo[d]thiazol-2-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (6.8 mg, 21.87 % yield) as an off-white solid.

[00282] MS (ESI) m/z 472.2 (M+H)

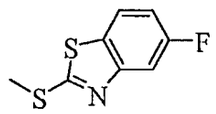
[00283] 1H NMR (500 MHz, DMSO-d6) δ ppm 8.17 (s, 1H), 7.95 (d, 1H, J = 7.97 Hz), 7.67 (d, 1H, J = 8.25 Hz), 7.39 (t, 1H, J = 7.97 Hz), 7.27 (s, 1H), 7.22 (t, 1H, J = 8.52 Hz), 4.70 (q, 2H, J = 7.06 Hz), 4.06 (s, 3H), 2.88 – 2.99 (m, 2H), 1.65 (br s, 1H), 1.45 (t, 3H, J = 7.01 Hz), 0.74 – 0.84 (m, 4H), 0.64 – 0.73 (m, 4H)

Example 40



Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(5-fluorobenzo[d]thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

40A Preparation of 5-fluoro-2-(methylthio)benzo[d]thiazole

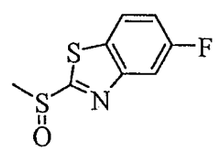


[00284] To a solution of 5-fluoro-2-mercaptobenzothiazole (0.15 g, 0.810 mmol) in THF (8.10 mL) cooled to 0 °C was added sodium hydride (0.036 g, 0.891 mmol). After stirring 10 min, iodomethane (0.076 mL, 1.215 mmol) was added and the reaction mixture was slowly warmed to room temperature over 2 h. The reaction was diluted with ethyl acetate and quenched with saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. 5-fluoro-2-(methylthio)benzo[d]thiazole (0.178 g, 110 % yield) was isolated as a white solid. Material was used without any further purification.

[00285] MS (ESI) m/z 200.0 (M+H)

[00286] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.68 (dd, 1H, J = 8.81, 5.04 Hz), 7.56 (dd, 1H, J = 9.57, 2.52 Hz), 7.07 (td, 1H, J = 8.81, 2.52 Hz), 2.80 (s, 3H)

40B Preparation of 5-fluoro-2-(methylsulfinyl)benzo[d]thiazole



[00287] 5-Fluoro-2-(methylthio)benzo[d]thiazole (example **40A**, 0.178 g, 0.893 mmol) was dissolved in CH_2Cl_2 (5.96 mL). mCPBA (0.154 g, 0.893 mmol) was added in one portion and the reaction mixture was stirred at room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate and diluted with dichloromethane. The aqueous layer was extracted with dichloromethane (2 x). The combined organic were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. 5-Fluoro-2-(methylsulfinyl)benzo[d]thiazole (0.180 g, 94 % yield) was isolated as a white solid and used without further purification.

[00288] MS (ESI) m/z 216.0 (M+H)

[00289] 1H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.97 (dd, 1H, *J* = 9.07, 4.95 Hz), 7.76 (dd, 1H, *J* = 9.07, 2.47 Hz), 7.27 – 7.34 (m, 1H), 3.10 (s, 3H)

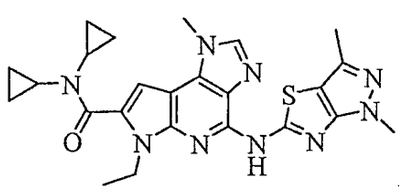
40 Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(5-fluorobenzo[d]thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00290] To a solution of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J,** 50 mg, 0.148 mmol) in DMF (1.5mL) was added sodium hydride (17.73 mg, 0.443 mmol). After 20 min, 5-fluoro-2-(methylsulfinyl)benzo[d]thiazole (example **40B,** 95 mg, 0.443 mmol) was added in one portion. The reaction mixture was stirred at room temperature. The reaction mixture was diluted with ethyl acetate and quenched with water. The aqueous layer was extracted with ethyl acetate (2 x). The combined organic layers were washed with 10% lithium chloride solution (2 x), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography using an Isco 12 g column eluting with 0-5% MeOH/CH_2Cl_2 to provide *N,N*-dicyclopropyl-6-ethyl-4-(5-fluorobenzo[d]thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (13 mg, 17.07 % yield).

[00291] MS (CI) m/z 490.2 (M+H)

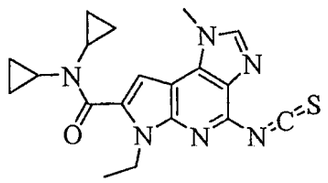
[00292] 1H NMR (400 MHz, DMSO-d_6) δ ppm 11.53 (br s, 1H), 8.19 (s, 1H), 7.95 - 8.02 (m, 1H), 7.47 (d, 1H, *J* = 9.82 Hz), 7.28 (s, 1H), 7.09 (t, 1H, *J* = 8.18 Hz), 4.69 (q, 2H, *J* = 7.13 Hz), 4.06 (s, 3H), 2.89 – 3.02 (m, 2H), 1.45 (t, 3H, *J* = 7.05 Hz), 0.74 – 0.81 (m, 4H), 0.63 – 0.71 (m, 4H)

Example 41



Preparation of *N,N*-dicyclopropyl-4-(1,3-dimethyl-1*H*-pyrazolo[3,4-d]thiazol-5-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

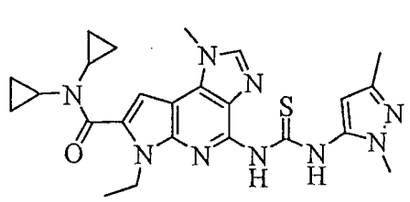
41A Preparation of *N,N*-dicyclopropyl-6-ethyl-4-isothiocyanato-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00293] To a mixture of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (194.5 mg, 0.575 mmol) in dichloromethane (2874 μL) in a round bottom flask under nitrogen was added 1,1'-thiocarbonyldi-2(1H)-pyridone (133 mg, 0.575 mmol). The reaction mixture was stirred at room temperature for 16h. The reaction mixture was concentrated under reduced pressure. *N,N*-Dicyclopropyl-6-ethyl-4-isothiocyanato-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide was isolated as a yellow sticky solid. Material was used as is in subsequent reactions.

[00294] MS (ESI) m/z 381.1 (M+H)

41B Preparation of *N,N*-dicyclopropyl-4-(3-(1,3-dimethyl-1*H*-pyrazol-5-yl)thioureido)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00295] To a flask charged with *N,N*-dicyclopropyl-6-ethyl-4-isothiocyanato-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **41A,** 0.0342 g, 0.090 mmol) was added THF (0.449 mL). 5-Amino-1,3-dimethylpyrazole (0.012 g, 0.108 mmol) was added followed by sodium hydride

(3.60 mg, 0.090 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate and quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate. The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude material was used without further purification.

[00296] MS (ESI) m/z 492.2 (M+H)

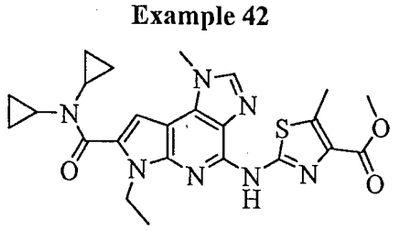
41 Preparation of *N,N*-dicyclopropyl-4-(1,3-dimethyl-1*H*-pyrazolo[3,4-d]thiazol-5-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00297] *N,N*-Dicyclopropyl-4-(3-(1,3-dimethyl-1*H*-pyrazol-5-yl)thioureido)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **41B,** 41 mg, 0.083 mmol) was dissolved in chloroform (2780 μL) and cooled to 0 °C. NIS (18.76 mg, 0.083 mmol) was slowly added and the reaction was warmed to room temperature. The reaction mixture was concentrated. Methanol and ether were added and the mixture was filtered. After standing for a week, product precipitated out of the solution. The product was triturated with methanol. *N,N*-Dicyclopropyl-4-(1,3-dimethyl-1*H*-pyrazolo[3,4-d]thiazol-5-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide was isolated as a pale yellow solid (8.1 mg, 20% yield).

[00298] MS (ESI) m/z 490.3 (M+H)

[00299] 1H NMR (400 MHz, DMSO-d_6) δ ppm 11.39 (s, 1H), 8.17 (s, 1H), 7.26 (s, 1H), 4.66 (q, 2H, J = 7.03 Hz), 4.05 (s, 3H), 3.85 (s, 3H) 2.88 – 3.00 (m, 2H), 2.33 (s, 3H), 1.43 (t, 3H, J = 7.03 Hz), 0.72 – 0.82 (m, 4H), 0.61 – 0.73 (m, 4H)

Example 42



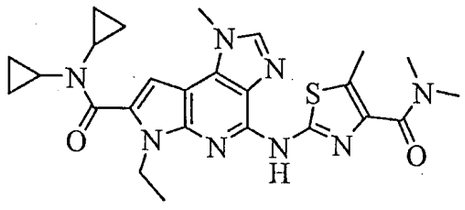
Methyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-5-methylthiazole-4-carboxylate

[00300] Methyl 3-bromo-2-oxobutanoate (320 mg, 1.642 mmol) was added to a suspension of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **2B,** 435 mg, 1.094 mmol) in EtOH (10 ml) and the reaction mixture was heated at 65 °C for 2h. The solvent was removed *in vacuo* and the residue purified by silica gel chromatography (2-10% MeOH/dichloromethane) to give methyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-5-methylthiazole-4-carboxylate (380 mg , 70% yield) as yellow solid.

[00301] MS (ESI) rt = 0.87 min, m/z 494 (M+H)

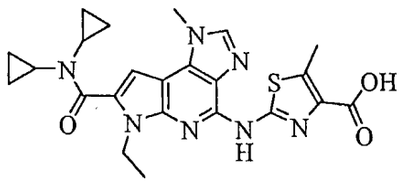
[00302] 1H NMR (CHLOROFORM-d) δ: 9.41 (br. s., 1H), 7.78 (s, 1H), 6.89 (s, 1H), 4.73 (q, J = 7.0 Hz, 2H), 4.03 (s, 3H), 3.95 (s, 3H), 2.80 - 2.87 (m, 2H), 2.77 (s, 3H), 1.54 (t, J = 7.0 Hz, 3H), 0.83 - 0.90 (m, 4H), 0.73 - 0.80 (m, 4H).

Example 43



2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N,N*,5-trimethylthiazole-4-carboxamide

43A Preparation of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-5-methylthiazole-4-carboxylic acid



[00303] 1N Aqueous NaOH (0.962 mL, 0.962 mmol) was added to a suspension of methyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-5-methylthiazole-4-carboxylate (example **41**, 0.19 g, 0.385 mmol) in ethanol (2 mL) and the mixture was heated at 60 °C for 2h. The reaction was cooled to room temperature and acidified with 1N HCl to pH 4. The reaction mixture was concentrated and the residue triturated 5x with methanol. The combined methanol washes were concentrated, and the remaining solid washed 3x with 2:1 ether/dichloromethane provided 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-5-methylthiazole-4-carboxylic acid (105 mg , 57% yield).

[00304] MS (ESI) rt = 0.79 min, m/z 480 (M+H)

43 Preparation of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N,N*,5-trimethylthiazole-4-carboxamide

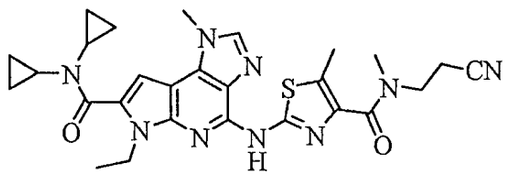
[00305] A mixture of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-5-methylthiazole-4-carboxylic acid (**43A**, 30 mg, 0.063 mmol), dimethylamine, 40% aqueous (0.016 mL, 0.125 mmol) and HATU (35.7 mg, 0.094 mmol) in DMF (1 mL) was stirred at room temperature for 3h. The solvent was evaporated off and the residue purified by silica gel chromatography (2-10% MeOH/dichloromethane). The material was further purified by preparative HPLC to give of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo [2,3-b]pyridin-4-ylamino)-*N,N*,5-trimethylthiazole-4-carboxamide (20 mg , 62.5% yield) as off-white solid.

[00306] MS (ESI) m/z 507 (M+H)

[00307] 1H NMR (400 MHz, CHLOROFORM-d) δ: 7.79 (s, 1H), 6.90 (s, 1H), 4.73 (q, J = 7.0 Hz, 2H), 4.05 (s, 3H), 3.12 (s., 3H), 3.11 (s, 3H), 2.80 - 2.87 (m, 2H), 2.53 (s, 3H), 1.53 (t, J = 7.2 Hz, 3H), 0.83 - 0.91 (m, 4H), 0.74 - 0.80 (m, 4H)

Examples **44-49** were prepared using the similar protocol as described for example 42

Example 44

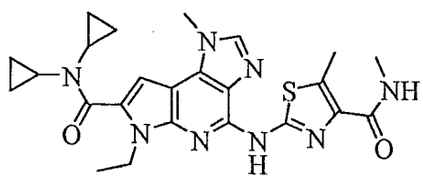


***N*-(2-cyanoethyl)-2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-N,5-dimethylthiazole-4-carboxamide**

[00308] MS (ESI) m/z 546 (M+H).

[00309] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.34 (br. s., 1 H) 7.75 (d, J=5.94 Hz, 1 H) 6.90 (s, 1 H) 4.74 (q, J=7.04 Hz, 2 H) 4.06 (s, 3 H) 3.80 (t, J=6.71 Hz, 2 H) 3.11 - 3.32 (m, 3 H) 2.95 (t, J=6.71 Hz, 2 H) 2.78 - 2.91 (m, 2 H) 2.58 (d, J=15.85 Hz, 3 H) 1.54 (t, J=7.04 Hz, 3 H) 0.70 - 0.94 (m, 8 H).

Example 45

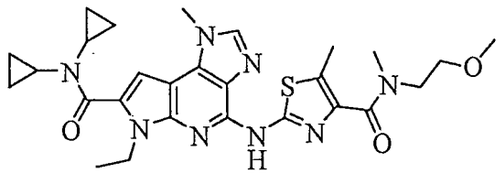


2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*,5-dimethylthiazole-4-carboxamide

[00310] MS (ESI) m/z 493 (M+H).

[00311] 1H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.84 (s, 1 H) 7.40 (d, J=4.99 Hz, 1 H) 6.90 (s, 1 H) 4.73 (q, J=6.94 Hz, 2 H) 4.08 (s, 3 H) 2.99 (d, *J*=4.99 Hz, 3 H) 2.73 - 2.91 (m, 5 H) 2.14 (s, 1 H) 1.53 (t, *J*=7.07 Hz, 3 H) 0.66 - 0.97 (m, 8 H).

Example 46

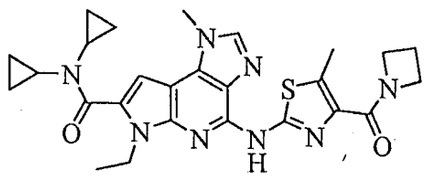


2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*-(2-methoxyethyl)-*N*,5-dimethylthiazole-4-carboxamide

[00312] MS (ESI) m/z 551 (M+H).

[00313] 1H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.73 (d, J=3.05 Hz, 1 H) 6.90 (s, 1 H) 4.74 (q, J=7.21 Hz, 2 H) 4.05 (s, 3 H) 3.72 (dd, *J*=13.73, 4.58 Hz, 2 H) 3.61 - 3.68 (m, 1 H) 3.57 (t, *J*=5.41 Hz, 1 H) 3.27 - 3.45 (m, 3 H) 3.17 (d, *J*=8.32 Hz, 3 H) 2.79 - 2.88 (m, 2 H) 2.54 (d, *J*=5.83 Hz, 3 H) 1.54 (t, *J*=7.07 Hz, 3 H) 0.73 - 0.92 (m, 8 H).

Example 47

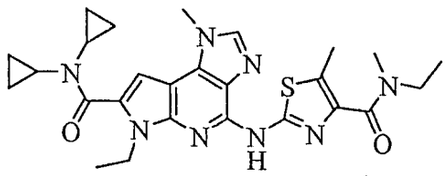


4-(4-(azetidine-1-carbonyl)-5-methylthiazol-2-ylamino)-*N*,*N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00314] MS (ESI) m/z 519 (M+H).

[00315] 1H NMR (500 MHz, CHLOROFORM-d) δ ppm 8.50 - 9.65 (m, 1 H) 8.00 (s, 1 H) 6.88 (s, 1 H) 4.68 (q, J=7.21 Hz, 2 H) 4.59 (t, *J*=7.63 Hz, 2 H) 4.18 (t, *J*=7.77 Hz, 2 H) 4.09 (s, 3 H) 2.78 - 2.89 (m, 2 H) 2.72 (s, 3 H) 2.30 (quin, *J*=7.70 Hz, 2 H) 1.49 (t, *J*=7.07 Hz, 3 H) 0.72 - 0.92 (m, 8 H).

Example 48

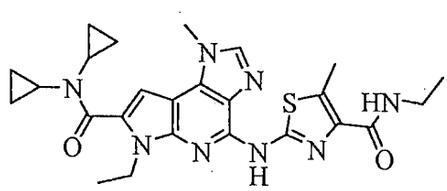


2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*-ethyl-*N*,5-dimethylthiazole-4-carboxamide

[00316] MS (ESI) m/z 521 (M+H).

[00317] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.77 (s, 1 H) 6.89 (s, 1 H) 4.74 (q, *J*=7.04 Hz, 2 H) 4.04 (s, 3 H) 3.36 – 3.66 (m, 2 H) 3.07 (d, *J*=14.09 Hz, 3 H) 2.72 – 2.90 (m, 2 H) 2.51 (s, 3 H) 2.11 (s, 1 H) 1.54 (t, *J*=7.04 Hz, 3 H) 1.13 – 1.35 (m, 3 H) 0.66 – 0.90 (m, 8 H).

Example 49

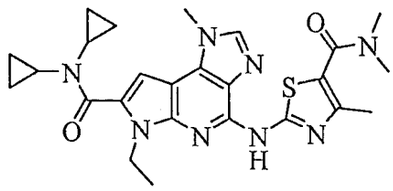


2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-4-ylamino)-*N*-ethyl-5-methylthiazole-4-carboxamide

[00318] MS (ESI) m/z 508 (M+H).

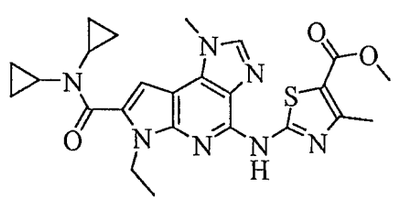
[00319] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.78 (s, 1 H) 6.89 (s, 1 H) 4.73 (q, J=7.04 Hz, 2 H) 4.42 (q, J=7.12 Hz, 2 H) 4.04 (s, 3 H) 2.78 – 2.91 (m, 2 H) 2.75 (s, 3 H) 2.15 (s, 1 H) 1.54 (t, *J*=7.04 Hz, 3 H) 1.44 (t, *J*=7.04 Hz, 3 H) 0.68 – 0.91 (m, 8 H).

Example 50



2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N,N*,4-trimethylthiazole-5-carboxamid

50A Preparation of methyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-methylthiazole-5-carboxylate

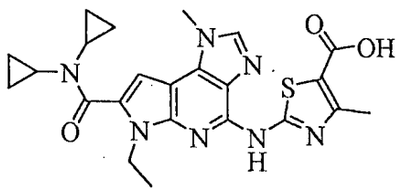


[00320] Methyl 2-bromo-3-oxobutanoate (213 mg, 1.094 mmol, prepared following the procedure described by Abu T. Khan et al. in *Tetrahedron Letters* **2006**, *47*, 2751-2754) was added to a suspension of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **2B**, 290 mg, 0.730 mmol) in ethanol (5 ml) and the reaction mixture was heated at 65 °C for 2h. LC/MS shows completion of reaction (reaction remained as suspension all the time). The reaction mixture was concentrated to remove ethanol, and taken up in dichloromethane. The solution was washed with saturated sodium bicarbonate and the aqueous layer was back extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by flash chromatography using an automated ISCO system (40 g column, eluting with 0-5% methanol / dichloromethane) to afford methyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-methylthiazole-5-carboxylate (301 mg, 0.610 mmol, 84 % yield) as a white solid.

[00321] MS (ESI) m/z 494.4 (M+H).

[00322] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 7.75 (s, 1H), 6.92 (s, 1H), 4.76 (q, J = 7.0 Hz, 2H), 4.08 (s, 3H), 3.92 (s, 3H), 2.82 - 2.89 (m, 2H), 2.71 (s, 3H), 1.59 (t, J = 7.0 Hz, 3H), 0.85 - 0.93 (m, 4H), 0.75 - 0.82 (m, 4H)

50B Preparation of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-methylthiazole-5-carboxylic acid



[00323] A mixture of methyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-methylthiazole-5-carboxylate (example **50A,** 288 mg, 0.583 mmol) and 1N NaOH (5.83 mL, 5.830 mmol) in methanol (5 mL) was heated at 65 °C for 18h. Methanol was evaporated and the aqueous solution was acidified to pH 4 with 1N HCl, solids crashed out of solution and were retained after filtration to afford the desired acid in pure form. The aqueous mixture was then extracted with dichloromethane, The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography using an automated ISCO system (40 g column, eluting with 0-8% methanol / dichloromethane). A total of 260 mg of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-methylthiazole-5-carboxylic acid (93 % yield)was obtained as a yellow solid.

[00324] MS (ESI) m/z 480.2 (M+H).

[00325] ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.03 (br. s., 1H), 7.06 (s, 1H), 4.40 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 2.96 (s, 1H), 2.69 - 2.76 (m, 2H), 2.36 (s, 3H), 1.20 (t, J = 6.9 Hz, 3H), 0.56 (d, J = 5.5 Hz, 4H), 0.45 - 0.50 (m, 4H).

50 Preparation of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N,N*,4-trimethylthiazole-5-carboxamide

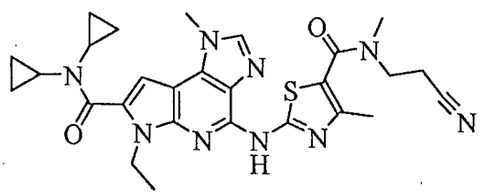
[00326] A mixture of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-methylthiazole-5-carboxylic acid (example **50B,** 51 mg, 0.106 mmol), dimethylamine (40% in water, 0.027 mL, 0.213 mmol), HATU (52.6 mg, 0.138 mmol) and 2,6-lutidine (0.025 mL, 0.213 mmol) in DMF (1 mL) was stirred at room temperature for 2h. Solvent was evaporated and the residue was purified by flash chromatography on silica gel using an automated ISCO system (24 g column, eluting with 2-8% methanol / dichloromethane). The product was further purified by preparative HPLC. 2-(7-(Dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N,N*,4-trimethylthiazole-5-carboxamide (17 mg, 0.032 mmol, 30.0 % yield) was obtained as a off-white solid.

[00327] MS (ESI) m/z 507.1 (M+H).

[00328] ^{1}H NMR (400 MHz, METHANOL-d_4) δ: 8.75 (s, 1H), 7.27 (s, 1H), 4.66 (q, J = 7.0 Hz, 2H), 4.21 (s, 3H), 3.19 (s, 6H), 2.95 - 3.02 (m, 2H), 2.39 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H), 0.86 - 0.93 (m, 4H), 0.78 - 0.84 (m, 4H)

Examples **51-55** were synthesized using the same method as used for **50**.

Example 51

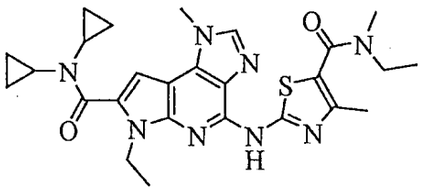


***N*-(2-cyanoethyl)-2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*,4-dimethylthiazole-5-carboxamide**

[00329] MS (ESI) m/z 546.1 (M+H).

[00330] ^{1}H NMR ($CDCl_3$) δ: 7.77 (s, 1H), 6.89 (s, 1H), 4.71 (q, J = 6.9 Hz, 2H), 4.05 (s, 3H), 3.81 (t, J = 6.6 Hz, 2H), 3.31 (s, 3H), 2.78 - 2.86 (m, 4H), 2.44 (s, 3H), 1.53 (t, J = 7.0 Hz, 3H), 0.83 - 0.90 (m, 4H), 0.73 - 0.79 (m, 4H).

Example 52

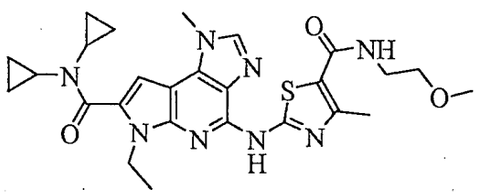


2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*-ethyl-*N*,4-dimethylthiazole-5-carboxamide

[00331] MS (ESI) m/z 521.1 (M+H).

[00332] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (s, 1H), 6.88 (s, 1H), 4.72 (q, J = 7.0 Hz, 2H), 4.04 (s, 3H), 3.57 (q, J = 7.2 Hz, 2H), 3.11 (s, 3H), 2.79 - 2.86 (m, 2H), 2.40 (s, 3H), 1.51 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 0.82 - 0.90 (m, 4H), 0.73 - 0.79 (m, 4H).

Example 53

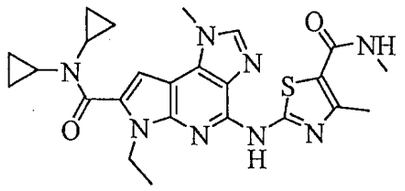


2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*-(2-methoxyethyl)-4-methylthiazole-5-carboxamide

[00333] MS (ESI) m/z 537.1 (M+H).

[00334] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (s, 1H), 6.89 (s, 1H), 6.13 (t, J = 4.7 Hz, 1H), 4.74 (q, J = 7.0 Hz, 2H), 4.05 (s, 3H), 3.65 (q, J = 5.1 Hz, 2H), 3.58 (t, J = 4.8 Hz, 2H), 3.42 (s, 3H), 2.79 - 2.87 (m, 2H), 2.65 (s, 3H), 1.58 (t, J = 7.0 Hz, 3H), 0.83 - 0.90 (m, 4H), 0.73 - 0.80 (m, 4H).

Example 54

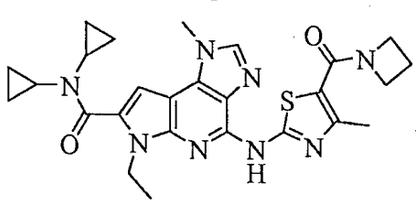


2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-*N*,4-dimethylthiazole-5-carboxamide

[00335] MS (ESI) m/z 493.1 (M+H).

[00336] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (s, 1H), 6.86 (s, 1H), 5.87 - 5.94 (m, J = 4.6 Hz, 1H), 4.66 (q, J = 7.1 Hz, 2H), 4.04 (s, 3H), 3.04 (d, J = 4.6 Hz, 3H), 2.79 - 2.87 (m, 2H), 2.62 (s, 3H), 1.51 (t, J = 7.0 Hz, 3H), 0.83 - 0.90 (m, 4H), 0.73 - 0.80 (m, 4H).

Example 55

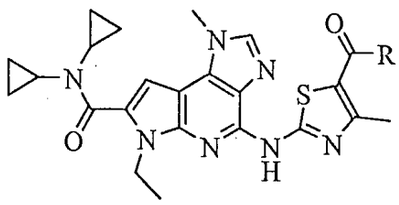


4-(5-(azetidine-1-carbonyl)-4-methylthiazol-2-ylamino)-*N*,*N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

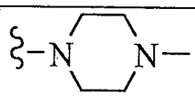
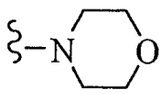
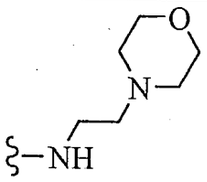
[00337] MS (ESI) m/z 519.1 (M+H).

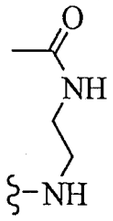
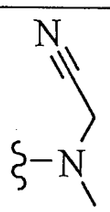
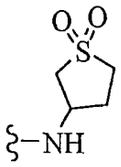
[00338] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (s, 1H), 6.90 (s, 1H), 4.73 (q, J = 7.0 Hz, 2H), 4.33 (br. s., 4H), 4.05 (s, 3H), 2.80 - 2.87 (m, 2H), 2.66 (s, 3H), 2.33 – 2.43 (m, 2H), 1.55 (t, J = 7.2 Hz, 3H), 0.83 - 0.90 (m, 4H), 0.73 - 0.80 (m, 4H).

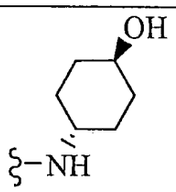
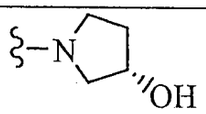
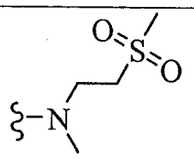
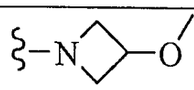
[00339] Examples **56-70** were synthesized using same procedure as used for **50**

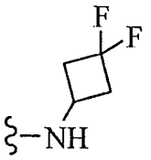
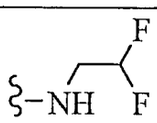
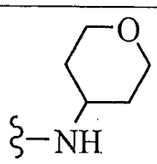
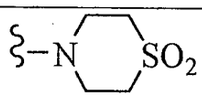


5

Ex. No.	R	Name	Retention time ((min)	MS (ESI) m/z
56		*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-((4-methyl-5-((4-methyl-1-piperazinyl)carbonyl)-1,3-thiazol-2-yl)amino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.43	562.31
57		*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-((4-methyl-5-(4-morpholinylcarbonyl)-1,3-thiazol-2-yl)amino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.70	549.25
58		*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-((4-methyl-5-((2-(4-morpholinyl)ethyl)carbamoyl)-1,3-thiazol-2-yl)amino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.46	592.3

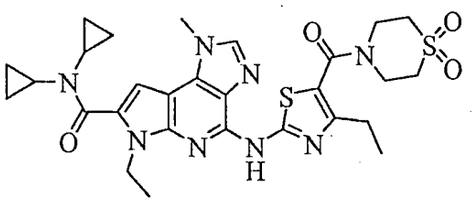
Ex. No.	R	Name	Retention time ((min)	MS (ESI) m/z
59		4-((5-((2-acetamidoethyl)carbamoyl)-4-methyl-1,3-thiazol-2-yl)amino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.51	564.27
60		4-((5-((cyanomethyl)(methyl)carbamoyl)-4-methyl-1,3-thiazol-2-yl)amino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.78	532.25
61		4-((5-((cyanomethyl)carbamoyl)-4-methyl-1,3-thiazol-2-yl)amino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.72	518.24
62		*N,N*-dicyclopropyl-4-((5-((1,1-dioxidotetrahydro-3-thiophenyl)carbamoyl)-4-methyl-1,3-thiazol-2-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.68	597.24

Ex. No.	R	Name	Retention time ((min)	MS (ESI) m/z
63		*N,N*-dicyclopropyl-6-ethyl-4-((5-((trans-4-hydroxycyclohexyl)carbamoyl)-4-methyl-1,3-thiazol-2-yl)amino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.60	577.3
64		*N,N*-dicyclopropyl-6-ethyl-4-((5-(((3S)-3-hydroxy-1-pyrrolidinyl)carbonyl)-4-methyl-1,3-thiazol-2-yl)amino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.51	549.28
65		*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-((4-methyl-5-(methyl(2-(methylsulfonyl)ethyl)carbamoyl)-1,3-thiazol-2-yl)amino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.59	599.26
66		*N,N*-dicyclopropyl-6-ethyl-4-((5-((3-methoxy-1-azetidinyl)carbonyl)-4-methyl-1,3-thiazol-2-yl)amino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.80	549.28

Ex. No.	R	Name	Retention time ((min)	MS (ESI) m/z
67		*N,N*-dicyclopropyl-4-((5-((3,3-difluorocyclobutyl)carbamoyl)-4-methyl-1,3-thiazol-2-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	2.06	569.27
68		*N,N*-dicyclopropyl-4-((5-((2,2-difluoroethyl)carbamoyl)-4-methyl-1,3-thiazol-2-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.88	543.23
69		*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-((4-methyl-5-(tetrahydro-2H-pyran-4-ylcarbamoyl)-1,3-thiazol-2-yl)amino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.87	563.26
70		*N,N*-dicyclopropyl-4-((5-((1,1-dioxido-4-thiomorpholinyl)carbonyl)-4-methyl-1,3-thiazol-2-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	1.66	597.26

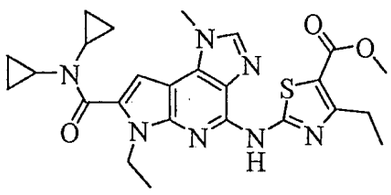
Analysis Condidtions- Column- Mac-Mod Halo 4.6 x 50 mm 2.7 um; Gradient-4 min from 0%B to 100%B; Flow rate- 4 mL/min; Solvent- A = 5 :95 Acetonitrile : Water; B = 90 :5 Acetonitrile : Water; Modifier = 10 mM NH_4OAc

Example 71



***N,N*-dicyclopropyl-6-ethyl-4-(4-ethyl-5-(1,1-dioxothiomorpholine-4-carbonyl)thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

71A Preparation of methyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-ethylthiazole-5-carboxylate



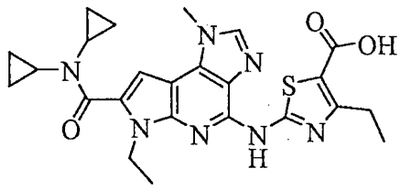
[00340] To a stirred suspension of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (103 mg, 0.259 mmol) in EtOH (5 ml) was added freshly prepared methyl 2-bromo-3-oxopentanoate[1] (81 mg, 0.389 mmol) at room temperature. The slurry was then stirred at 65 °C for 2h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo* to afford a yellow solid. The solid was then taken up in methylene chloride and washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate and concentrated *in*

vacuo. The crude residue was then purified by silica-gel flash chromatography using an Isco 40 g column eluting from 0-5% methanol/methylene chloride to afford methyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-ethylthiazole-5-carboxylate (37.5 mg, 28.5 % yield) as a white solid.

[00341] MS (ESI) m/z 508.4 (M+H)

[00342] 1H NMR (CDCl3) δ ppm 9.38 (br s, 1 H), 7.75 (s, 1 H), 6.92 (s, 1 H), 4.76 (q, 2 H, J = 6.94 Hz), 4.08 (s, 3H), 3.92 (s, 3H), 3.14 (q, 2H, J = 7.68 Hz), 2.85 (m, 2H), 1.59 (t, 3H, J = 6.94 Hz), 1.34 (t, 3H, J = 7.49 Hz), 0.78-0.91 (m, 8H)

71B Preparation of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-ethylthiazole-5-carboxylic acid



[00343] To a stirred solution of methyl 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-ethylthiazole-5-carboxylate (example **71A**, 103 mg, 0.203 mmol) in MeOH (2mL) was added NaOH (1.420 mL, 1.420 mmol). The solution was then stirred at 65 °C for 18 hrs. The reaction mixture was then cooled to room temperature and concentrated *in vacuo* to afford yellow slurry. The mixture was then diluted with water, brought to pH 4 with 1N HCl, and the precipitate collected by vacuum filtration. The filtrate was then extracted with CH_2Cl_2; the organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude residue was then purified by silica-gel flash chromatography using an Isco 40 g column eluting from 0-8% MeOH/CH_2Cl_2. Desired fractions were combined with the collected precipitate and concentrated to afford 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-ethylthiazole-5-carboxylic acid (126 mg, 126 % yield) as an orange/yellow solid.

[00344] MS (ESI) m/z 494.2 (M+H)

[00345] 1H NMR (CDCl3) δ ppm 8.23 (s, 1 H), 7.28 (s, 1H), 4.62 (q, 2 H, *J* = 6.94 Hz), 4.07 (s, 3H), 3.04 (q, 2H, *J* = 7.49 Hz), 3.00 (m, 2H), 1.42 (t, 3H, *J* = 7.07 Hz), 1.23 (t, 3H, *J* = 7.63 Hz), 0.67-0.79 (m, 8H)

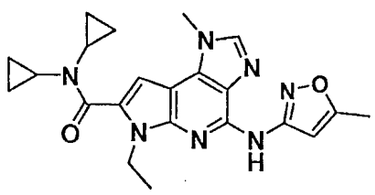
71 Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(4-ethyl-5-(1,1-dioxothiomorpholine-4-carbonyl)thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00346] To a stirred solution of 2-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4-ethylthiazole-5-carboxylic acid (example **69B,** 33 mg, 0.067 mmol), HATU (50.8 mg, 0.134 mmol), 2,6-lutidine (0.020 mL, 0.174 mmol), and DMF (1 mL) was added thiomorpholine 1,1-dioxide (27.1 mg, 0.201 mmol). The solution was then stirred at 50 °C for 1.5 hrs. The reaction was then cooled to room temperature and diluted with methylene chloride. The solution was then washed with saturated aqueous sodium bicarbonate, 10% LiCl in H_2O, and saturated aqueous sodium bicarbonate again. The organic phase was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude residue was then purified by silica-gel flash chromatography using an Isco 40 g column eluting from 0-6% MeOH/CH_2Cl_2 to give *N,N*-dicyclopropyl-6-ethyl-4-(4-ethyl-5-(1,1-dioxothiomorpholine -4-carbonyl)thiazol-2-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (21.7 mg, 52.6 % yield) as a pale yellow solid.

[00347] MS (ESI) m/z 611.3 (M+H)

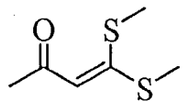
[00348] 1H NMR (CDCl3) δ ppm 7.68 (s, 1 H), 6.83 (s, 1 H), 4.65 (q, 2 H, *J* = 7.04), 4.13 (m, 4H), 3.99 (s, 3H), 3.05 (m, 4H), 2.76 (m, 2H), 2.68 (q, 2H, *J* = 7.56 Hz), 1.46 (t, 3H, *J* = 7.04 Hz), 1.25 (t, 3H, *J* = 7.59 Hz), 0.68-0.80 (m, 8H)

Example 72



N,N-dicyclopropyl-6-ethyl-1-methyl-4-(5-methylisoxazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

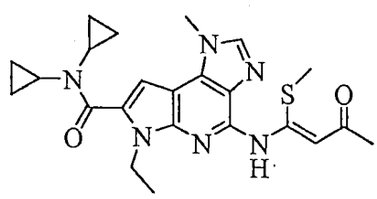
72A Preparation of 4,4-bis(methylthio)but-3-en-2-one



[00349] A solution of acetone (2.205 mL, 30.0 mmol) in carbon disulfide (1.81 mL, 30.0 mmol) was added to a suspension of sodium *tert*-butoxide (5.76 g, 60.0 mmol) in benzene (30 mL) while keeping the reaction temperature not exceeding 10 °C. The reaction mixture was stirred at room temperature for 3h and iodomethane (3.75 mL, 60.0 mmol) was added at 10 °C. The resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed twice with water. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using an automated ISCO system (80 g column, eluting with 10-35% ethyl acetate / hexanes) to give 4,4-bis(methylthio)but-3-en-2-one (3.456 g, 71.0 % yield) as a yellow solid.

[00350] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.04 (s, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 2.20 (s, 3H).

72B Preparation of (*Z*)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-(methylthio)-3-oxobut-1-enylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00351] Sodium hydride (2.84 g, 71.1 mmol) was added to a solution of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J,** 8.02 g, 23.70 mmol) in DMF (60 mL) and the

reaction mixture stirred at room temperature for 1 h. 4,4-bis(methylthio)but-3-en-2-one (example **70A,** 5.77 g, 35.5 mmol) in DMF (10 ml) was added and stirring continued for three days. LC/MS showed about 75% completion. The reaction mixture was diluted with ethyl acetate and water was added. An off-white precipitate formed and was collected by filtration to give 5.1 g of product. The filtrate was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (3x50 ml), the combined organic layers were washed with saturated sodium bicarbonate and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using an ISCO system (220 g column, eluting with 2-8% methanol / dichloromethane) to give (*Z*)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-(methylthio)-3-oxobut-1-enylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (6.6 g, 61.5% yield) along with 2.2 g of recovered **1J**.

[00352] MS (ESI) m/z 453.3 (M+H).

[00353] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 14.42 (s, 1H), 8.16 (s, 1H), 7.24 (s, 1H), 5.54 (s, 1H), 4.52 (q, J = 7.0 Hz, 2H), 4.05 (s, 3H), 2.89 - 2.97 (m, 2H), 2.43 (s, 3H), 2.14 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H), 0.71 - 0.80 (m, 4H), 0.63 - 0.70 (m, 4H).

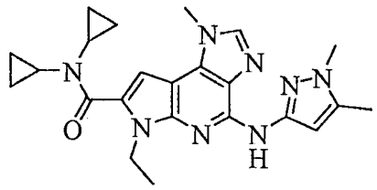
72 Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methylisoxazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00354] A mixture of (*Z*)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-(methylthio)-3-oxobut-1-enylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (22 mg, 0.049 mmol) and hydroxylamine (50% aqueous solution, 3.13 µL, 0.051 mmol) in ethanol (1 mL) was heated at reflux for 3h and LC/MS showed completion of reaction. The reaction mixture was diluted with methanol and purified by preparative HPLC to furnish *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methylisoxazol-3-ylamino)-1,6-dihy droimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (9 mg, 43.3 % yield) as a white solid.

[00355] MS (ESI) m/z 420.1 (M+H).

[00356] ^{1}H NMR (400 MHz, METHANOL-d_4) δ: 8.45 (s, 1H), 7.26 (s, 1H), 6.58 (s, 1H), 4.63 (q, J = 7.2 Hz, 2H), 4.17 (s, 3H), 2.94 - 3.02 (m, 2H), 2.33 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H), 0.85 - 0.92 (m, 4H), 0.77 - 0.84 (m, 4H).

Example 73



***N,N*-dicyclopropyl-4-(1,5-dimethyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

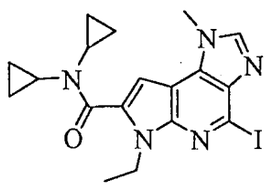
[00357] A mixture of (*Z*)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-(methylthio)-3-oxobut-1-enylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **72B**, 70 mg, 0.155 mmol) and *tert*-butyl 1-methylhydrazinecarboxylate (0.046 mL, 0.309 mmol) in acetic acid (1 mL) wan stirred at 35 °C for 4 h (monitored by LC/MS until no starting material left). Formic acid (0.5 mL) was added and stirred at 60 °C for 6 h. Solvent was evaporated and the crude product was purified by flash chromatography on silica gel using an automated ISCO system (12 g column, eluting with 2-10% methanol / dichloromethane). The impure product was further purified by preparative HPLC to give *N,N*-dicyclopropyl-4-(1,5-dimethyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (45 mg, 63.9 % yield) as an off-white solid.

[00358] MS (ESI) m/z 433.2 (M+H).

[00359] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 7.63 (s, 1H), 6.94 (s, 1H), 6.85 (s, 1H), 4.65 (q, J = 7.0 Hz, 2H), 3.99 (s, 3H), 3.71 (s, 3H), 2.79 - 2.85 (m, 2H), 2.33 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H), 0.82 - 0.87 (m, 4H), 0.72 - 0.78 (m, 4H)

Alternative synthesis of example 73

73A Preparation of 4-iodo-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00360] To a stirred suspension of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (34.4 mg, 0.102 mmol) in diiodomethane (102 µL) at 60 °C was slowly added isoamyl nitrite (27.4 µL, 0.203 mmol). The reaction mixture was stirred at 60 °C 5 h. After cooling to rt, the reaction mixture was diluted with dichloromethane. Saturated aqueous sodium bicarbonate was added and the aqueous layer was extracted with dichloromethane (3x). The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was placed on the pump for 16 h to remove any additional diiodomethane. LCMS was deemed pure enough to be carried forward crude. The product was used immediately in the next reaction.

[00361] MS (ESI) m/z 450.1 (M+H)

73 Prepararation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1,5-dimethyl-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

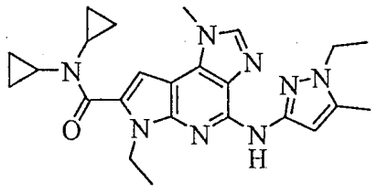
[00362] To a vial containing 1,5-dimethyl-1*H*-pyrazol-3-amine (13.60 mg, 0.122 mmol), $Pd_2(dba)_3$ (4.67 mg, 5.10 µmol), Xantphos (5.90 mg, 10.20 µmol), and cesium carbonate (100 mg, 0.306 mmol) was added *N,N*-dicyclopropyl-6-ethyl-4-iodo-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (45.8 mg, 0.102 mmol) in DME (1020 µL). The reaction mixture was sparged with argon for 5 min, the vial was capped, and the reaction mixture was heated at 90 °C 1 h. The reaction mixture was diluted with dichloromethane and vacuum filtered through Celite. The filtrate was concentrated *in vacuo*. The crude residue was purified via flash column chromatography using an ISCO 12 g column eluting with 1 - 10% MeOH/CH_2Cl_2). *N,N*-Dicyclopropyl-4-(1,5-dimethyl-1*H*-pyrazol-3-ylamino)-6-

ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (14 mg, 31.7 % yield) was isolated as an off-white solid.

[00363] MS (ESI) m/z 433.2 (M+H).

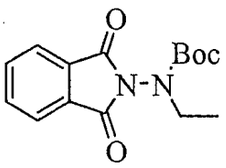
[00364] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 7.63 (s, 1H), 6.94 (s, 1H), 6.85 (s, 1H), 4.65 (q, J = 7.0 Hz, 2H), 3.99 (s, 3H), 3.71 (s, 3H), 2.79 - 2.85 (m, 2H), 2.33 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H), 0.82 - 0.87 (m, 4H), 0.72 - 0.78 (m, 4H)

Example 74



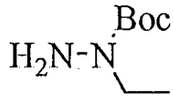
***N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-methyl-1H-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

74A Preparation of *tert*-butyl 1,3-dioxoisoindolin-2-yl(ethyl)carbamate



[00365] Diisopropyl azodicarboxylate (2.92 mL, 15.00 mmol) was added in one portion to a solution of *tert*-butyl 1,3-dioxoisoindolin-2-ylcarbamate (2.62 g, 10 mmol, prepared following the procedure described by Nicolas Brosse et al. in *Eur. J. Org. Chem.* 4757-4764, **2003**), triphenylphosphine (3.93 g, 15.00 mmol) and ethanol (0.691 g, 15.00 mmol) in THF (20 mL) at 0 °C and the reaction solution was stirred at room temperature for 1h (monitored by TLC until completion). Solvent was evaporated and the residue was purified by flash chromatography on silica gel using an automated ISCO system (80 g column, eluting with 5-35% ethyl acetate / hexanes) to provide *tert*-butyl 1,3-dioxoisoindolin-2-yl(ethyl)carbamate (2.6 g, 90 % yield) as a white solid which was used as it in the next step

74B Preparation of *tert*-butyl 1-ethylhydrazinecarboxylate



[00366] Methylhydrazine (1.415 mL, 26.9 mmol) was added to a solution of *tert*-butyl 1,3-dioxoisoindolin-2-yl(ethyl)carbamate (example **74A**, 5.2 g, 17.91 mmol) in THF (40 mL) at 0 °C and the reaction mixture was stirred at room temperature overnight. A white precipitate formed and was filtered off through a pad of Celite, The filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 ml) and extracted with 1N HCl (3x30 ml), the acid layer was washed with ethyl acetate (50 ml) and basified to pH 10 by addition of 20% NaOH. The basic solution was then extracted with ethyl acetate (3x50 ml) and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give *tert*-butyl 1-ethylhydrazinecarboxylate (2.5 g, 87 % yield) as colorless oil.

[00367] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.90 (br. s., 2H), 3.35 (q, J = 7.0 Hz, 2H), 1.42 (s, 9H), 1.07 (t, J = 7.0 Hz, 3H)

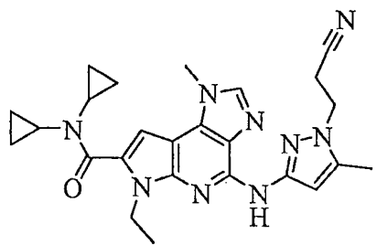
74 Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00368] A mixture of (*Z*)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-(methylthio)-3-oxobut-1-enylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **74B**, 70 mg, 0.155 mmol) and *tert*-butyl 1-ethylhydrazinecarboxylate (49.6 mg, 0.309 mmol) in acetic acid (1 mL) wan stirred at 35 °C for 4 h (monitored by LC/MS until no starting material left). Formic acid (1 mL) was added and the reaction mixture stirred at 60 °C for 6 h. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel using an automated ISCO system (12 g column, eluting with 2-10% methanol / dichloromethane). The material was further purified by preparative HPLC to afford *N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (38 mg, 53.4 % yield) as an off-white solid.

[00369] MS (ESI) m/z 447.3 (M+H).

[00370] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.61 (s, 1H), 6.93 (s, 1H), 6.84 (s, 1H), 4.66 (q, J = 7.1 Hz, 2H), 4.02 (q, J = 7.2 Hz, 2H), 3.98 (s, 3H), 2.79 - 2.85 (m, 2H), 2.34 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H), 1.41 (t, J = 7.2 Hz, 3H), 0.82 - 0.87 (m, 4H), 0.72 - 0.78 (m, 4H).

Example 75



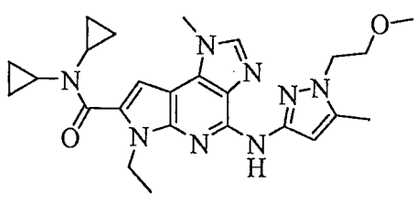
4-(1-(2-cyanoethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-*N*,*N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00371] The title compound was prepared using a method analogous to that used to prepare example **74**.

[00372] MS (ESI) m/z 472.2 (M+H).

[00373] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (s, 1H), 7.64 (s, 1H), 6.99 (s, 1H), 6.85 (s, 1H), 4.65 (q, J = 7.0 Hz, 2H), 4.25 (t, J = 6.8 Hz, 2H), 4.01 (s, 3H), 2.92 (t, J = 6.7 Hz, 2H), 2.79 - 2.86 (m, 2H), 2.41 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H), 0.82 - 0.88 (m, 4H), 0.72 - 0.80 (m, 4H).

Example 76



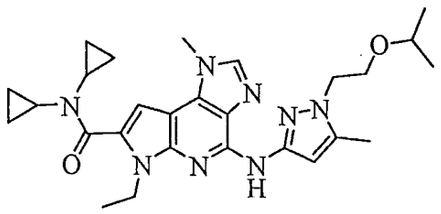
***N*,*N*-dicyclopropyl-6-ethyl-4-(1-(2-methoxyethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00374] The title compound was prepared using a method analogous to that used to prepare example **74**.

[00375] MS (ESI) m/z 477.2 (M+H).

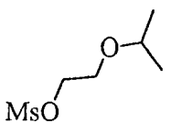
[00376] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.61 (s, 1H), 6.94 (s, 1H), 6.84 (s, 1H), 4.66 (q, J = 6.8 Hz, 2H), 4.12 (t, J = 5.5 Hz, 2H), 3.98 (s, 3H), 3.74 (t, J = 5.8 Hz, 2H), 3.32 (s, 3H), 2.78 - 2.86 (m, 2H), 2.36 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H), 0.81 - 0.89 (m, 4H), 0.71 - 0.80 (m, 4H).

Example 77



***N,N*-dicyclopropyl-6-ethyl-4-(1-(2-isopropoxyethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

77A Preparation of 2-isopropoxyethyl methanesulfonate

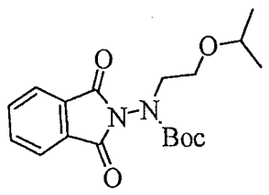


[00377] A round bottom flask was charged with 2-isopropoxyethanol (0.5 mL, 4.34 mmol) and dichloromethane (21.68 mL) and was cooled to 0 °C. Triethylamine (1.208 mL, 8.67 mmol) was added along with a tip of DMAP. Methanesulfonyl chloride (0.338 mL, 4.34 mmol) was added dropwise. The reaction mixture was slowly warmed to rt over 2 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and transferred to a separatory funnel. The aqueous layer was extracted with dichloromethane (2 x). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*.

2-Isopropoxyethyl methanesulfonate (1 g) was isolated as a clear oil and was immediately used in the next reaction.

[00378] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 4.34 - 4.40 (m, 2H), 3.67 – 3.71 (m, 2H), 3.60 – 3.67 (m, 1H), 3.07 (s, 3H), 1.18 (d, 6H, J = 8.0 Hz)

77B Preparation of *tert*-butyl 1,3-dioxoisoindolin-2-yl(2-isopropoxyethyl)carbamate

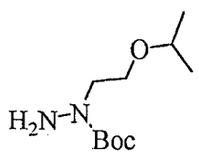


[00379] A round bottom flask charged with 2-isopropoxyethyl methanesulfonate (example **77A,** 0.791 g, 4.34 mmol) in acetonitrile (21.70 mL) was stirred under an atmosphere of nitrogen. *tert*-Butyl 1,3-dioxoisoindolin-2-ylcarbamate (1.138 g, 4.34 mmol) was added along with potassium carbonate (2.399 g, 17.36 mmol) and benzyltriethylammonium chloride (0.198 g, 0.868 mmol). The reaction mixture was heated at 50 °C 24 h and cooled to rt over the weekend. The reaction mixture was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous sodium sulfate, vacuum filtered through a plug of silica gel and concentrated *in vacuo*. The crude oil was used without additional purification (1.26 g, 83% yield).

[00380] MS (ESI) m/z 249.2 ($M-C_4H_9CO_2$)

[00381] 1H NMR (400 MHz, CHLOROFORM-d) as a mixture of rotomers δ ppm 1H NMR (400 MHz, CHLOROFORM-d) d ppm 7.86 - 7.94 (m, 2 H), 7.73 - 7.82 (m, 2 H), 3.79 - 3.90 (m, 2 H), 3.58 - 3.66 (m, 2 H), 3.41 - 3.55 (m, 1 H), 1.31 - 1.56 (m, 9 H), 0.87 - 1.05 (m, 6 H)

77C Preparation of *tert*-butyl 1-(2-isopropoxyethyl)hydrazinecarboxylate



[00382] To a solution of *tert*-butyl 1,3-dioxoisoindolin-2-yl(2-isopropoxyethyl)carbamate (example **77B,** 1.262 g, 3.62 mmol) in tetrahydrofuran (24.15 mL) at 0 °C was slowly added methylhydrazine (0.289 mL, 5.43 mmol). The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was filtered to remove the white precipitate and the filtrate was concentrated *in vacuo*. The semisolid was triturated with ethyl acetate (2 x) and the triturant was concentrated *in vacuo*. This process was repeated to ultimately provide *tert*-butyl 1-(2-isopropoxyethyl)hydrazinecarboxylate (0.665 g, 84% yield) as a yellow oil.

[00383] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 3.52 - 3.65 (m, 5 H), 1.48 (s, 9 H), 1.15 (d, 6 H, J = 6.27 Hz)

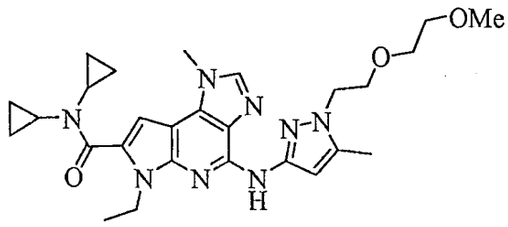
77 Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(1-(2-isopropoxyethyl)-5-methyl-1H-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00384] This compound was prepared according to example **73** using *tert*-butyl 1-(2-isopropoxyethyl)hydrazinecarboxylate (example **77C,** 29.8 mg, 0.137 mmol) to provide *N,N*-dicyclopropyl-6-ethyl-4-(1-(2-isopropoxyethyl)-5-methyl-1H-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (16.72 mg, 48.7% yield) as a white solid.

[00385] MS (ESI) m/z 505.4 (M+H)

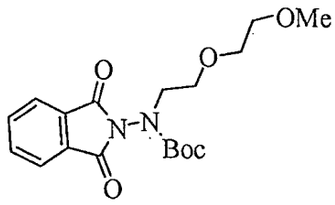
[00386] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.89 (s, 1 H), 6.99 (s, 1 H), 6.88 (s, 1H), 4.65 (q, 2 H, J = 7.03 Hz), 4.22 (t, 2H, J = 5.27 Hz), 4.06 (s, 3 H), 3.78 (t, 2H, J = 5.27 Hz), 3.52 (dt, 1H, J = 12.11, 6.12 Hz), 2.79 - 2.88 (m, 2 H), 2.41 (s, 3H), 1.50 (t, 3 H, J = 7.03 Hz), 1.09 (d, 6H, J = 6.27 Hz), 0.82 - 0.91 (m, 4 H), 0.71 - 0.81 (m, 4 H)

Example 78



N,N-dicyclopropyl-6-ethyl-4-(1-(2-(2-methoxyethoxy)ethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

78A Preparation of *tert*-butyl 1,3-dioxoisoindolin-2-yl(2-(2-methoxyethoxy)ethyl) carbamate

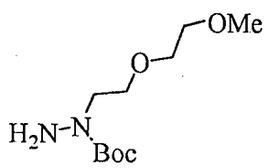


[00387] The compound was prepared according to Example **77B** using 1-bromo-2-(2-methoxyethoxy)ethane (0.259 mL, 1.906 mmol) to provide *tert*-butyl 1,3-dioxoisoindolin-2-yl(2-(2-methoxyethoxy)ethyl)carbamate (0.583 g, 84 % yield) as a pale yellow oil.

[00388] MS (ESI) m/z 265.2 ($M-C_4H_9CO_2$)

[00389] 1H NMR (400 MHz, CHLOROFORM-d) as a mixture of rotomers δ ppm 7.85 - 7.94 (m, 2 H), 7.73 - 7.82 (m, 2 H), 3.83 - 3.93 (m, 2 H), 3.67 - 3.74 (m, 2 H), 3.48 - 3.59 (m, 2 H), 3.30 - 3.43 (m, 2 H), 3.16 - 3.28 (m, 3 H), 1.29 - 1.55 (m, 9 H)

78B Preparation of *tert*-butyl 1-(2-(2-ethoxyethoxy)ethyl)hydrazinecarboxylate



[00390] The compound was prepared according to example **77C** using *tert*-butyl 1,3-dioxoisoindolin-2-yl(2-(2-methoxyethoxy)ethyl)carbamate (0.583 g, 1.600 mmol)

to provide *tert*-butyl 1-(2-(2-methoxyethoxy)ethyl)hydrazinecarboxylate (0.4 g, 107% yield) as a yellow oil.

[00391] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 3.51 - 3.70 (m, 8 H), 3.39 (s, 3 H), 1.48 (s, 9 H)

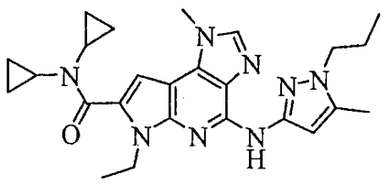
78 Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(1-(2-(2-methoxyethoxy)ethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00392] This compound was prepared according to example **74** using *tert*-butyl 1-(2-(2-methoxyethoxy)ethyl)hydrazinecarboxylate (example **78B,** 43.2 mg, 0.184 mmol) to provide *N,N*-dicyclopropyl-6-ethyl-4-(1-(2-(2-methoxyethoxy)ethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (17.34 mg, 36% yield) as a white solid.

[00393] MS (ESI) m/z 521.4 (M+H)

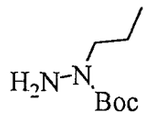
[00394] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.85 (br s, 1 H), 6.91 (s, 1 H), 6.87 (s, 1H), 4.65 (q, 2 H, *J* = 7.03 Hz), 4.20 (t, 2H, *J* = 5.27 Hz), 4.05 (s, 3 H), 3.87 (t, 2H, *J* = 5.65 Hz), 3.53 – 3.59 (m, 2H), 3.50 (ddd, 2H, *J* = 5.40, 2.89, 2.76 Hz), 2.77 - 2.87 (m, 2 H), 2.38 (s, 3H), 1.50 (t, 3 H, *J* = 7.03 Hz), 0.82 - 0.91 (m, 4 H), 0.71 - 0.79 (m, 4 H)

Example 79



Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methyl-1-propyl-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

79A Preparation of *tert*-butyl 1-propylhydrazinecarboxylate



[00395] To a solution of propylhydrazine, oxalic acid salt (0.5 g, 3.05 mmol) in ethanol (3 mL) in a round bottom flask under nitrogen was added triethylamine (0.425 mL, 3.05 mmol). The reaction mixture was cooled to 0 °C and BOC_2O (0.707 mL, 3.05 mmol) dissolved in ethanol (1 mL) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature for 16h. Ethanol was removed by concentration *in vacuo*. The residue was taken up in water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3x). The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was used as such in the next reaction.

[00396] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 3.30 - 3.36 (m, 2 H), 1.59 (dq, 3 H, J=14.40, 7.33 Hz), 1.48 (s, 9 H), 0.88 (t, 3 H, J=7.40 Hz)

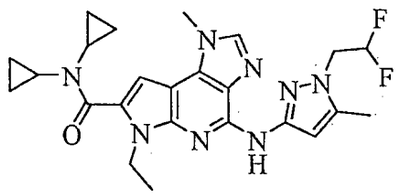
79 Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methyl-1-propyl-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00397] This compound was prepared according to example **74** using *tert*-butyl 1-propylhydrazinecarboxylate (example **79A,** 19.87 mg, 0.114 mmol) to provide *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methyl-1-propyl-1H-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (15.6 mg, 59% yield) as a white solid.

[00398] MS (ESI) m/z 461.4 (M+H)

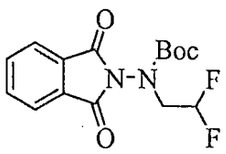
[00399] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.74 (br s, 1 H), 6.92 (s, 1 H), 6.86 (s, 1 H), 4.66 (q, 2 H, J = 7.11 Hz), 4.03 (s, 3 H), 3.95 (t, 2 H, J = 7.15 Hz), 2.78 - 2.87 (m, 2 H), 2.34 (s, 3 H), 1.87 (dq, 3 H, J = 14.49, 7.30 Hz), 1.50 (t, 3 H, J = 7.15 Hz), 0.96 (t, 3 H, J = 7.40 Hz), 0.83 - 0.89 (m, 4 H), 0.72 - 0.79 (m, 4 H)

Example 80



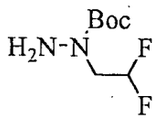
N,N-dicyclopropyl-4-(1-(2,2-difluoroethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

80A Preparation of *tert*-butyl 2,2-difluoroethyl(1,3-dioxoisoindolin-2-yl)carbamate



[00400] The title compound was prepared using a method analogous to that used to prepare example **77A**

80B Preparation of *tert*-butyl 1-(2,2-difluoroethyl)hydrazinecarboxylate



[00401] The title compound was prepared using a method analogous to that used to prepare example **77B**.

[00402] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 5.94 (tt, J = 56.3, 4.4 Hz, 1H), 3.74 (td, J = 13.8, 4.4 Hz, 2H), 1.48 (s, 9H)

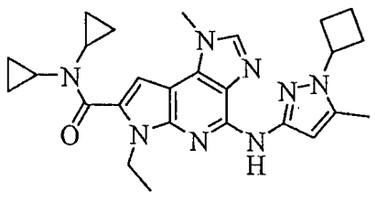
80 Preparation of *N,N*-dicyclopropyl-4-(1-(2,2-difluoroethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00403] The title compound was prepared using a method analogous to that used to prepare example **73**.

[00404] MS (ESI) m/z 483.3 (M+H).

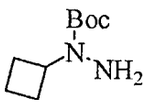
[00405] ^{1}H NMR 500 MHz, (CHLOROFORM-d) δ: 8.17 (br. s., 1H), 7.66 (s, 1H), 7.01 (s, 1H), 6.85 (s, 1H), 6.05 (tt, J = 56.0, 4.4 Hz, 1H), 4.65 (q, J = 6.9 Hz, 2H), 4.30 (td, J = 13.2, 4.3 Hz, 2H), 3.99 (s, 3H), 2.79 - 2.86 (m, 2H), 2.36 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H), 0.81 - 0.88 (m, 4H), 0.72 - 0.79 (m, 4H).

Example 81



4-(1-cyclobutyl-5-methyl-1*H*-pyrazol-3-ylamino)-*N*,*N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

81A Preparation of *tert*-butyl 1-cyclobutylhydrazinecarboxylate



[00406] The title compound was prepared following the procedure described by So Ok Park et al. in *J. Comb. Chem.* 11, 315-326, **2009**.

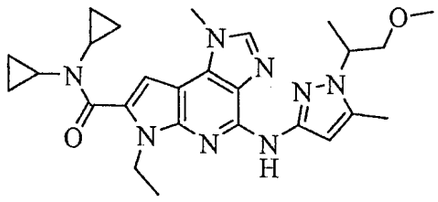
81 Preparation of 4-(1-cyclobutyl-5-methyl-1*H*-pyrazol-3-ylamino)-*N*,*N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00407] The title compound was prepared using a method analogous to that used to prepare example **73**.

[00408] MS (ESI) m/z 473.4(M+H).

[00409] ^{1}H NMR (500 MHz, CHLOROFORM-d) δ: 8.05 (s, 1H), 6.91 (s, 1H), 6.79 (s, 1H), 4.68 (quin, J = 8.4 Hz, 1H), 4.61 (q, J = 7.1 Hz, 2H), 4.07 (s, 3H), 2.80 - 2.87 (m, 2H), 2.69 - 2.79 (m, 2H), 2.37 - 2.47 (m, 2H), 2.32 (s, 3H), 1.78 - 1.98 (m, 2H), 1.47 (t, J = 7.1 Hz, 3H), 0.82 - 0.91 (m, 4H), 0.72 - 0.80 (m, 4H).

Example 82



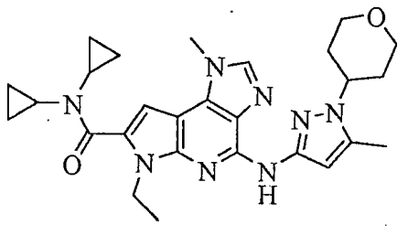
***N,N*-dicyclopropyl-6-ethyl-4-(1-(1-methoxypropan-2-yl)-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00410] Prepared as described in example **77**.

[00411] MS (ESI) m/z 491 (M+H).

[00412] 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.18 (br. s., 1 H) 7.63 (s, 1 H) 6.93 (s, 1 H) 6.85 (s, 1 H) 4.66 (q, *J*=7.04 Hz, 2 H) 4.29 - 4.48 (m, *J*=13.31, 6.82, 6.82, 6.71 Hz, 1 H) 4.00 (s, 3 H) 3.55 - 3.79 (m, 2 H) 3.29 (s, 3 H) 2.72 - 2.92 (m, 2 H) 2.36 (s, 3 H) 1.49 (t, *J*=7.04 Hz, 3 H) 1.46 (d, *J*=6.82 Hz, 2 H) 0.68 - 0.93 (m, 8 H).

Example 83



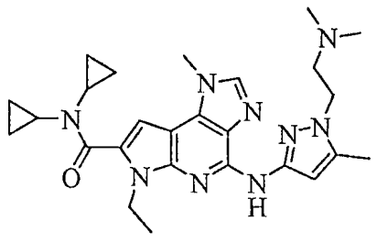
***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00413] Prepared using similar procedure as for example **77**.

[00414] MS (ESI) m/z 503 (M+H).

[00415] 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.12 (s, 1 H) 7.64 (s, 1 H) 6.95 (s, 1 H) 6.86 (s, 1 H) 4.66 (q, *J*=7.21 Hz, 2 H) 4.09 - 4.23 (m, 3 H) 4.01 (s, 3 H) 3.55 (td, *J*=12.00, 1.80 Hz, 2 H) 2.73 - 2.89 (m, 2 H) 2.37 (s, 3 H) 2.25 - 2.36 (m, 2 H) 1.84 (dd, *J*=12.76, 2.22 Hz, 2 H) 1.50 (t, *J*=7.07 Hz, 3 H) 0.71 - 0.91 (m, 8 H).

Example 84



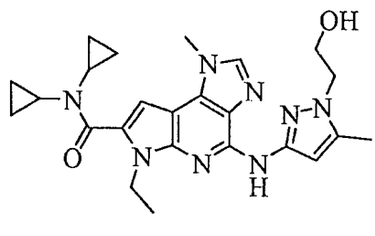
***N,N*-dicyclopropyl-4-(1-(2-(dimethylamino)ethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00416] Prepared using similar procedure as for example **77**.

[00417] MS (ESI) m/z 490 (M+H).

[00418] 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.08 (s, 1 H) 7.64 (s, 1 H) 6.96 (s, 1 H) 6.86 (s, 1 H) 4.65 (q, *J*=7.21 Hz, 2 H) 4.24 (br. s., 2 H) 4.01 (s, 3 H) 3.01 - 3.22 (m, 2 H) 2.70 - 2.89 (m, 2 H) 2.50 (br. s., 6 H) 2.37 (s, 3 H) 1.49 (t, *J*=7.07 Hz, 3 H) 0.71 - 0.91 (m, 8 H).

Example 85



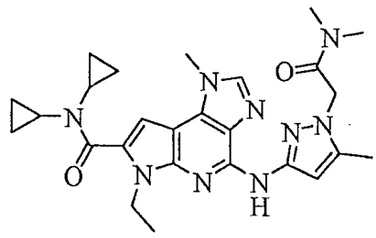
N,N-dicyclopropyl-6-ethyl-4-(1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00419] Prepared using similar procedure as for example 77.

[00420] MS (ESI) m/z 463 (M+H).

[00421] 1H NMR (500 MHz, MeOD) δ ppm 7.93 (s, 1 H) 7.16 (s, 1 H) 6.88 (s, 1 H) 4.60 (q, *J*=7.21 Hz, 2 H) 4.09 (t, *J*=5.55 Hz, 2 H) 4.05 (s, 3 H) 3.88 (t, *J*=5.55 Hz, 2 H) 2.88 - 3.00 (m, 2 H) 2.37 (s, 3 H) 1.43 (t, *J*=7.07 Hz, 3 H) 0.62 - 0.98 (m, 8 H).

Example 86



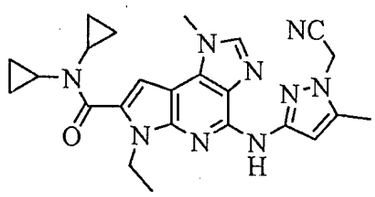
N,N-dicyclopropyl-4-(1-(2-(dimethylamino)-2-oxoethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00422] Prepared using similar procedure as for example 77.

[00423] MS (ESI) m/z 504 (M+H).

[00424] 1H NMR (500 MHz, MeOD) δ ppm 7.93 (s, 1 H) 7.16 (s, 1 H) 6.99 (s, 1 H) 4.97 (s, 2 H) 4.61 (q, *J*=6.94 Hz, 2 H) 4.05 (s, 3 H) 3.15 (s, 3 H) 2.98 (s, 3 H) 2.79 - 2.97 (m, 2 H) 2.29 (s, 3 H) 1.44 (t, *J*=7.07 Hz, 3 H) 0.72 - 0.91 (m, 8 H).

Example 87



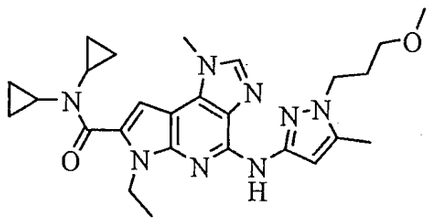
4-(1-(cyanomethyl)-5-methyl-1*H*-pyrazol-3-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00425] Prepared using similar procedure as for example **77**.

[00426] MS (ESI) m/z 458 (M+H).

[00427] 1H NMR (400 MHz, CHLOROFORM-*d*) ™ ppm 8.17 (s, 1 H) 7.67 (s, 1 H) 7.10 (s, 1 H) 6.87 (s, 1 H) 4.93 (s, 2 H) 4.65 (q, *J*=7.04 Hz, 2 H) 4.01 (s, 3 H) 2.76 - 2.92 (m, 2 H) 2.43 (s, 3 H) 1.50 (t, *J*=7.04 Hz, 3 H) 0.68 - 0.93 (m, 8 H).

Example 88



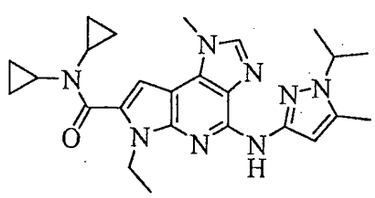
N,N-dicyclopropyl-6-ethyl-4-(1-(3-methoxypropyl)-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00428] Prepared using similar procedure as for example **77**.

[00429] MS (ESI) m/z 491 (M+H).

[00430] 1H NMR (400 MHz, CHLOROFORM-*d*) ™ ppm 8.11 (s, 1 H) 7.62 (s, 1 H) 6.92 (s, 1 H) 6.78 - 6.89 (m, 1 H) 4.66 (q, *J*=7.04 Hz, 2 H) 4.06 (t, *J*=6.60 Hz, 2 H) 3.98 (s, 3 H) 3.29 - 3.39 (m, 4 H) 2.75 - 2.91 (m, 2 H) 2.34 (s, 3 H) 2.08 (dq, *J*=6.38, 6.16 Hz, 2 H) 1.50 (t, *J*=7.04 Hz, 3 H) 0.70 - 0.94 (m, 8 H).

Example 89



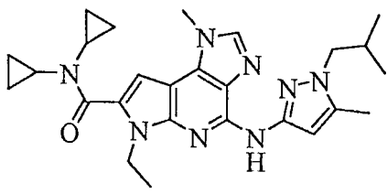
***N,N*-dicyclopropyl-6-ethyl-4-(1-isopropyl-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00431] Prepared using similar procedure as for example 77.

[00432] MS (ESI) m/z 461 (M+H).

[00433] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.15 (s, 1 H) 7.62 (s, 1 H) 6.91 (s, 1 H) 6.85 (s, 1 H) 4.66 (q, *J*=7.19 Hz, 2 H) 4.25 - 4.48 (m, 1 H) 3.99 (s, 3 H) 2.66 - 2.90 (m, *J*=7.13, 7.13, 3.85, 3.47 Hz, 2 H) 2.34 (s, 3 H) 1.38 - 1.58 (m, 9 H) 0.68 - 0.91 (m, 8 H).

Example 90



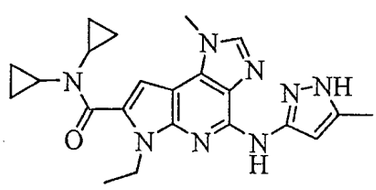
***N,N*-dicyclopropyl-6-ethyl-4-(1-isobutyl-5-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00434] Prepared using similar procedure as for example 77.

[00435] MS (ESI) m/z 475 (M+H).

[00436] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.11 (s, 1 H) 7.62 (s, 1 H) 6.93 (s, 1 H) 6.85 (s, 1 H) 4.66 (q, J=7.04 Hz, 2 H) 3.99 (s, 3 H) 3.74 (d, *J*=7.48 Hz, 2 H) 2.74 - 2.89 (m, 2 H) 2.33 (s, 3 H) 2.18 - 2.29 (m, 1 H) 1.50 (t, *J*=7.04 Hz, 3 H) 0.94 (d, *J*=6.60 Hz, 6 H) 0.72 - 0.88 (m, 8 H).

Example 91



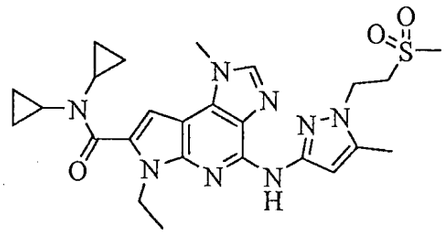
Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methyl-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00437] Prepared using similar protocol as for example **72** from hydrazine.

[00438] MS (ESI) m/z 419.3 (M+H)

[00439] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.70 (br s, 1 H), 7.91 (br s, 1 H), 6.87 (s, 1 H), 6.09 (br s, 1 H), 4.64 (q, 2 H, *J* = 7.03 Hz), 4.08 (s, 3 H), 2.74 - 2.95 (m, 2 H), 2.41 (s, 3 H), 1.51 (t, 3 H, *J* = 7.15 Hz), 0.81 - 0.95 (m, 4 H), 0.70 - 0.81 (m, 4 H)

Example 92



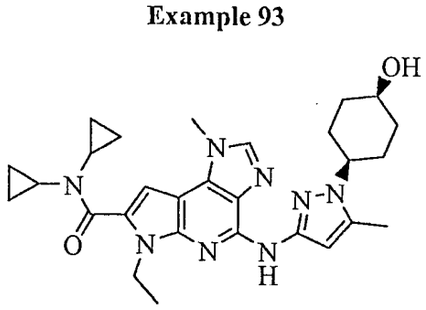
***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-((5-methyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)amino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00440] Prepared using the same procedure as used for example **77**.

[00441] MS (ESI) m/z 525.3 (M+H)

[00442] 1H NMR (CDCl3) δ ppm 8.25 (br s, 1H), 7.75 (s, 1H), 6.86 (s, 1H), 6.77 (s, 1H), 4.54 (q, 2H, J = 8 Hz), 4.36 (t, 2H, J = 8 Hz), 3.97 (s, 3H), 3.58 (t, 2H, J = 8 Hz), 2.71-2.77 (m, 2H), 2.44 (s, 3H), 2.34 (s, 3H), 1.41 (t, 3H, J = 8 Hz), 0.75-0.78 (m, 4H), 0.67-0.71 (m, 4H).

Example 93



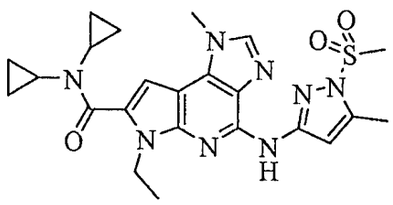
N,N-dicyclopropyl-6-ethyl-4-((1-(cis-4-hydroxycyclohexyl)-5-methyl-1*H*-pyrazol-3-yl)amino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00443] Prepared using the same procedure as used for example 77.

[00444] MS (ESI) m/z 517.4 (M+H)

[00445] 1H NMR (CDCl3) δ ppm 8.14 (br s, 1H), 7.56 (s, 1H), 6.83 (s, 1H), 6.76 (s, 1H), 4.59 (q, 2H, J = 8 Hz), 4.01-4.02 (m, 1H), 3.93 (s, 3H), 3.88-3.93 (m, 1H), 2.73-2.77 (m, 2H), 2.28 (s, 3H), 2.25-2.33 (m, 2H), 1.93-1.96 (m, 2H), 1.59-1.73 (m, 4H), 1.42 (t, 3H, J = 8 Hz), 0.73-0.78 (m, 4H), 0.66-0.70 (m, 4H).

Example 94



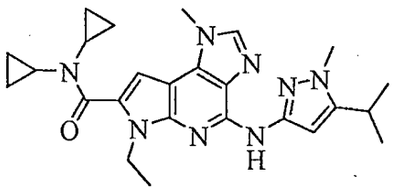
N,N-dicyclopropyl-6-ethyl-1-methyl-4-((5-methyl-1-(methylsulfonyl)-1*H*-pyrazol-3-yl)amino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00446] Prepared using the same procedure as used for example 77.

[00447] MS (ESI) m/z 497.3 (M+H)

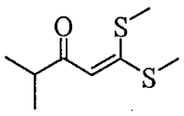
[00448] 1H NMR (CDCl3) δ ppm 8.46 (br s, 1H), 7.75 (s, 1H), 7.16 (s, 1H), 6.78 (s, 1H), 4.54 (q, 2H, *J* = 8 Hz), 3.97 (s, 3H), 3.19 (s, 3H), 2.72-2.76 (m, 2H), 2.51 (s, 3H), 1.41 (t, 3H, *J* = 8 Hz), 0.72-0.78 (m, 4H), 0.66-0.69 (m, 4H).

Example 95



N,N-dicyclopropyl-6-ethyl-4-(5-isopropyl-1-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

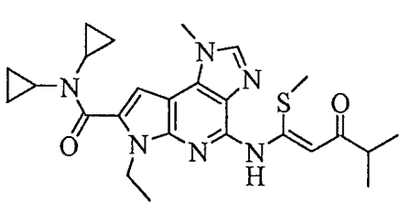
95A Preparation of 4-methyl-1,1-bis(methylthio)pent-1-en-3-one



[00449] The title compound was prepared using a method analogous to that used to prepare Example **70A**.

[00450] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.08 (s, 1H), 2.47 (s, 3H), 2.46 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H).

95B Preparation of (*Z*)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(4-methyl-1-(methylthio)-3-oxopent-1-enylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00451] The title compound was prepared using a method analogous to that used to prepare example **70B**.

[00452] MS (ESI) m/z 481.4 (M+H).

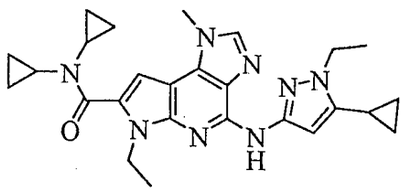
95 Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(5-isopropyl-1-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00453] The title compound was prepared using a method analogous to that used to prepare example **73**.

[00454] MS (ESI) m/z 461.4 (M+H).

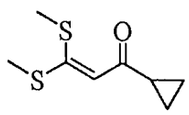
[00455] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (s, 1H), 7.07 (s, 1H), 6.86 (s, 1H), 4.60 (q, J = 6.9 Hz, 2H), 4.02 (s, 3H), 3.79 (s, 3H), 2.93 – 3.01 (m, 1H), 2.79 - 2.86 (m, 2H), 1.52 (t, J = 7.1 Hz, 3H), 1.35 (d, J = 6.9 Hz, 6H), 0.82 - 0.89 (m, 4H), 0.72 - 0.78 (m, 4H).

Example 96



***N,N*-dicyclopropyl-4-(5-cyclopropyl-1-ethyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

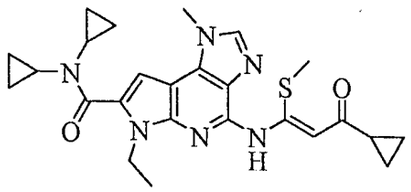
96A Preparation of 1-cyclopropyl-3,3-bis(methylthio)prop-2-en-1-one



[00456] The title compound was prepared using a method analogous to that used to prepare example **72A**.

[00457] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.23 (s, 1H), 2.50 (s, 3H), 2.48 (s, 3H), 1.86 - 1.94 (m, 1H), 1.09 (quin, J = 3.7 Hz, 2H), 0.82 - 0.88 (m, 2H).

96B Preparation of (*Z*)-*N,N*-dicyclopropyl-4-(3-cyclopropyl-1-(methylthio)-3-oxoprop-1-enylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00458] The title compound was prepared using a method analogous to that used to prepare example **72B**.

[00459] MS (ESI) m/z 479.3 (M+H).

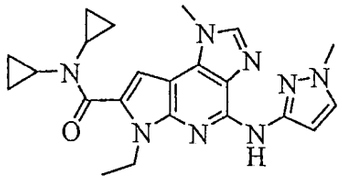
[00460] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.81 (s, 1H), 7.75 (s, 1H), 6.85 (s, 1H), 5.58 (s, 1H), 4.62 (q, J = 7.0 Hz, 2H), 4.00 (s, 3H), 2.75 - 2.85 (m, 2H), 2.45 (s, 3H), 1.76 - 1.86 (m, 1H), 1.46 (t, J = 7.0 Hz, 3H), 1.17 - 1.28 (m, 2H), 0.69 - 0.91 (m, 10H).

96 Preparation of *N,N*-dicyclopropyl-4-(5-cyclopropyl-1-ethyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00461] The title compound was prepared using a method analogous to that used to prepare example **73**.

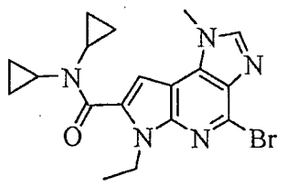
[00462] MS (ESI) m/z 473.3 (M+H).

Example 97



***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-methyl-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

97A Preparation of 4-bromo-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo [4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00463] A round bottom flask charged with 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (134.4 mg, 0.397 mmol) under an atmosphere of nitrogen was treated with dibromomethane (397 µL). Isoamyl nitrate (107 µL, 0.794 mmol) was added and the reaction mixture was heated at 60 °C 3.5 h and cooled to rt. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The organics were dired over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. 4-Bromo-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (0.156 g, 0.388 mmol, 98% yield) was isolated as a brown glassy solid. The product was used immediately in the next reaction.

[00464] MS (ESI) m/z 404.2 (M+H)

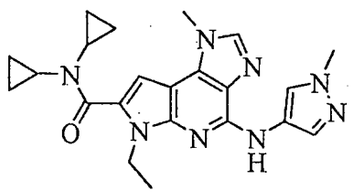
97 Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-methyl-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00465] To a vial containing 1-methyl-1*H*-pyrazol-3-amine (11.89 mg, 0.122 mmol), $Pd_2(dba)_3$ (4.67 mg, 5.10 µmol), Xantphos (5.90 mg, 10.20 µmol), and cesium carbonate (100 mg, 0.306 mmol) was added 4-bromo-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **97A,** 41.0 mg, 0.102 mmol) in DME (1020 µL). The reaction mixture was sparged with argon for 5 min, the vial was capped, and the reaction mixture was heated at 60 °C for 4 h and 80 °C for 16h. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography using an Isco 40 g column eluting with 0 – 5% MeOH/ CH_2Cl_2 followed by additional purification with preparative HPLC. *N,N*-Dicyclopropyl-6-ethyl-1-methyl-4-(1-methyl-1H-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (13 mg, 0.030 mmol, 29.5% yield) was isolated as a white solid.

[00466] MS (ESI) m/z 419.3 (M+H)

[00467] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.17 (s, 1 H), 7.64 (s, 1 H), 7.31 (d, 1H, J = 2.26 Hz), 7.16 (d, 1 H, J = 2.26 Hz), 6.86 (s, 1 H), 4.65 (q, 2 H, J = 7.03 Hz), 4.01 (s, 3 H), 3.85 (s, 3H), 2.78 - 2.87 (m, 2 H), 1.49 (t, 3 H, J = 7.15 Hz), 0.81 - 0.89 (m, 4 H), 0.71 - 0.80 (m, 4 H)

Example 98

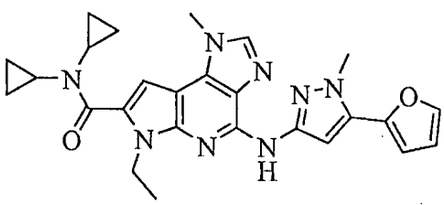


***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-methyl-1*H*-pyrazol-4-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00468] Prepared using similar procedure as used for example **97**.

[00469] ^{1}H NMR (500 MHz, CHLOROFORM-d) δ: 8.15 (s, 1H), 7.72 (s, 1H), 7.67 (s, 1H), 7.66 (br. s., 1H), 6.85 (s, 1H), 4.65 (q, J = 7.2 Hz, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 2.79 - 2.86 (m, 2H), 1.50 (t, J = 7.1 Hz, 3H), 0.81 - 0.89 (m, 4H), 0.73 - 0.79 (m, 4H).

Example 99



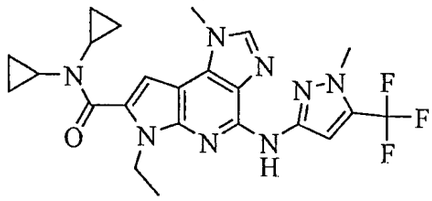
***N,N*-dicyclopropyl-6-ethyl-4-((5-(2-furyl)-1-methyl-1*H*-pyrazol-3-yl)amino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00470] Prepared in a similar method used for example **73**.

[00471] MS (ESI) m/z 485.4 (M+H)

[00472] 1H NMR (CDCl3) δ ppm 8.03 (br s, 1H), 7.58 (s, 1H), 7.48 (m, 1H), 7.35 (s, 1H), 6.79 (s, 1 H), 6.54 (d, 1H, J = 3.3 Hz), 6.47 (m, 1H), 4.58 (q, 2 H, J = 7.04 Hz), 3.94 (s, 3H), 3.93 (s, 3H), 2.74 (m, 2H), 1.44 (t, 3H), 0.69-0.79 (m, 8H)

Example 100



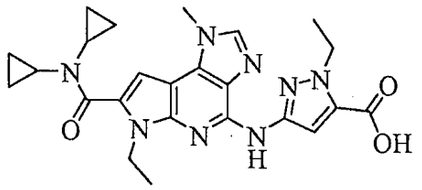
***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-((1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)amino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00473] Prepared in a similar method used for example **73**.

[00474] MS (ESI) m/z 487.3 (M+H)

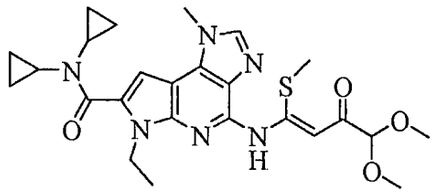
[00475] 1H NMR (CDCl3) δ ppm 7.41 (s, 1 H), 7.12 (s, 1H), 6.78 (s, 1 H), 4.52 (q, 2H, J = 7.04 Hz), 4.11 (s, 3H), 3.86 (s, 3H), 2.74 (m, 2H), 1.42 (t, 3H, J = 7.15 Hz), 0.67-0.80 (m, 8H)

Example 101



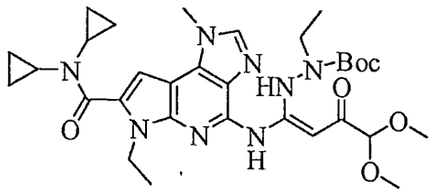
3-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-1-ethyl-1*H*-pyrazole-5-carboxylic acid

101A Preparation of (*Z*)-*N,N*-dicyclopropyl-4-(4,4-dimethoxy-1-(methylthio)-3-oxobut-1-enylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00476] Sodium hydride (142 mg, 3.55 mmol) was added to 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J,** 400 mg, 1.182 mmol) in DMF (7 mL) at room temperature and the mixture stirred for 30 min, 1,1-dimethoxy-4,4-bis(methylthio)but-3-en-2-one (394 mg, 1.773 mmol) was added and stirring continued overnight. The reaction mixture was diluted with ethyl acetate and washed with water, 10% lithium chloride and water. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using an automated ISCO system (80 g column, eluting with 2-5% methanol / dichloromethane). (*Z*)-*N,N*-Dicyclopropyl-4-(4,4-dimethoxy-1-(methylthio)-3-oxobut-1-enylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (484 mg, 0.944 mmol, 80 % yield) was obtained as a yellow solid.

101B Preparation of (*Z*)-*tert*-butyl 2-(1-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4,4-dimethoxy-3-oxobut-1-enyl)-1-ethylhydrazinecarboxylate

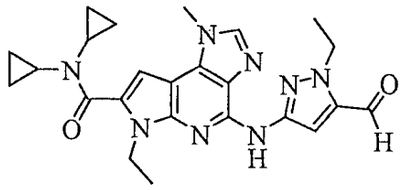


[00477] A mixture of (Z)-*N,N*-dicyclopropyl-4-(4,4-dimethoxy-1-(methylthio)-3-oxobut-1-enylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **101A,** 160 mg, 0.312 mmol) and *tert*-butyl 1-ethylhydrazinecarboxylate (125 mg, 0.780 mmol) in acetic acid (2 mL) wan stirred at 35 °C overnight. Solvent was evaporated and the crude product was purified by flash chromatography on silica gel using an automated ISCO system (40 g column, eluting

with 2-8% methanol/dichloromethane). (*Z*)-*tert*-Butyl 2-(1-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4,4-dimethoxy-3-oxobut-1-enyl)-1-ethylhydrazinecarboxylate (195 mg, 0.312 mmol, 100 % yield) was obtained as a yellow solid.

[00478] MS (ESI) m/z 625.5 (M+H).

101C Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-formyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00479] A mixture of (*Z*)-*tert*-butyl 2-(1-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4,4-dimethoxy-3-oxobut-1-enyl)-1-ethylhydrazinecarboxylate (187 mg, 0.299 mmol) and TFA (25% in dichloroethane, 1.0 mL, 2.99 mmol) was heated at 60 °C for 0.5h and LC/MS showed completion of reaction. Solvent was evaporated and the residue was partitioned between saturated sodium bicarbonate and dichloromethane. The layers were separated and aqueous layer was extracted with dichloromethane two more times. The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using an automated ISCO system (24 g column, eluting with 1-5% methanol / dichloromethane). *N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-formyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (80 mg, 0.174 mmol, 58.0 % yield) was obtained as a yellow solid.

[00480] MS (ESI) m/z 461.4 (M+H).

[00481] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.88 (s, 1H), 8.25 (s, 1H), 7.76 (s, 1H), 7.67 (s, 1H), 6.87 (s, 1H), 4.67 (d, J = 7.2 Hz, 2H), 4.52 (q, J = 7.1 Hz, 2H), 4.02 (s, 3H), 2.80 - 2.86 (m, 2H), 1.52 (t, J = 7.1 Hz, 3H), 1.44 (t, J = 7.2 Hz, 3H), 0.83 - 0.89 (m, 4H), 0.73 - 0.79 (m, 4H)

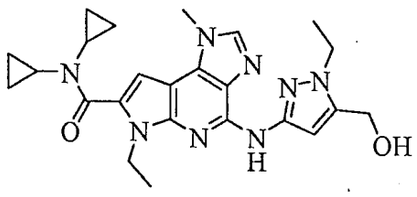
101 Preparation of 3-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-1-ethyl-1*H*-pyrazole-5-carboxylic acid

[00482] A mixture of *N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-formyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **101C,** 27 mg, 0.059 mmol) and OXONE (79 mg, 0.129 mmol) in DMF was stirred at room temperature for 20 hrs. Water was added and the mixture was extracted with dichloromethane 3 times. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified with preparative HPLC to give 3-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo [2,3-b]pyridin-4-ylamino)-1-ethyl-1*H*-pyrazole-5-carboxylic acid (20 mg, 98% yield)

[00483] MS (ESI) m/z 477.4 (M+H).

[00484] ^{1}H NMR (500 MHz, METHANOL-d_4) δ: 7.96 (s, 1H), 7.48 (s, 1H), 7.18 (s, 1H), 4.70 (q, J = 6.9 Hz, 2H), 4.60 (q, J = 7.2 Hz, 2H), 4.09 (s, 3H), 2.94 – 3.00 (m, 2H), 1.45 (t, J = 6.94 Hz, 3H), 1.44 (t, J = 7.21 Hz, 3H), 0.85 - 0.92 (m, 4H), 0.77 - 0.82 (m, 4H)

Example 102



***N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

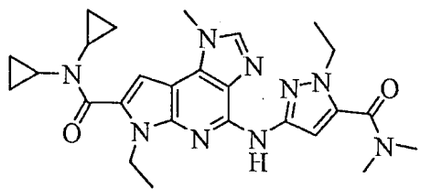
[00485] Sodium boronhydride (10 wt% on alumina, 13.14 mg, 0.035 mmol) was added to *N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-formyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **101C,** 16 mg, 0.035 mmol) in methanol (1 mL) at room temperature and the reaction mixture stirred for 0.5h. The solid alumina was filtered off and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on

silica gel using an automated ISCO system (4 g column, eluting with 2-10% methanol / dichloromethane). *N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (14 mg, 86 % yield) was obtained as a white solid.

[00486] MS (ESI) m/z 563.4 (M+H).

[00487] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.59 (s, 1H), 7.08 (s, 1H), 6.81 (s, 1H), 4.72 (d, J = 4.7 Hz, 2H), 4.57 (q, J = 7.2 Hz, 2H), 4.15 (q, J = 7.3 Hz, 2H), 3.97 (s, 3H), 2.76 – 2.84 (m, 3H), 1.46 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.1 Hz, 3H), 0.81 - 0.87 (m, 4H), 0.71 - 0.76 (m, 4H)

Example 103



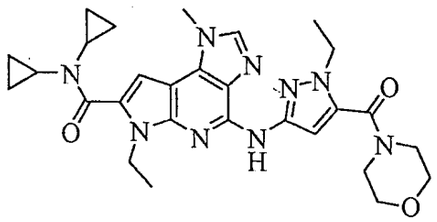
***N,N*-dicyclopropyl-4-(5-(dimethylcarbamoyl)-1-ethyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00488] A mixture of 3-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-1-ethyl-1H-pyrazole-5-carboxylic acid (example **101**, 28 mg, 0.059 mmol), HATU (26.8 mg, 0.071 mmol) and dimethylamine (2M in THF, 59 μL, 0.118 mmol) in DMF (1 mL) was stirred at room temperature for 2h. Water was added and the reaction mixture was extracted with ethyl acetate 3 times. The combined organic layers were washed twice with 10% lithium chloride, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude was purified by preparative HPLC (Phenomenex Luna 5u C18 column, 21.2x250 mm column, retention time 15.317 min, 30-100% gradient aqueous methanol over 20 minutes containing 10 mM ammonium acetate, flow rate 20 ml/min and monitoring at 254 nm). *N,N*-dicyclopropyl-4-(5-(dimethylcarbamoyl)-1-ethyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydro imidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (20 mg, 66.9 % yield) was obtained as an off-white solid.

[00489] MS (ESI) m/z 504.5 (M+H).

[00490] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.38 (br. S, 1H), 7.75 (s, 1H), 7.28 (s, 1H), 6.86 (s, 1H), 4.61 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 7.0 Hz, 5H), 4.03 (s, 3H), 3.27 (s, 3H), 3.17 (s, 3H), 2.79 - 2.86 (m, 2H), 1.47 (t, J = 7.14 Hz, 3H), 1.46 (t, J = 7.14 Hz, 3H), 0.83 - 0.89 (m, 4H), 0.73 - 0.78 (m, 4H)

Example 104



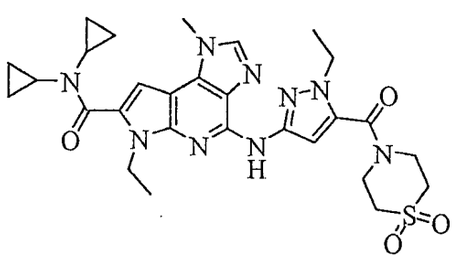
***N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-(morpholine-4-carbonyl)-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00491] The title compound was prepared using a method analogous to that used to prepare example **103**.

[00492] MS (ESI) m/z 546.5 (M+H).

[00493] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.19 (s, 1H), 6.87 (s, 1H), 4.60 (q, J = 6.9 Hz, 2H), 4.28 (q, J = 7.2 Hz, 5H), 4.07 (s, 3H), 3.82 (br. s., 5H), 3.76 (br. s., 3H), 2.74 - 2.93 (m, 4H), 1.48 (t, J = 7.14 Hz, 3H), 1.47 (t, J = 7.14 Hz, 3H), 0.84 - 0.90 (m, 4H), 0.74 - 0.78 (m, 4H).

Example 105



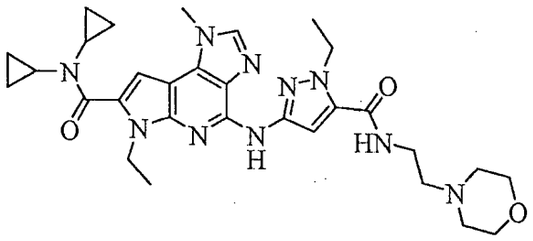
***N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-(thiomorpholine 1,1-dioxide -4-carbonyl)-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00494] The title compound was prepared using a method analogous to that used to prepare example **103**.

[00495] MS (ESI) m/z 594.5 (M+H).

[00496] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.19 (s, 1H), 6.83 (s, 1H), 4.55 (q, J = 7.03 Hz, 2H), 4.20 - 4.34 (m, 6H), 4.06 (s, 3H), 3.13 (br. s., 4H), 2.77 - 2.89 (m, 2H), 1.46 (t, J = 7.21 Hz, 3H), 1.43 (t, J = 7.21 Hz, 3H), 0.82 - 0.88 (m, 4H), 0.72 - 0.77(m, 4H).

Example 106



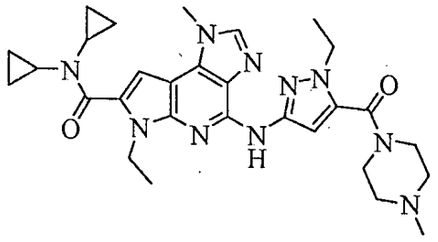
***N,N*-dicyclopropyl-6-ethyl-4-(1-ethyl-5-(2-morpholinoethylcarbamoyl)-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00497] The title compound was prepared using a method analogous to that used to prepare example **103**.

[00498] MS (ESI) m/z 589.6 (M+H).

[00499] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.68 (s, 1H), 7.45 (s, 1H), 6.87 (s, 1H), 4.64 (q, J = 6.9 Hz, 2H), 4.54 (q, J = 7.2 Hz, 2H), 4.03 (s, 3H), 3.77 (br. s., 4H), 3.61 (br. s., 2H), 2.80 - 2.87 (m, 2H), 2.67 (br. s., 2H), 2.57 (br. s., 3H), 1.71 (br. s., 3H), 1.53 (t, J = 7.1 Hz, 3H), 1.46 (t, J = 7.1 Hz, 3H), 0.84 - 0.90 (m, 4H), 0.74 - 0.79 (m, 4H).

Example 107



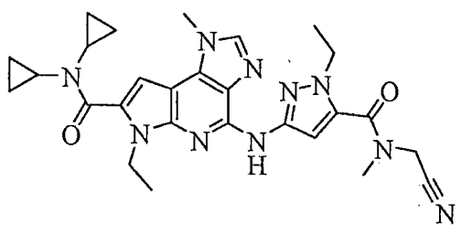
N,N-dicyclopropyl-6-ethyl-4-(1-ethyl-5-(4-methylpiperazine-1-carbonyl)-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00500] The title compound was prepared using a method analogous to that used to prepare example **103**.

[00501] MS (ESI) m/z 559.5 (M+H).

[00502] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 7.66 (s, 1H), 7.26 (s, 1H), 6.87 (s, 1H), 4.63 (q, J = 6.9 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 4.02 (s, 3H), 3.88(br. s., 4H), 2.80 - 2.86 (m, 2H), 2.54 (br. s., 4H), 2.40 (br. s., 3H), 1.48 (t, J = 7.1 Hz, 3H), 1.47 (t, J = 7.1 Hz, 3H), 0.82 - 0.90 (m, 4H), 0.73 - 0.79 (m, 4H).

Example 108



4-(5-((cyanomethyl)(methyl)carbamoyl)-1-ethyl-1*H*-pyrazol-3-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

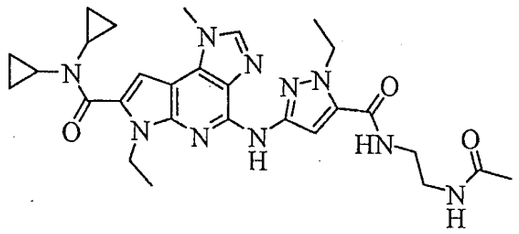
[00503] The title compound was prepared using a method analogous to that used to prepare example **103**.

[00504] MS (ESI) m/z 529.3 (M+H).

[00505] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.37 (br. s., 1H), 7.77 (s, 1H), 7.39 (s, 1H), 6.86 (s, 1H), 4.62 (q, J = 7.2 Hz, 2H), 4.54 (br. s., 2H), 4.27 - 4.34 (m, 1H), 4.04 (s,

3H), 3.41 (br. s., 3H), 2.79 - 2.86 (m, 2H), 1.47 (t, J = 7.2 Hz, 6H), 0.83 - 0.89 (m, 4H), 0.73 - 0.78 (m, 4H).

Example 109



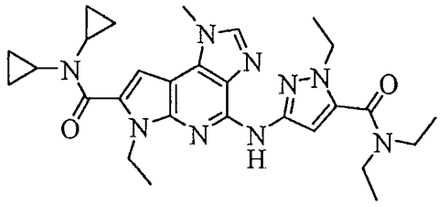
4-((5-((2-acetamidoethyl)carbamoyl)-1-ethyl-1*H*-pyrazol-3-yl)amino)-*N*,*N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00506] The title compound was prepared using a method analogous to that used to prepare example **103**.

[00507] MS (ESI) m/z 561.5 (M+H).

[00508] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (br. s., 2H), 7.40 (s, 1H), 6.72 (s, 1H), 4.48 - 4.56 (m, 4H), 3.99 (s, 3H), 3.61 - 3.66 (m, 2H), 3.52 - 3.58 (m, 2H), 2.81 (m, 2H), 2.02 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 6.9 Hz, 3H), 1.26 (s, 1H), 0.82 – 0.90 (m, 4H), 0.70 - 0.77 (m, 4H)

Example 110



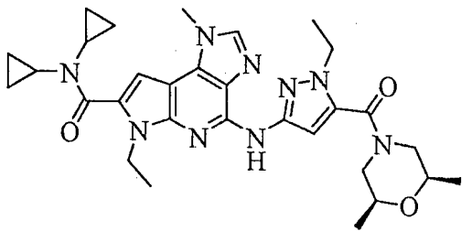
***N*,*N*-dicyclopropyl-4-((5-(diethylcarbamoyl)-1-ethyl-1*H*-pyrazol-3-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00509] The title compound was prepared using a method analogous to that used to prepare example **103**.

[00510] MS (ESI) m/z 532.4 (M+H).

[00511] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (br. S., 1H), 7.70 (s, 1H), 7.23 (s, 1H), 6.85 (s, 1H), 4.62 (q, J = 6.9 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 4.00 (s, 3H), 3.51 - 3.62 (m, 4H), 2.77 - 2.85 (m, 2H), 1.40 - 1.47 (m, 6H), 1.27 (t, J = 7.1 Hz, 6H), 0.80 - 0.88 (m, 4H), 0.72 - 0.77 (m, 4H)

Example 111



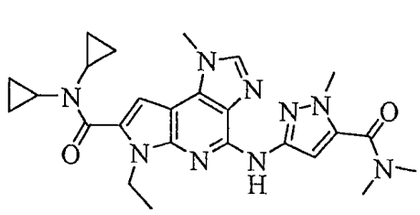
***N,N*-dicyclopropyl-4-((5-(((2R,6S)-2,6-dimethyl-4-morpholinyl)carbonyl)-1-ethyl-1*H*-pyrazol-3-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00512] The title compound was prepared using a method analogous to that used to prepare example **103**.

[00513] MS (ESI) m/z 574.4 (M+H).

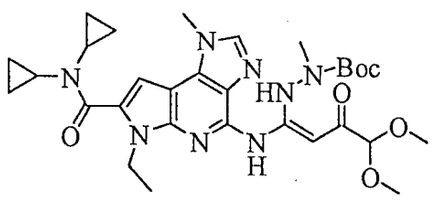
[00514] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.30 (br. S., 1H), 7.72 (s, 1H), 7.21 (s, 1H), 6.86 (s, 1H), 4.62 (q, J = 6.9 Hz, 2H), 4.21 – 4.28 (m, 2H), 4.07 - 4.20 (m, 2H), 4.01 (s, 3H), 3.61 (br. s, 2H), 2.91 (br. s, 1H), 2.79 - 2.85 (m, 2H), 2.60 (br. S. 1H), 1.47 (t, J = 7.2 Hz, 3H), 1.45 (t, J = 7.2 Hz, 3H), 1.07 - 1.36 (m, 6H), 0.81 - 0.88 (m, 4H), 0.72 - 0.78 (m, 4H)

Example 112



N,N-dicyclopropyl-4-(5-(dimethylcarbamoyl)-1-methyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

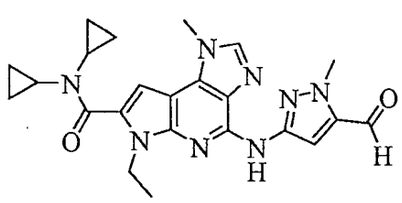
112A Preparation of (*Z*)-*tert*-butyl 2-(1-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-4,4-dimethoxy-3-oxobut-1-enyl)-1-methylhydrazinecarboxylate



[00515] The title compound was prepared using a method analogous to that used to prepare example **101B**.

[00516] MS (ESI) m/z 611.7 (M+H).

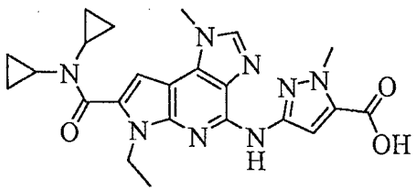
112B Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(5-formyl-1-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00517] The title compound was prepared using a method analogous to that used to prepare Example **101C**.

[00518] MS (ESI) m/z 447.3 (M+H).

112C Preparation of 3-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydro imidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-1-methyl-1*H*-pyrazole-5-carboxylic acid



[00519] The title compound was prepared using a method analogous to that used to prepare example **101**.

[00520] MS (ESI) m/z 463.3 (M+H).

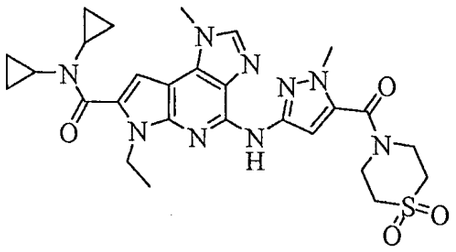
112 Preparation of *N,N*-dicyclopropyl-4-(5-(dimethylcarbamoyl)-1-methyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00521] A mixture of 3-(7-(dicyclopropylcarbamoyl)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-4-ylamino)-1-methyl-1H-pyrazole-5-carboxylic acid (39.8 mg, 0.086 mmol), HATU (49.0 mg, 0.129 mmol) and dimethylamine, 2M in THF (0.086 mL, 0.172 mmol) in DMF (2 mL) was stirred at room temperature for 2h. Water was added and the reaction mixture was extracted with ethyl acetate 3 times. The combined organic layers were washed twice with 10% lithium chloride, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude was purified by preparative HPLC to give *N,N*-dicyclopropyl-4-(5-(dimethylcarbamoyl)-1-methyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (23 mg, 54.1 % yield) as an off-white solid.

[00522] MS (ESI) m/z 490.2 (M+H).

[00523] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.67 (s, 1H), 7.34 (s, 1H), 6.86 (s, 1H), 4.61 (q, J = 7.0 Hz, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 3.29 (s, 3H), 3.16 (s, 3H), 2.79 - 2.86 (m, 2H), 1.47 (t, J = 7.0 Hz, 3H), 0.82 - 0.89 (m, 4H), 0.72 - 0.79 (m, 4H).

Example 113



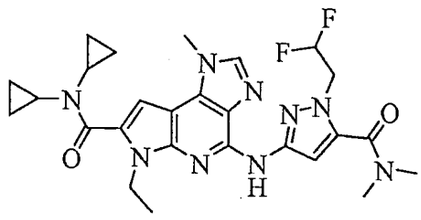
N,N-dicyclopropyl-6-ethyl-4-(1-methyl-5-(thiomorpholine 1,1-dioxide -4-carbonyl)-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00524] The title compound was prepared using a method analogous to that used to prepare example **112**.

[00525] MS (ESI) m/z 580.3 (M+H).

[00526] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (s., 1H), 7.69 (s, 1H), 7.30 (s, 1H), 6.83 (s, 1H), 4.57 (q, J = 6.8 Hz, 2H), 4.31 (br. s., 4H), 4.00 (s, 3H), 3.93 (s, 3H), 3.15 (br. s., 4H), 2.77 - 2.88 (m, 2H), 1.45 (t, J = 7.0 Hz, 3H), 0.80 - 0.91 (m, 4H), 0.69 - 0.80 (m, 4H).

Example 114



N,N-dicyclopropyl-4-(1-(2,2-difluoroethyl)-5-(dimethylcarbamoyl)-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

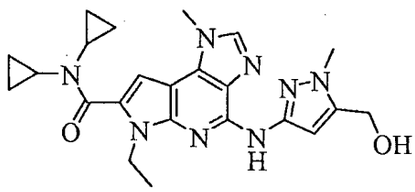
[00527] The title compound was prepared using a method analogous to that used to prepare Example **112**; except utilizing example **80A**.

[00528] MS (ESI) m/z 540.4(M+H).

[00529] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 8.41 (br. s., 1H), 7.73 (s, 1H), 7.43 (s, 1H), 6.86 (s, 1H), 6.17 (tt, J = 55.9, 4.2 Hz, 1H), 4.57 - 4.72 (m, 4H), 4.01 (s,

3H), 3.30 (s, 3H), 3.16 (s, 3H), 2.78 - 2.86 (m, 2H), 1.47 (t, J = 7.0 Hz, 3H), 0.80 - 0.89 (m, 4H), 0.71 - 0.80 (m, 4H).

Example 115



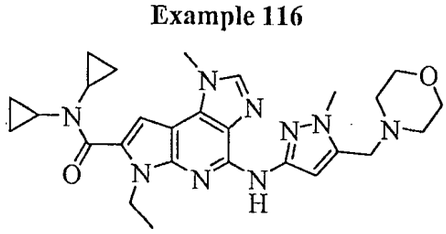
N,N-dicyclopropyl-6-ethyl-4-(5-(hydroxymethyl)-1-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00530] Title compound was prepared by a method similar to that used for example **102**.

[00531] MS (ESI) m/z 449.3 (M+H)

[00532] 1H NMR (CDCl3) δ ppm 8.11 (br s, 1H), 7.67 (s, 1 H), 7.16 (s, 1 H), 6.88 (s, 1 H), 4.75 (d, 2 H, *J* = 5.94 Hz), 4.67 (q, 2H, *J* = 7.26 Hz), 4.03 (s, 3H), 3.89 (s, 3H), 2.84 (m, 2H), 1.68 (t, 3H, *J* = 6.16 Hz), 1.50 (t, 3H, *J* = 7.15 Hz), 0.75-0.89 (m, 8H)

Example 116



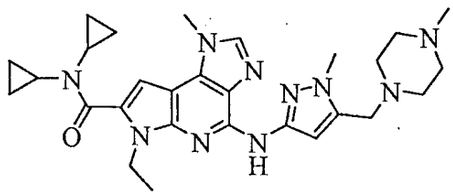
***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-methyl-5-(morpholinomethyl)-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00533] To a stirred solution of *N,N*-dicyclopropyl-6-ethyl-4-(5-formyl-1-methyl-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **112B**, 22 mg, 0.049 mmol) and molecular seives 4Å (30 mg) in MeOH (2 mL) was added morpholine (0.017 mL, 0.197 mmol). After the solution was stirred at room temperature for 12 hrs, sodium borohydride (7.46 mg, 0.197 mmol) was then added and stirred for 3 hrs. The solution was brought to pH = 4 with 1N HCl, neutralized with saturated aqueous sodium bicarbonate, and then extracted with CH_2Cl_2. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel flash chromatography using an Isco 40 g column eluting from 0-10% MeOH/CH_2Cl_2 to yield *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-methyl-5-(morpholinomethyl)-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (14.3 mg, 0.027 mmol, 54.9 % yield) as a white solid.

[00534] MS (ESI) m/z 518.3 (M+H)

[00535] 1H NMR (CDCl3) δ ppm 7.99 (br s, 1 H), 7.57 (s, 1 H), 6.99 (s, 1 H), 6.78 (s, 1H), 4.56 (q, 2 H *J* = 7.04 Hz), 3.93 (s, 3H), 3.77 (s, 3H), 3.64 (m, 4H), 3.48 (s, 2H), 2.75 (m, 2H), 2.45 (m, 4H), 1.42 (t, 3H *J* = 7.02 Hz), 0.66-0.80 (m, 8H)

Example 117



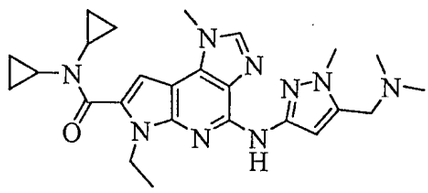
***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(1-methyl-5-((4-methylpiperazin-1-yl)methyl)-1*H*-pyrazol-3-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00536] Synthesized using a method analogous to that used to prepare example **116**.

[00537] MS (ESI) m/z 531.4 (M+H)

[00538] 1H NMR (CDCl3) δ ppm 8.05 (br s, 1 H), 7.60 (s, 1 H), 7.01 (s, 1H), 6.78 (s, 1 H), 4.56 (q, 2 H *J* = 6.75 Hz), 3.95 (s, 3H), 3.72 (s, 3H), 3.61 (s, 2H), 2.96 (m, 4H), 2.76 (m, 4H), 2.74 (m, 2H), 2.71 (s, 3H), 1.42 (t, 3H, *J* = 7.04 Hz), 0.67-0.80 (m, 8H)

Example 118



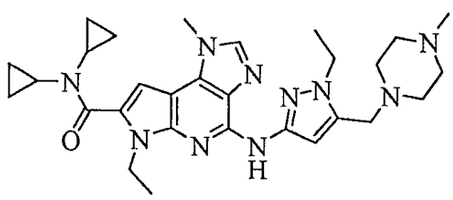
***N,N*-dicyclopropyl-4-(5-((dimethylamino)methyl)-1-methyl-1*H*-pyrazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

[00539] Synthesized using a method analogous to that used to prepare example **116**.

[00540] MS (ESI) m/z 476.4 (M+H)

[00541] 1H NMR (CDCl3) δ ppm 7.45 (s, 1 H), 7.33 (s, 1H), 6.84 (s, 1 H), 4.52 (q, 2H, *J* = 7.04 Hz), 4.25 (s, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 2.80 (s, 6H), 2.77 (m, 2H), 1.37 (t, 3H, *J* = 6.82 Hz), 0.64-0.87 (m, 8H)

Example 119



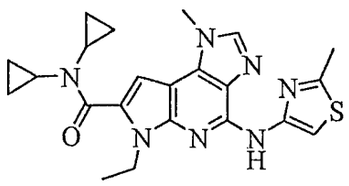
N,N-dicyclopropyl-6-ethyl-4-(1-ethyl-5-((4-methylpiperazin-1-yl)methyl)-1*H*-pyrazol-3-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00542] Prepared using interemediate **101B** and procedure as used for example **116**.

[00543] MS (ESI) m/z 545.4 (M+H)

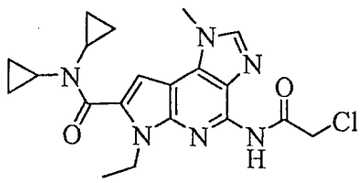
[00544] 1H NMR (CDCl3) δ ppm 8.03 (s, 1 H), 7.57 (s, 1 H), 7.00 (s, 1H), 6.78 (s, 1 H), 4.55 (q, 2 H, *J* = 7.04 Hz), 4.03 (q, 2H, *J* = 5.72 Hz), 3.94 (s, 3H), 3.60 (s, 2H), 2.93 (br s, 3H), 2.63-2.84 (br m, 10H), 1.42 (t, 3H, *J* = 7.04 Hz), 1.35 (t. 3H, *J* = 7.26 Hz), 0.69-0.79 (m, 8H)

Example 120



N,N-dicyclopropyl-6-ethyl-1-methyl-4-(2-methylthiazol-4-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

120A Preparation of 4-(2-chloroacetamido)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00545] To a round bottom flask charged with 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J**, 47.2 mg, 0.139 mmol) was added dichloromethane (697 µL) and triethylamine (35.0 µL, 0.251 mmol). Chloroacetyl chloride (12.20 µL, 0.153 mmol) was added dropwise. The reaction mixture was stirred at rt for 16h. Additional chloroacetyl chloride (12.20 µL, 0.153 mmol) was added. The reaction mixture was diluted with

dichloromethane. The organics were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. 4-(2-Chloroacetamido)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (58.5 mg, 101 % yield) was isolated as an orange paste. Material was used in subsequent reactions with no further purification.

[00546] MS (ESI) m/z 415.0 (M+H)

[00547] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.04 (br s, 1H), 6.90 (s, 1H), 5.31 (s, 2H), 4.62 (q, 2H, J = 7.11 Hz), 4.24 (s, 3H), 2.77 – 2.88 (m, 2H), 1.47 (t, 3H, J = 7.03 Hz), 0.83 – 0.92 (m, 4H), 0.71 – 0.80 (m, 4H)

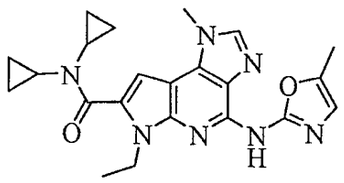
120 Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(2-methylthiazol-4-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00548] To a solution of 4-(2-chloroacetamido)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (58.5 mg, 0.141 mmol) in DMF (176 μL) was added thioacetamide (12.71 mg, 0.169 mmol). The vial was capped and the reaction mixture was heated at 80 °C 3 h. The reaction mixture was concentrated *in vacuo*. The crude residue was taken up in MeOH and purified by prep-HPLC. *N,N*-Dicyclopropyl-6-ethyl-1-methyl-4-(2-methylthiazol-4-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (4.05 mg, 6.6% yield) was isolated as an off-white solid.

[00549] MS (ESI) m/z 436.0 (M+H)

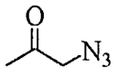
[00550] 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.78 (s, 1H), 8.08 (s, 1H), 7.74 (s, 1H), 7.20 (s, 1H), 4.55 (q, 2H, J = 7.19 Hz), 4.03 (s, 3H), 2.87 – 2.98 (m, 2H), 2.65 (s, 3H), 1.34 (t, 3H, J = 7.03 Hz), 0.73 – 0.81 (m, 4H), 0.62 – 0.69 (m, 4H)

Example 121



***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methyloxazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

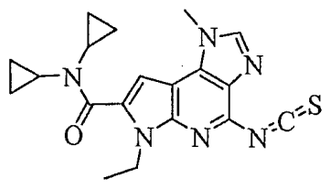
121A Preparation of 1-azidopropan-2-one



[00551] To a solution of chloroacetone (0.680 mL, 8.53 mmol) in acetone (10 mL) and water (5.00 mL) was added sodium azide (0.555 g, 8.53 mmol). The reaction mixture was stirred at rt 3.5 h. The reaction mixture was concentrated under reduced pressure. The remaining aqueous solution was extracted with dichloromethane (2 x). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 1-azidopropan-2-one (0.641 g, 6.47 mmol, 76 % yield) as a brown oil. This material was used without any purification.

[00552] 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 3.96 (s, 2H), 2.21 (s, 3H)

121B Preparation of *N,N*-dicyclopropyl-6-ethyl-4-isothiocyanato-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00553] To a mixture of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J**, 194.5 mg, 0.575 mmol) in dichloromethane (2874 µL) in a round bottom flask under nitrogen was added 1,1'-thiocarbonyldi-2(1*H*)-pyridone (133 mg, 0.575 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure. *N,N*-Dicyclopropyl-6-ethyl-4-isothiocyanato-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (180 mg, 94% yield) was isolated as a yellow sticky solid. The material was used as is in subsequent reactions.

[00554] MS (ESI) m/z 381.1 (M+H)

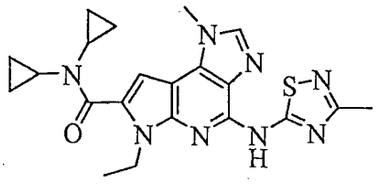
121 Preparation of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(5-methyloxazol-2-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00555] To a solution of *N,N*-dicyclopropyl-6-ethyl-4-isothiocyanato-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **121B**, 45.7 mg, 0.120 mmol) in dioxane (343 μL) was added 1-azidopropan-2-one (14.28 mg, 0.144 mmol) and triphenylphosphine (37.8 mg, 0.144 mmol). The contents of the flask were immersed into a preheated oil bath for 35 min and cooled to room temperature. The residue was diluted with ethyl acetate and quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on an Isco 12 g column eluting with 1 – 10% MeOH/CH_2Cl_2. The pale yellow solid was taken up in MeOH and further purified by preparative HPLC. *N,N*-Dicyclopropyl-6-ethyl-1-methyl-4-(5-methyloxazol-2-ylamino)-1,6-dihydro imidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide was isolated (10 mg, 25% yield) as a white solid.

[00556] MS (ESI) m/z 420.0 (M+H)

[00557] 1H NMR (400 MHz, DMSO-d_6) δ ppm 9.86 (s, 1H), 8.05 (s, 1H), 7.18 (s, 1H), 6.66 (d, 1H, J = 1.51 Hz), 4.41 (q, 2H, J = 7.28 Hz), 4.02 (s, 3H), 2.85 – 2.98 (m, 2H), 2.21 – 2.29 (m, 3H), 1.27 (t, 3H, J = 7.15 Hz), 0.71 – 0.80 (m, 4H), 0.60 – 0.70 (m, 4H)

Example 122



***N,N*-dicyclopropyl-6-ethyl-1-methyl-4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide**

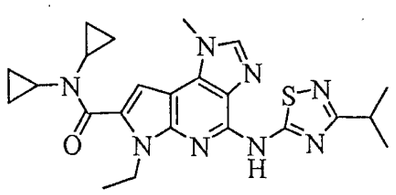
[00558] A mixture of *N,N*-dicyclopropyl-6-ethyl-4-isothiocyanato-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **121B**, 0.042

g, 0.111 mmol), acetamidine hydrochloride (10.49 mg, 0.111 mmol), and Hünig'sBase (0.058 mL, 0.333 mmol) in DMF (0.617 mL) was stirred at rt ON. Diethyl azodicarboxylate (0.088 mL, 0.222 mmol) was added and stirring continued at room temperature for 16 h. The reaction mixture was concentrated. The residue was taken up in MeOH and purified by preparative HPLC. *N,N*-Dicyclopropyl-6-ethyl-1-methyl-4-(3-methyl-1,2,4-thiadiazol-5-ylamino)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (4.32 mg, 9% yield) was isolated as a pale yellow solid.

[00559] MS (ESI) m/z 437.1 (M+H)

[00560] 1H NMR (400 MHz, MeOD) δ ppm 8.10 (s, 1 H), 7.28 (s, 1 H), 4.73 (q, 2 H, *J* = 7.19 Hz), 4.13 (s, 3 H), 2.93 - 3.01 (m, 2 H), 2.53 (s, 3 H), 1.53 (t, 3 H, *J* = 7.03 Hz), 0.83 - 0.92 (m, 4 H), 0.76 - 0.83 (m, 4 H)

Example 123



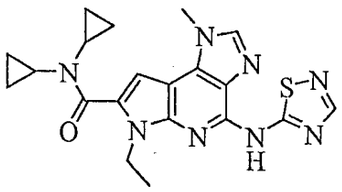
Preparation of *N,N*-dicyclopropyl-6-ethyl-4-(3-isopropyl-1,2,4-thiadiazol-5-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00561] This compound was prepared according to example **122** using isobutyrimidamide hydrochloride (15.08 mg, 0.123 mmol) and disopropyl azodicarboxylate (47.8 µL, 0.246 mmol). *N,N*-Dicyclopropyl-6-ethyl-4-(3-isopropyl-1,2,4-thiadiazol-5-ylamino)-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (21 mg, 34.9 % yield) was isolated as an off-white solid.

[00562] MS (ESI) m/z 465.3 (M+H)

[00563] 1H NMR (400 MHz, DMSO-d_6) δ ppm 12.24 (s, 1H), 8.18 (s, 1H), 7.28 (s, 1H), 4.64 (q, 2H, *J* = 6.94 Hz), 4.06 (s, 3H), 3.10 (ddd, 1H, *J* = 13.93, 6.90, 6.78 Hz), 2.86 – 3.00 (m, 2H), 1.42 (t, 3H, *J* = 7.03 Hz), 1.32 (s, 3H), 1.31 (s, 3H), 0.72 – 0.81 (m, 4H), 0.63 – 0.71 (m, 4H)

Example 124



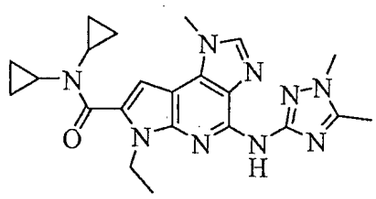
4-(1,2,4-thiadiazol-5-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00564] A mixture of *N,N*-dicyclopropyl-6-ethyl-1-methyl-4-thioureido-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (**example 2B,** 30 mg, 0.075 mmol) and 1,1-dimethoxy-*N,N*-dimethylmethanamine (1 g, 8.39 mmol) was heated at 50 °C for 2h. Excess 1,1-dimethoxy-*N,N*-dimethylmethanamine was evaporated *in vacuo* and the crude example was dissolved in dichloromethane (1 mL) and *O*-(mesitylsulfonyl)hydroxylamine (24.4 mg, 0.113 mmol) was added. The reaction mixture was stirred at room temperature for 3h. Water was added and the layers were separated. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by preparative HPLC to give 4-(1,2,4-thiadiazol-5-ylamino)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (7 mg, 19.20 % yield) as a yellow solid.

[00565] MS (ESI) m/z 423.0 (M+H).

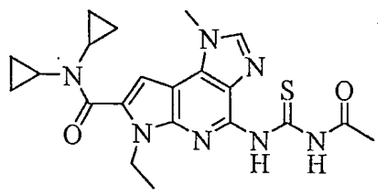
[00566] ^{1}H NMR (500 MHz, CD_3OD) δ: 8.32 (s, 1H), 8.27 (s, 1H), 7.38 (d, J = 4.4 Hz, 1H), 7.28 (s, 1H), 4.74 (q, J = 7.0 Hz, 2H), 4.15 (s, 3H), 2.94 - 3.00 (m, 2H), 1.53 (t, J = 7.0 Hz, 3H), 0.82 - 0.89 (m, 4H), 0.75 - 0.82 (m, 4H)

Example 125



N,N-dicyclopropyl-4-(1,5-dimethyl-1*H*-1,2,4-triazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

125A Preparation of 4-(3-acetylthioureido)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



[00567] To a solution of 4-amino-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **1J**, 60 mg, 0.177 mmol) in acetone (1.182 mL) was added acetyl isothiocyanate (0.020 mL, 0.230 mmol). The reaction mixture was stirred at room temperature for 6h. LC/MS showed still half of the starting material left. Another 0.5 equivalent of acetyl isothiocyanate was added and the reaction mixture was heated at 35 °C overnight. Solvent was evaporated and the crude product was purified by flash chromatography on silica gel using an automated ISCO system (24 g column, eluting with 2-8% methanol / dichloromethane). 4-(3-Acetylthioureido)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (34 mg, 43.6 % yield) was obtained as a yellow solid.

[00568] MS (ESI) m/z 440.1 (M+H).

125 Preparation of *N,N*-dicyclopropyl-4-(1,5-dimethyl-1*H*-1,2,4-triazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide

[00569] A mixture of 4-(3-acetylthioureido)-*N,N*-dicyclopropyl-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (example **125A**, 17 mg, 0.039 mmol) and methylhydrazine (2.486 µL, 0.046 mmol) in acetic acid (0.5 mL) was heated at 80 °C for 4h, LC/MS showed starting material still remaining. Additional methylhydrazine (2.486 µL, 0.046 mmol) was added and heating continued for another 2h, reaction complete. Solvent was evaporated and the crude

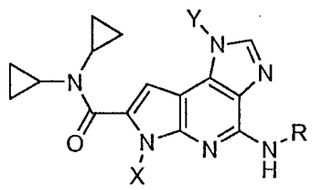
was purified by preparative HPLC to furnish *N,N*-dicyclopropyl-4-(1,5-dimethyl-1*H*-1,2,4-triazol-3-ylamino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide (5.2 mg, 30.7 % yield) as an off-white solid.

[00570] MS (ESI) m/z 434.3 (M+H).

[00571] ^{1}H NMR ($CDCl_3$) δ: 7.96 (s, 1H), 7.65 (s, 1H), 6.83 (s, 1H), 4.67 (q, J = 7.1 Hz, 2H), 4.01 (s, 3H), 3.82 (s, 3H), 2.77 - 2.84 (m, 2H), 2.43 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H), 0.79 - 0.86 (m, 4H), 0.71 - 0.77 (m, 4H).

WHAT IS CLAIMED IS:

1. A compound of the formula



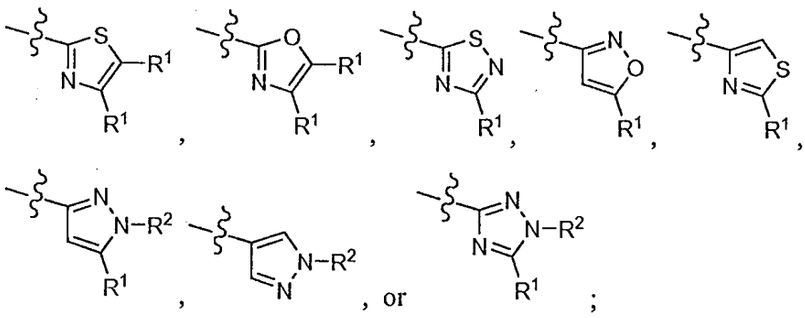
(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

X is C_{1-4} alkyl;

Y is C_{1-4} alkyl;

R is



any of which are optionally fused with a 5 or 6 membered carbocycle or heterocycle, said heterocycle having one heteroatom selected from NR^3 or S, said fused carbocycle or heterocycle being optionally substituted with 0-3 R^1.

R^1 is H, halo, CN, C_{1-6} alkyl substituted with 0-3 R^c, CF_3, $CONR^aR^a$, NR^aR^a, $COOR^b$, SO_2-C_{1-4}alkyl, $C(O)R^d$, cycloalkyl substituted with 0-3 R^e, furanyl, tetrahydropyranyl or pyridinyl;

R^2 is H, C_{1-6} alkyl substituted with 0-3 R^c, $C(O)O$-C_{1-4}alkyl, SO_2-C_{1-4}alkyl, cycloalkyl substituted with 0-3 R^e, tetrahydropyranyl or R^2 is absent;

R^3 is H, $C(O)O$-C_{1-4}alkyl, or R^3 is absent;

R^a is H, C_{1-6} alkyl substituted with 0-3 R^e, C_{3-6} cycloalkyl substituted with 0-3 R^e, tetrahydropyranyl or dioxotetrahydrothiophenyl;

R^b is H or C_{1-6} alkyl;

R^c is H, halo, CN, OH, O-C_{1-4}alkyl, O-C_{1-4}alkyl-O-C_{1-4}alkyl, NH_2, $N(C_{1-4}$ alkyl$)_2$, $C(O)N(C_{1-4}$alkyl$)_2$, SO_2-C_{1-4}alkyl, or morpholinyl or piperazinyl either of which are optionally substituted with 0-1 C_{1-4}alkyl;

R^d is C_{1-6} alkyl, or azeridinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, dioxidothiomorpholinyl or tetrahydropyranyl, any of which are substituted with 0-2 R^e; and

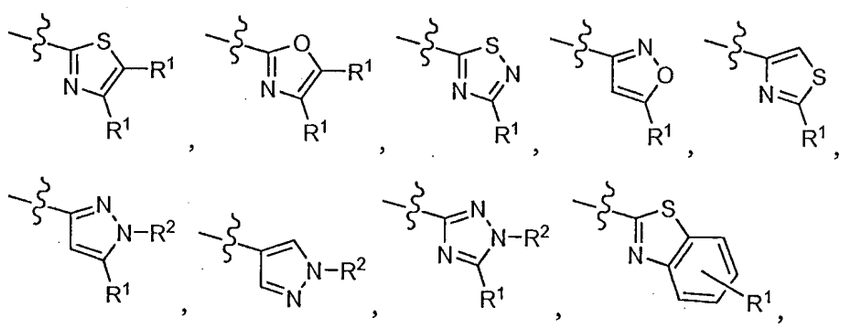
R^e is H, halo, CN, C_{1-4} alkyl, OH, O-C_{1-4}alkyl, SO_2-C_{1-4}alkyl, NHC(O)-C_{1-4}alkyl, morpholinyl, OC(O)-C_{1-4}alkyl, $C(O)N(C_{1-4}$alkyl$)_2$, or O-C_{1-4}alkyl-O-C_{1-4}alkyl.

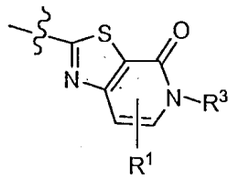
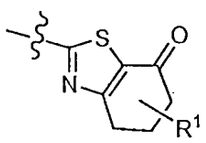
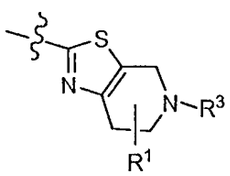
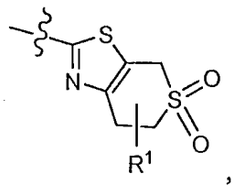
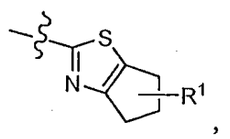
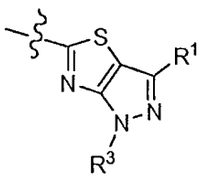
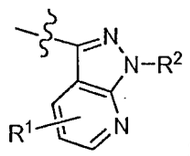
2. The compound according to claim 1 wherein

X is ethyl;

Y is methyl; and

R is



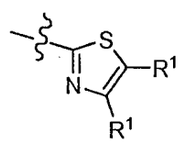
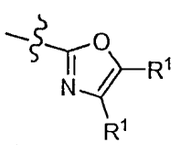
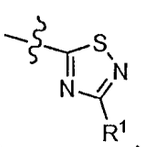
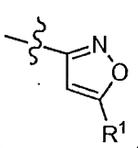
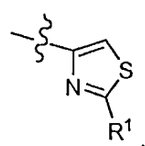
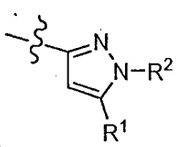
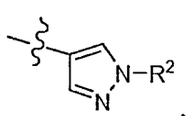
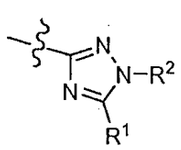
any of which are optionally substituted with 0-3 R^1;

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

3. The compound according to claim 2

wherein

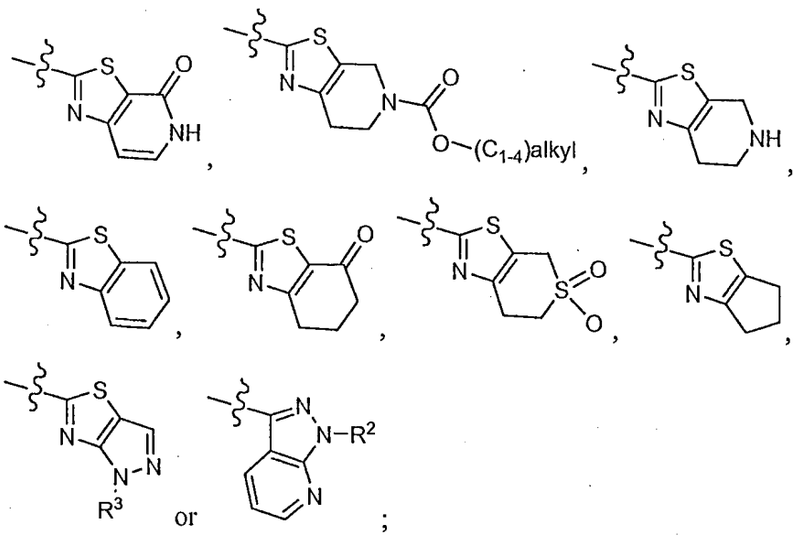
R is

4. The compound according to claim 2

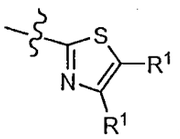
wherein

R is



any of which are optionally substituted with 0-2 R^1

5. The compound according to claim 2 wherein



R is ;

R^1 is H, halo, CN, C_{1-6} alkyl substituted with 0-3 R^c, CF_3, $CONR^aR^a$, $COOR^b$, SO_2-C_{1-4}alkyl, $C(O)R^d$, cycloalkyl substituted with 0-3 R^e, or pyridinyl;

R^a is H, C_{1-6} alkyl substituted with 0-3 R^e, C_{3-6} cycloalkyl substituted with 0-3 R^e, tetrahydropyranyl, or dioxotetrahydrothiophenyl;

R^b is H or C_{1-6} alkyl;

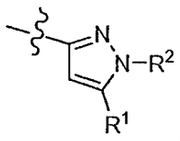
R^c is H, halo, OH, O-C_{1-4}alkyl, SO_2-C_{1-4}alkyl or morpholinyl;

R^d is C_{1-6} alkyl, or azetidinyl, pyrrolidinyl, morpholinyl, piperazinyl or dioxidothiomorpholinyl, any of which are substituted with 0-2 R^e; and

R^e is H, halo, CN, OH, O-C_{1-4}alkyl, SO_2-C_{1-4}alkyl, NHC(O)-C_{1-4}alkyl or morpholinyl;

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

6. The compound according to claim 2 wherein

R is  ;

R^1 is H, halo, C_{1-6} alkyl substituted with 0-3 R^c, CF_3, $CONR^aR^a$, $COOR^b$, $C(O)R^d$, cycloalkyl substituted with 0-3 R^e, or furanyl;

R^2 is H, C_{1-6} alkyl substituted with 0-3 R^c, SO_2-C_{1-4}alkyl, cycloalkyl substituted with 0-3 R^e, or tetrahydropyranyl;

R^a is H, or C_{1-6} alkyl substituted with 0-3 R^e;

R^b is H or C_{1-6} alkyl;

R^c is H, halo, CN, OH, O-C_{1-4}alkyl, O-C_{1-4}alkyl-O-C_{1-4}alkyl, NH_2, $N(C_{1-4}$ alkyl$)_2$, $C(O)N(C_{1-4}$alkyl$)_2$, SO_2-C_{1-4}alkyl, or morpholinyl or piperazinyl, either of which are optionally substituted with 0-1 C_{1-4}alkyl;

R^d is C_{1-6} alkyl, or morpholinyl, piperazinyl or dioxidothiomorpholinyl, any of which are substituted with 0-2 R^e;

R^e is H, C_{1-4} alkyl, CN, OH, NHC(O)-C_{1-4}alkyl or morpholinyl;

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

7. The compound according to claim 6 wherein

R^1 is C_{1-6} alkyl substituted with 0-3 R^c; and

R^2 is C_{1-6} alkyl.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and one or more compounds of any of claims 1-7 or pharmaceutically acceptable salts, tautomers or stereoisomers thereof.

9. A compound of any of claims 1-7 or pharmaceutically acceptable salts, tautomers or stereoisomers thereof, for use in therapy.

10. Use of a compound of any of claims 1-7 or pharmaceutically acceptable salts, tautomers or stereoisomers thereof, for the manufacture of a medicament for the treatment of myeloproliferative diseases or cancer.

11. Use of a compound according to Claim 10, wherein the cancer is selected from solid tumors of the pancreas, prostate, lung, head and neck, breast, colon, ovary, gastric cancer, multiple myeloma, melanoma, neuroblastoma, glioblastoma, systemic mastocytosis,and hematological malignancies such as acute myelogenous leukemia (including refractory acute myeloid leukemia) and acute lymphoid leukemia

12. Use of a compound according to Claim 10, wherein the myeloproliferative disease is polycythemia vera, essential thrombocytopenia or primary myelofibrosis.

13. One or more compound(s) according to claim 1 as an active agent for treating myeloproliferative diseases or cancer in a mammal.

14. One or more compound(s) as an active agent for treating cancer according to claim 13, wherein the cancer is selected from solid tumors of the pancreas, prostate, lung, head and neck, breast, colon, ovary, gastric cancer, multiple myeloma, melanoma, neuroblastoma, glioblastoma, systemic mastocytosis,and hematological malignancies such as acute myelogenous leukemia (including refractory acute myeloid leukemia) and acute lypmphoid leukemia

15. One or more compound(s) as an active agent for treating myeloproliferative disease according to claim 13, wherein the myeloproliferative disease is polycythemia vera, essential thrombocytopenia or primary myelofibrosis.

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INHIBIDORES DE JAK2 Y SU USO EN EL TRATAMIENTO DE ENFERMEDADES MIELOPROLIFERATIVAS Y CANCER

Campo de la Invención

La presente invención se refiere a compuestos novedosos que son útiles como agentes anticancerosos/antiproliferativos. La presente invención también se refiere a un procedimiento de uso de los compuestos en el tratamiento de enfermedades proliferativas, tales como cáncer, y a composiciones farmacéuticas que contienen los compuestos.

Antecedentes de la Invención

Los esfuerzos para identificar nuevas estrategias terapéuticas para la enfermedad *Ph (-)* mieloproliferativa se han reforzado por las observaciones de la activación constitutiva de la ruta de señalización de JAK-Stat en pacientes con MPD. En particular, se ha observado una mutación simple de valina a fenilalanina en el residuo 617 (JAK2-V617F) en JAK2 en la mayoría de los pacientes PV (95%), ET (50-60%) y PMF (50-60%) (Tabla 2, Kralovics et al., 2005; Baxter et al., 2005; Tefferi et al., 2005). La mutación V617F reside en la región del gen *JAK2* que codifica el dominio pseudocinasa que se cree que funciona como un dominio autoinhibidor para regular la actividad tirosina-cinasa de JAK2. También se observan con menor frecuencia (<5% en PV y

ET) mutaciones en el exón 12 de JAK2 que también da como resultado una actividad cinasa de JAK2 constitutiva y son mutuamente exclusivas con lesiones en JAK2V617F (Pardanari et al., 2007; Scott et al., 2007). JAK2 es un miembro de una familia de tirosina-cinasas no receptoras que también incluye JAK1, Tyk2 y JAK3 y funcionan como mediadores de la señalización de receptores de citocinas (para una revisión, véase Murray, 2007). Tras una unión de citocina a su receptor afín, los miembros de la familia JAK de unión al receptor se activan y fosforilan un STAT, un factor de transcripción latente, que, tras la fosforilación mediada por JAK, experimenta dimerización y traslocación hacia el núcleo para regular la expresión génica. Estudios genéticos y bioquímicos han establecido combinaciones distintas de acoplamiento de un miembro de la familia JAK con un receptor individual de citocina. Por ejemplo, el acoplamiento del receptor de eritropoyetina (EPO), trombopoyetina (TPO) y factor estimulador de colonias de granulocitos (GM-CSF) da como resultado una activación de JAK2 predominante para mediar la señalización corriente abajo. De acuerdo con la patofisiología de MPD asociada con la mutación JAK2-V617F, estas citocinas promueven la diferenciación y la expansión de los tipos celulares PV, ET y PMF, respectivamente, subyacentes. A diferencia de otros sucesos de activación genética, la expresión de JAK2-V617F no es suficiente para

promover la transformación en sistemas de modelos basados en células y se ha demostrado que requiere la co-expresión de los receptores de citocinas tipo I, resaltando una codependencia funcional importante de la interacción del receptor JAK-citocina (Lu et al., 2005). De forma interesante, se han identificado mutaciones de activación en el receptor TPO (MLP, sustitución de triptófano por leucina en el residuo 515) en pacientes con MPD afligidos con PMF y ET JAK2-V617F *negativo* (5% y 1% respectivamente), dando como resultado la activación constitutiva de JAK2-Stat (Pikman et al., 2006). Estas observaciones indican que la transducción de señal de JAK-Stat puede activarse a través de la mutación en MPD en múltiples puntos de la ruta de una manera mutuamente exclusiva y sugiere la posible presencia de mutaciones adicionales de la ruta en MPD JAK2 - V617F y MPL-W515L negativo.

La importante validación de la señalización de JAK2 como un accionador de MPD *Ph (-)* emergió de modelos de roedor en los que la señalización del mutante JAK2-V617F se reconstituyó en el compartimento hematopoyético de células madre. Varios laboratorios demostraron que la transducción viral de JAK2-V617F en médula ósea de ratón y posteriormente la reimplantación en los ratones receptores reconstituyó varios aspectos de la MPD humana (Wernig et al., 2006, Lacout et al., 2006, Bumm et al., 2006, Zaeleskas et al., 2006).

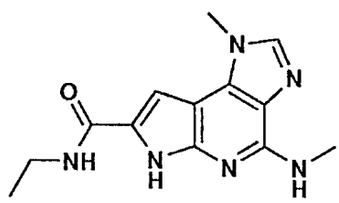
Estas características incluían hematocrito elevado, esplenomegalia de hematopoyesis extramedular, granulocitosis y fibrosis de la médula ósea, todo ello también se manifiesta en policitemia vera. De forma interesante, a diferencia de la afección humana, no se observó trombocitosis en estos modelos murinos y se sugirió que era atribuible a acontecimientos genéticos secundarios que contribuyen a la expansión plaquetaria (Wernig et al., 2006). Una reconstrucción similar de la mutación del receptor TPO (MPL-W515L) en médula ósea de roedores dio como resultado una enfermedad mieloproliferativa con un comienzo más rápido que en animales JAK2-V617F que era reminiscente de la mielofibrosis primaria incluyendo esplenomegalia, hepatomegalia y fibrosis de la reticulina de médula ósea (Pikman et al., 2006). También a diferencia del modelo JAK2-V617F, ratones que expresan MPL-W515L presentaban trombocitosis dramática que quizás indicaba una función más dominante de la activación del receptor en comparación con JAK2-V617F en la expansión de este linaje. Sin embargo, estas observaciones acentúan colectivamente el papel de MPL-W515L y JAK2-V617F como mutaciones de dirección subyacentes en la progresión de la MPD humana.

Una cuestión clave para la base genética de MPD es el papel de acontecimientos genéticos adicionales que contribuyen a la progresión de la enfermedad aparte de JAK2 y MPL. Varias líneas de evidencias sugieren modificaciones

genéticas adicionales en la progresión de la enfermedad MPD. De hecho, la recombinación mitótica sucede con frecuencia en pacientes con MPD para generar dos alelos JAK2-V617F, indicando una selección de clones celulares homocigotos para la cinasa mutada (Levine et al., 2005). En este sentido, sería importante desarrollar animales agénicos JAK2-V617F condicionales y determinar las consecuencias fenotípicas del homocigoto contra cargas JAK2-V617F de heterocigoto. Adicionalmente, existen evidencias de un alelo de la línea germinal heredada que precede y predispone pacientes a adquirir JAK2-V617F (Goerttler et al., 2005; Levine et al., 2006) así como la pérdida de la región cromosómica 20q en algunos pacientes con MPD. Aunque se observa clínicamente la conversión de MPD a AML a niveles moderados y se observan traslocaciones cromosómicas de activación de JAK en leucemia, los datos epidemiológicos sugieren que es cuestionable que JAK2-V617F sea un conductor genético en este contexto, lo que sugiere que son necesarias modificaciones genéticas adicionales para la transformación leucémica total (Theocharides et al., 2007). A pesar de las presentes observaciones, la inhibición de JAK2 con inhibidores de moléculas pequeñas es suficiente para modular la progresión de la enfermedad en modelos animales preclínicos, lo que sugiere que la activación de JAK2 es suficiente para el mantenimiento de MPD (Paradani et al., 2007). Será importante

identificar estas modificaciones genéticas adicionales y descifrar cómo contribuyen estos cambios genéticos a la progresión de la enfermedad de PV, ET y PMF en el contexto de JAK2-V617F y MPL-W515L. También será importante aplicar estrategias para identificar si otros componentes de la ruta de JAK2 están mutados en pacientes de MPD no asociados con la adquisición de JAK2-V617F, el exón 12 de JAK2 o mutaciones de MPL-W515L.

La publicación de patente WO2006/122137 describe compuestos que son útiles como inhibidores de IKK. El Ejemplo N° A171 describe el compuesto de fórmula

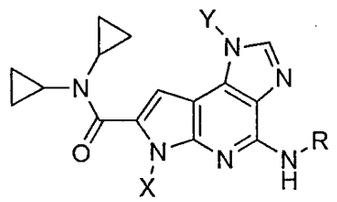


que se encontró que tenía una débil actividad frente a JAK2 en el ensayo que se describe más adelante en el presente documento.

Descripción Detallada de la Invención

La presente invención proporciona compuestos de fórmula I, composiciones farmacéuticas que emplean los compuestos y procedimientos de uso de los compuestos.

De acuerdo con la presente invención, se describen compuestos de fórmula I



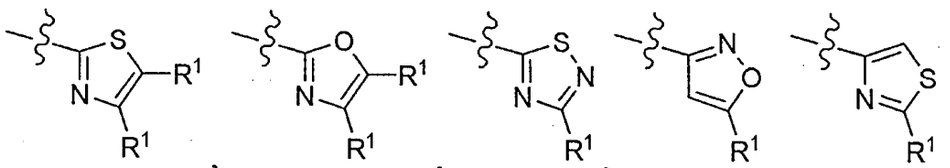
(I)

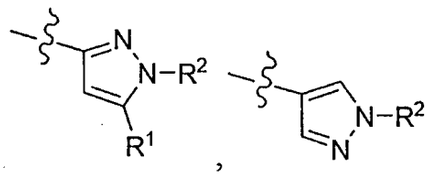
o su estereoisómero, tautómero o sal del mismo farmacéuticamente aceptable, en la que:

Y es alquilo C_{1-4};

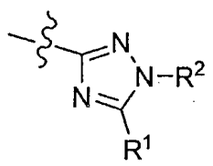
X es alquilo C_{1-4};

R es





o



;

cualquiera de los cuales está opcionalmente fusionada con un carbociclo o heterociclo de 5 ó 6 elementos que tiene un heteroátomo seleccionado entre NR^3 o S, estando el carbociclo o heterociclo fusionado opcionalmente sustituido con 0-3 R^1.

R^1 es H, halo, CN, alquilo C_{1-6} sustituido con 0-3 R^c, CF_3, $CONR^aR^a$, NR^aR^a, $COOR^b$, SO_2-alquilo C_{1-4}, $C(O)R^d$, cicloalquilo sustituido con 0-3 R^e, furanilo,

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tetrahidropiranilo o piridinilo;

R^2 está ausente, H, alquilo C_{1-6} sustituido con 0-3 R^c, C(O)O-alquilo C_{1-4}, SO_2-alquilo C_{1-4}, cicloalquilo sustituido con 0-3 R^e, o tetrahidropiranilo;

R^3 está ausente, H, o C(O)O-alquilo C_{1-4};

R^a es H, alquilo C_{1-6} sustituido con 0-3 R^e, cicloalquilo C_{3-6} sustituido con 0-3 R^e, tetrahidropiranilo o dioxotetrahidrotiofenilo;

R^b es H o alquilo C_{1-6};

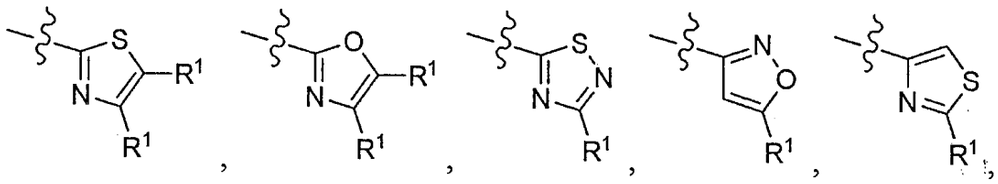
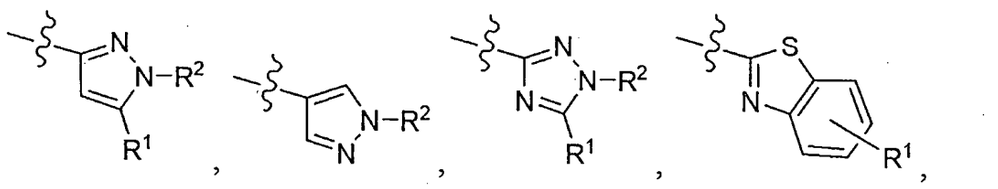
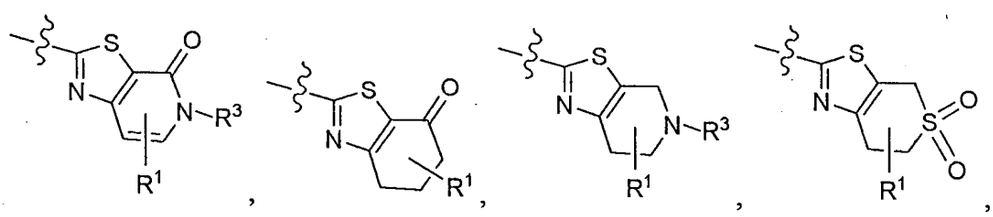
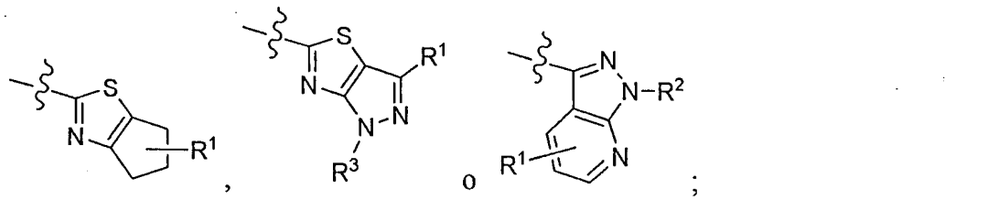
R^c es H, halo, CN, OH, O-alquilo C_{1-4}, O-alquil C_{1-4}-O-alquilo C_{1-4}, NH_2, N(alquilo C_{1-4})$_2$, C(O)N(alquilo C_{1-4})$_2$, SO_2-alquilo C_{1-4}, o morfolinilo o piperazinilo, cualquiera de los cuales está opcionalmente sustituido con 0-1 alquilo C_{1-4};

R^d es alquilo C_{1-6}, o azeridinilo, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, dioxidotiomorfolinilo o tetrahidropiranilo, cualquiera de los cuales está sustituido con 0-2 R^e; y

R^e es H, halo, CN, alquilo C_{1-4}, OH, O-alquilo C_{1-4}, SO_2-alquilo C_{1-4}, NHC(O)-alquilo C_{1-4}, morfolinilo, OC(O)-alquilo C_{1-4}, C(O)N(alquilo C_{1-4})$_2$, o O-alquil C_{1-4}-O-alquilo C_{1-4}.

Otra modalidad son compuestos de Fórmula (I), en la que:

R es

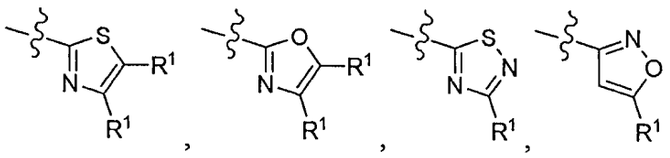
cualquiera de los cuales está opcionalmente sustituido con 0-3 R^1.

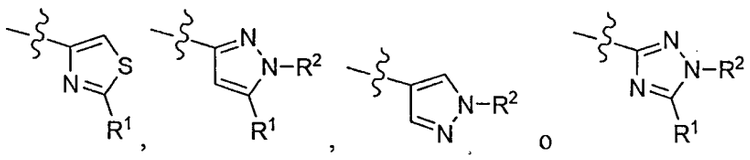
Otra modalidad son compuestos de Fórmula (I), en la que:

Y es metilo; y

X es etilo.

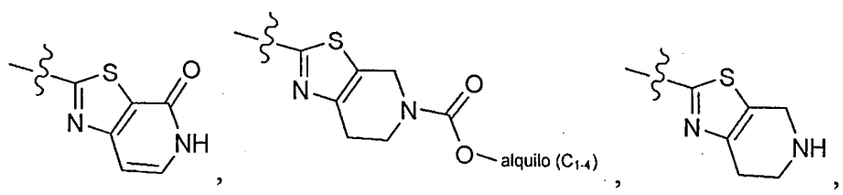
Otra modalidad son compuestos de Fórmula (I), en la que:

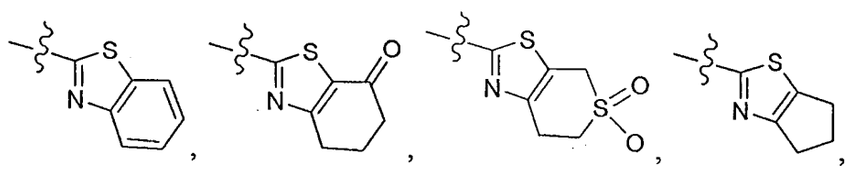




Otra modalidad son compuestos de Fórmula (I), en la que:

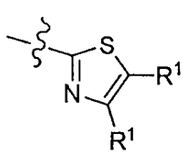
R es





cualquiera de los cuales está opcionalmente sustituido con 0-2 R^1.

Otra modalidad son compuestos de Fórmula (I), en la que



R^1 es ;

R^1 es H, halo, CN, alquilo C_{1-6} sustituido con 0-3 R^c, CF_3, $CONR^aR^a$, $COOR^b$, SO_2-alquilo C_{1-4}, $C(O)R^d$, cicloalquilo sustituido con 0-3 R^e, o piridinilo;

R^a es H, alquilo C_{1-6} sustituido con 0-3 R^e, cicloalquilo C_{3-6} sustituido con 0-3 R^e, tetrahidropiranilo o dioxotetrahidrotiofenilo;

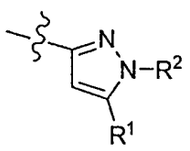
R^b es H o alquilo C_{1-6};

R^c es H, halo, OH, O-alquilo C_{1-4}, SO_2-alquilo C_{1-4} o morfolinilo;

R^d es alquilo C_{1-6}, o azetidinilo, pirrolidinilo, morfolinilo, piperazinilo o dioxidotiomorfolinilo, cualquiera de los cuales está sustituido con 0-2 R^e;

R^e es H, halo, CN, OH, O-alquilo C_{1-4}, SO_2-alquilo C_{1-4}, $NHC(O)$-alquilo C_{1-4} o morfolinilo.

Otra modalidad son compuestos de Fórmula (I), en la que:

R es ; 

R^1 es H, halo, alquilo C_{1-6} sustituido con 0-3 R^c, CF_3, $CONR^aR^a$, $COOR^b$, $C(O)R^d$, cicloalquilo sustituido con 0-3 R^e o furanilo;

R^2 es H, alquilo C_{1-6} sustituido con 0-3 R^c, SO_2-alquilo C_{1-4}, cicloalquilo sustituido con 0-3 R^e, o tetrahidropiranilo;

R^a es H, o alquilo C_{1-6} sustituido con 0-3 R^e;

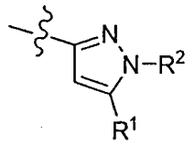
R^b es H o alquilo C_{1-6};

R^c es H, halo, CN, OH, O-alquilo C_{1-4}, O-alquil C_{1-4}-O-alquilo C_{1-4}, NH_2, N(alquilo C_{1-4})$_2$, C(O)N(alquilo C_{1-4})$_2$, SO_2-alquilo C_{1-4}, o morfolinilo o piperazinilo, cualquiera de los cuales está opcionalmente sustituido con 0-1 alquilo C_{1-4};

R^d es alquilo C_{1-6} o morfolinilo, piperazinilo o dioxidotiomorfolinilo, cualquiera de los cuales está sustituido con 0-2 R^e; y

R^e es H, alquilo C_{1-4}, CN, OH, NHC(O)-alquilo C_{1-4} o morfolinilo.

Otra modalidad son compuestos de Fórmula (I), en la que:

R es ; 

R^1 es alquilo C_{1-6} sustituido con 0-3 R^c; y

R^2 es alquilo C_{1-6}.

Otra modalidad son compuestos de Fórmula (I), en la que el compuesto de fórmula (I) se selecciona entre los compuestos ejemplificados.

En otra modalidad la presente invención proporciona una composición farmacéutica que comprende un vehículo farmacéuticamente aceptable y uno o más de los compuestos de la presente invención o un estereoisómero, tautómero, sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

En otra modalidad, la presente invención proporciona una composición farmacéutica que comprende un compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo y un vehículo farmacéuticamente aceptable.

En otra modalidad, la presente invención proporciona una composición farmacéutica, que comprende un vehículo farmacéuticamente aceptable y una cantidad terapéuticamente eficaz de uno o más de los compuestos de la presente invención o un estereoisómero, tautómero, sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

En otra modalidad, la presente invención proporciona un procedimiento para tratar trastornos proliferativos y/o cáncer que comprende administrar a un paciente que necesita el tratamiento una cantidad terapéuticamente eficaz de uno o más de los compuestos de la presente invención o un estereoisómero, tautómero, sal, solvato o profármaco farmacéuticamente aceptable de los mismos, junto con uno o más agentes anti-cáncer diferentes, o un estereoisómero, tautómero, sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

En otra modalidad, la presente invención proporciona un procedimiento para tratar trastornos proliferativos y/o cáncer que comprende administrar a un paciente que necesita el tratamiento una cantidad

terapéuticamente eficaz de uno o más de los compuestos de la presente invención o un estereoisómero, tautómero, sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

En otra modalidad, la presente invención proporciona un procedimiento para tratar a un paciente que necesita tratamiento para un trastorno proliferativo y/o cáncer, que comprende la administración de un compuesto de la presente invención o un estereoisómero, tautómero, sal farmacéuticamente aceptable, solvato o forma de profármaco del mismo en una cantidad eficaz para tratar el trastorno proliferativo y/o cáncer.

En otra modalidad, la presente invención proporciona un procedimiento de tratamiento de síndromes mieloproliferativos, tales como policitemia vera, trombocitopenia esencial y mielofibrosis primaria, tumores sólidos del páncreas, próstata, pulmón, cabeza y cuello, mama, colon, ovario, cáncer gástrico así como otros tipos de tumores que incluyen mieloma múltiple, melanoma, neuroblastoma, glioblastoma, mastocitosis sistémica y neoplasias malignas hematológicas tales como leucemia mielógena aguda (incluyendo leucemia mieloide aguda refractaria) y leucemia linfoide aguda.

En otra modalidad, la presente invención proporciona un procedimiento novedoso, que comprende la

administración de un compuesto de la presente invención o un estereoisómero, tautómero, sal farmacéuticamente aceptable, solvato o forma de profármaco del mismo en una cantidad eficaz para tratar un trastorno proliferativo y/o cáncer.

En otra modalidad, la presente invención proporciona un procedimiento para tratar trastornos proliferativos y/o cáncer que comprende la administración a un paciente que necesita el tratamiento de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I) o un estereoisómero, tautómero, sal farmacéuticamente aceptable, solvato o forma de profármaco del mismo, en combinación con uno o más agentes anti-cancerosos o agentes antiproliferativos diferentes y/u otro agente, o un estereoisómero, tautómero, sal farmacéuticamente aceptable, solvato o forma de profármaco del mismo.

En otra modalidad, la presente invención proporciona un procedimiento para tratar trastornos proliferativos y/o cáncer que comprende la administración a un paciente que necesita el tratamiento de una cantidad terapéuticamente eficaz de uno o más de los compuestos de la presente invención o un estereoisómero, tautómero, sal farmacéuticamente aceptable, solvato o forma de profármaco del mismo, en combinación con uno o más agentes anti-cancerosos diferentes o un estereoisómero, tautómero, sal farmacéuticamente aceptable, solvato o forma de profármaco

del mismo.

En otra modalidad, la presente invención proporciona un compuesto de la presente invención para uso en terapia.

En otra modalidad, la presente invención proporciona un compuesto de la presente invención para uso en terapia para tratar un trastorno proliferativo y/o cáncer.

En otra modalidad, la presente invención también proporciona el uso de un compuesto de fórmula I de la presente invención para la fabricación del medicamento para el tratamiento de un trastorno proliferativo y/o cáncer.

La presente invención puede realizarse en otras formas específicas sin apartarse del espíritu o de los atributos esenciales de la misma. La presente invención abarca todas las combinaciones de aspectos preferidos y/o modalidades de la invención apuntadas en el presente documento. Se entiende que todas y cada una de las modalidades de la presente invención pueden tomarse junto con cualquier otra modalidad o modalidades para describir modalidades adicionales más preferidas. También debe entenderse que cada elemento individual de las modalidades preferidas es su propia modalidad preferida independiente. Además, cualquier elemento de una modalidad pretende combinarse con todos y cada uno de los otros elementos de cualquier modalidad para describir una modalidad adicional.

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DEFINICIONES

Las siguientes son definiciones de términos que pueden usarse en la presente descripción. La definición inicial proporcionada para un grupo o término en el presente documento se aplica a un grupo o término por toda la presente descripción individualmente o como parte de otro grupo, a menos que se indique otra cosa.

Los compuestos de la presente invención pueden tener uno o más centros asimétricos. A menos que se indique otra cosa, todas las formas quirales (enantioméricas y diastereoméricas) y racémicas de los compuestos de la presente invención se incluyen en la presente invención. Muchos isómeros geométricos de olefinas, dobles enlaces C=N y similares también pueden estar presentes en los compuestos, y todos estos isómeros estables se contemplan en la presente invención. Se describen isómeros geométricos cis y trans de los compuestos de la presente invención y pueden aislarse en forma de una mezcla de isómeros o en forma de formas isoméricas separadas. Los presentes compuestos pueden aislarse de forma ópticamente activa o racémica. Se conoce bien en la técnica cómo preparar formas ópticamente activas, tales como por resolución de formas racémicas o mediante la síntesis de materiales de partida ópticamente activos. Se incluyen todos las formas quirales (enantioméricas y diastereoméricas) y racémicas y todas las formas isoméricas geométricas de una

estructura, a menos que se indique específicamente la forma estereoquímica o isomérica específica.

El término "sustituido", como se usa en el presente documento, significa que uno cualquiera o más hidrógenos en el átomo designado se reemplaza con una selección del grupo indicado, con la condición de que la valencia normal del átomo denominado no se exceda, y que la sustitución de como resultado un compuesto estable. Si un sustituyente es ceto (es decir, =O), entonces se reemplazan 2 hidrógenos en el átomo. Los sustituyentes ceto no están presentes en las porciones aromáticas. Los dobles enlaces de anillo, como se usa en el presente documento, son dobles enlaces que se forman entre dos átomos adyacentes en el anillo (por ejemplo, C=C, C=N o N=N).

Cuando cualquier variable (por ejemplo, R^3) aparece más de una vez en cualquier constituyente o fórmula para un compuesto, su definición en cada caso es independiente de su definición en cada caso diferente. Por lo tanto, por ejemplo, si se muestra que un grupo está sustituido con 0-2 R^3, entonces el grupo puede estar opcionalmente sustituido con hasta dos grupos R^3 y R^3 en cada caso se selecciona independientemente entre la definición de R^3. Además, las combinaciones de sustituyentes y/o variables únicamente se permite si las combinaciones dan como resultado compuestos estables.

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Cuando se muestra un enlace en un sustituyente para cruzar un enlace que conecta dos átomos en un anillo, entonces el sustituyente puede unirse a cualquier átomo en el anillo. Cuando se enumera un sustituyente sin indicar el átomo por el que el sustituyente está unido al resto del compuesto de una formulada determinada, entonces el sustituyente puede unirse por cualquier átomo en el sustituyente. Las combinaciones de sustituyentes y/o variables únicamente se permiten si las combinaciones dan como resultado compuestos estables.

En los casos en los que hay átomos de nitrógeno (por ejemplo, aminas) en los compuestos de la presente invención, estos pueden convertirse en N-óxidos por tratamiento con un agente de oxidación (por ejemplo, MCPBA y/o peróxido de hidrógenos) para producir otros compuestos de la presente invención. Por lo tanto, todos los átomos de nitrógeno mostrados e indicados se considera que incluyen tanto el nitrógeno mostrado como su derivado de N-óxido (N → O).

Como se usa en el presente documento, los términos "alquilo" o "alquileno" pretenden incluir grupos hidrocarburos alifáticos saturados tanto de cadena ramificada como lineal que tienen el número especificado de átomos de carbono. Por ejemplo, "alquilo C_{1-10}" (o alquileno), pretende incluir grupos alquilo C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 y C_{10}.

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Además, por ejemplo, "alquilo C_1-C_6" representa alquilo que tiene de 1 a 6 átomos de carbono. Los grupos alquilo pueden estar sin sustituir o sustituidos de modo que uno o más de sus hidrógenos se reemplazan por otro grupo químico. Los ejemplos de grupos alquilo incluyen, pero sin limitación, metilo (Me), etilo (Et), propilo (por ejemplo, n-propilo e isopropilo), butilo (por ejemplo, n-butilo, isobutilo, t-butilo), pentilo (por ejemplo, n-pentilo, isopentilo, neopentilo) y similares.

"Alquenilo" o "alquenileno" pretenden incluir cadenas de hidrocarburos de configuración lineal o ramificada y que tienen uno o más dobles enlaces carbono-carbono que pueden aparecer en cualquier punto estable a lo largo de la cadena. Por ejemplo, "alquenilo C_{2-6}" (o alquenileno) pretende incluir grupos alquenilo C_2, C_3, C_4, C_5 y C_6. Los ejemplos de alquenilo incluyen, pero sin limitación, etenilo, 1-propenilo, 2-propenilo, 2-butenilo, 3-butenilo, 2-pentenilo, 3, pentenilo, 4-pentenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo, 2-metil-2-propenilo, 4-metil-3-pentenilo y similares.

"Alquinilo" o "alquinileno" pretenden incluir cadenas de hidrocarburo de configuración lineal o ramificada y que tienen uno o más triples enlaces carbono-carbono que pueden aparecer en cualquier punto estable a lo largo de la cadena. Por ejemplo, "alquinilo C_{2-6}" (o alquinileno),

pretende incluir grupos alquinilo C_2, C_3, C_4, C_5 y C_6; tales como etinilo, propinilo, butinilo, pentinilo, hexinilo y similares.

"Halo" o "halógeno" incluye fluoro, cloro, bromo y yodo.

El término "cicloalquilo" se refiere a grupos alquilo ciclados, que incluyen sistemas de anillos mono-, bi- o poli-cíclicos. Cicloalquilo C_{3-10} pretende incluir grupos cicloalquilo C_3, C_4, C_5, C_6 y C_7. Los ejemplos de grupos cicloalquilo incluyen, pero sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, norbornilo y similares. Como se usa en el presente documento, "carbociclo" o "residuo carbocíclico" pretende indicar cualquier anillo monocíclico o bicíclico de 3, 4, 5, 6 ó 7 elementos o bicíclico o tricíclico de 7, 8, 9, 10, 11, 12 ó 13 elementos estable, que pueden estar saturados, parcialmente insaturados, insaturados o aromáticos. Los ejemplos de tales carbociclos incluyen, pero sin limitación, ciclopropilo, ciclobutilo, ciclobutenilo, ciclopentilo, ciclopentenilo, ciclohexilo, cicloheptenilo, cicloheptilo, cicloheptenilo, adamantilo, ciclooctilo, ciclooctenilo, ciclooctadienilo, [3.3.0]biciclooctano, [4.3.0]biciclononano, [4.4.0]biciclodecano, [2.2.2]biciclooctano, fluorenilo, fenilo, naftilo, indanilo, adamantilo, antracenilo y tetrahidronaftilo (tetralina). Como se ha mostrado

anteriormente, también se incluyen anillos puenteados en la definición de carbociclo (por ejemplo, [2.2.2]biciclooctano). Son carbociclos preferidos, a menos que se indique otra cosa, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo e indanilo. Cuando el término "carbociclo" se usa, pretenden incluir "arilo". Un anillo puenteado aparece cuando uno o más átomos de carbono se unen a dos átomos de carbono no adyacentes. Los puentes preferidos son uno o dos átomos de carbono. Se observa que un puente siempre convierte un anillo monocíclico en un anillo tricíclico. Cuando se puentea un anillo, los sustituyentes enumerados para el anillo también pueden estar presentes en el puente.

El término "arilo" se refiere a grupos aromáticos monocíclicos o bicíclicos que tienen de 6 a 12 átomos de carbono en la porción del anillo, tales como grupos fenilo, naftilo, bifenilo y difenilo, que pueden estar sustituidos.

El término "arilo sustituido" se refiere a un grupo arilo sustituido con, por ejemplo, uno a cuatro sustituyentes tales como alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, arilalquilo, halo, trifluorometoxi, trifluorometilo, hidroxi, alcoxi, alcanoilo, alcanoiloxi, ariloxi, arilalquiloxi, amino, alquilamino, arilamino, arilalquilamino, dialquilamino, alcanoilamino, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo,

carbamilo, alcoxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, ariloxi y similares. El sustituyente puede estar adicionalmente sustituido con hidroxi, halo, alquilo, alcoxi, alquenilo, alquinilo, arilo o arilalquilo.

El término "heteroarilo" se refiere a un grupo aromático opcionalmente sustituido, que es un sistema de anillos monocíclico de 4 a 7 elementos, bicíclico de 7 a 11 elementos o tricíclico de 10 a 15 elementos, que tiene al menos un anillo que contiene al menos un heteroátomo y al menos un átomo de carbono, por ejemplo, piridina, tetrazol, indazol.

Como se usa en el presente documento, las expresiones "heterociclo", "heterociclilo", "sistema heterocíclico" o "grupo heterocíclico" pretenden indicar un anillo heterocíclico monocíclico o bicíclico de 5, 6 ó 7 elementos o bicíclico de 7, 8, 9, 10, 11, 12, 13 ó 14 elementos estable que está saturado, parcialmente insaturado o completamente insaturado, que consiste en átomos de carbono y 1, 2, 3 ó 4 heteroátomos seleccionados independientemente entre N, O y S; e incluyendo cualquier grupo bicíclico en el que cualquiera de los anillos heterocíclicos que se han definido anteriormente está fusionado a un anillo benceno. Los heteroátomos de nitrógeno y azufre pueden estar oxidados (es decir, N $\rightarrow$ O y $S(O)_p$). El átomo de nitrógeno puede estar

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sustituido o sin sustituir (es decir, N o NR, en el que R es H u otro sustituyente, si se indica). El anillo heterocíclico puede estar unido a su grupo colgante en cualquier heteroátomo y átomo de carbono que dé como resultado una estructura estable. Los anillos heterocíclicos descritos en el presente documento pueden estar sustituidos en un átomo de carbono o en uno átomo de nitrógeno si el compuesto resultante es estable. Un nitrógeno en el heterociclo puede estar opcionalmente cuaternizado. Se prefiere que cuando el número total de átomos de S y O en el heterociclo exceda de 1, entonces estos heteroátomos no sean adyacentes entre sí. Se prefiere que el número total de átomos de S y O en el heterociclo no sea más de 1. Cuando se usa el término "heterociclo", pretende incluir heteroarilo.

Los ejemplos de heterociclos incluyen, pero sin limitación, acridinilo, azocinilo, benzoimidazolilo, benzofuranilo, benzotiofuranilo, benzoxazolilo, benzoxazolinilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, benzoimidazolinilo, carbazolilo, 4a*H*-carbazolilo, carbolinilo, cromanilo, cromenilo, cinnolinilo, decahidroquinolinilo, 2*H*,6*H*-1,5,2-ditiazinilo, dihidrofuro[2,3-*b*]tetrahidrofurano, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1*H*-indazolilo, indolenilo, indolinilo, indolizinilo, indolilo, 3H-indolilo,

isatinoilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolopiridinilo, isoxazolilo, isoxazolopiridinilo, metilenodioxifenilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidinilo, oxazolilo, oxindolilo, pirimidinilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxathinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, piperidonilo, 4-piperidonilo, piperonilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazol, piridoimidazol, piridotiazol, piridinilo, pirimidinilo, pirrolidinilo, pirrolinilo, 2-pirrolidonilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4*H*-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranoilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, tetrazolilo, 6*H*-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, tiazolilo, tienilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tiofenilo, triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo. También se incluyen anillos fusionados y compuestos espiro que contienen, por ejemplo, los heterociclos anteriores.

Los heterociclos de 5 a 10 elementos preferidos incluyen, pero sin limitación, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, pirazinilo, piperazinilo, piperidinilo, imidazolilo, imidazolidinilo, indolilo, tetrazolilo, isoxazolilo, morfolinilo, oxazolilo, oxadiazolilo, oxazolidinilo, tetrahidrofuranoilo, tiadiazinilo, tiadiazolilo, tiazolilo, triazinilo, triazolilo, benzoimidazolilo, 1*H*-indazolilo, benzofuranilo, benzotiofuranilo, benzotetrazolilo, benzotriazolilo, benzoisoxazolilo, benzoxazolilo, oxindolilo, benzoxazolinilo, benzotiazolilo, benzoisotiazolilo, isatinoilo, isoquinolinilo, octahidroisoquinolinilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, isoxazolopiridinilo, quinazolinilo, quinolinilo, isotiazolopiridinilo, tiazolopiridinilo, oxazolopiridinilo, imidazolopiridinilo y pirazolopiridinilo.

Los heterociclos de 5 a 6 elementos preferidos incluyen, pero sin limitación, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, pirazinilo, piperazinilo, piperidinilo, imidazolilo, imidazolidinilo, indolilo, tetrazolilo, isoxazolilo, morfolinilo, oxazolilo, oxadiazolilo, oxazolidinilo, tetrahidrofuranoilo, tiadiazinilo, tiadiazolilo, tiazolilo, triazinilo y triazolilo. También se incluyen anillos fusionados y compuestos espiro que contienen, por ejemplo, los

heterociclos anteriores.

En otra modalidad, los heterociclos incluyen, pero sin limitación, piridilo, piridinilo, isoxazilo, isoquinolinilo, tienilo, pirazolilo, furanilo, pirrolilo, tiazolilo, imidazolilo, pirazinilo, tiadiazolilo, pirimidinilo, piridazinilo, oxazolilo, isotiazolilo, oxadiazolilo, indanonilo, piperazinilo, piranilo o pirrolilo.

También se incluyen heterociclos más pequeños, tales como, epóxidos y aziridinas.

Como se usa en el presente documento, la expresión "grupo heterocíclico aromático" o "heteroarilo" pretende indicar hidrocarburos aromáticos monocíclicos y policíclicos estables que incluyen al menos un heteroátomo en el elemento de anillo tal como azufre, oxígeno o nitrógeno. Los grupos heteroarilo incluyen, sin limitación, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, furilo, quinolilo, isoquinolilo, tienilo, imidazolilo, tiazolilo, indolilo, pirroilo, oxazolilo, benzofurilo, benzotienilo, benzotiazolilo, isoxazolilo, pirazolilo, triazolilo, tetrazolilo, indazolilo, 1,2,4-tiadiazolilo, isotiazolilo, purinilo, carbazolilo, benzoimidazolilo, indolinilo, benzodioxolanilo, benzodioxano y similares. Los grupos heteroarilo pueden estar sustituidos o sin sustituir. El átomo de nitrógeno puede estar sustituido o sin sustituir (es decir, N o NR, en el que R es H u otro sustituyente, si se

indica). Los heteroátomos de nitrógeno y azufre opcionalmente pueden oxidarse (es decir, N → O y $S(O)_p$). Debe apreciarse que el número total de átomos de S y O en el heterociclo aromático no es más de 1. También se incluyen los anillos puenteados en la definición de heterociclo. Un anillo puenteado aparece cuando uno o más átomos (es decir, C, O, N o S) unen dos átomos de carbono o de nitrógeno no adyacentes. Los puentes preferidos incluyen, pero sin limitación, un átomo de carbono, dos átomos de carbono, un átomo de nitrógeno, dos átomos de nitrógeno y un grupo carbono-nitrógeno. Se observa que un puente siempre convierte un anillo monocíclico en un anillo tricíclico. Cuando un anillo se puentea, los sustituyentes enumerados para el anillo también pueden estar presentes en el puente.

La expresión "anillo carbocíclico" o "carbociclo" se refiere a anillos hidrocarburo saturados, parcialmente saturados o insaturados mono o bicíclicos estables que contienen 3-12 átomos. Particularmente, estos incluyen un anillo monocíclico que contiene 5 o 6 átomos o un anillo bicíclico que contiene 9 o 10 átomos. Los valores adecuados incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, dihidroindenilo y tetrahidronaftilo. La expresión "opcionalmente sustituido" cuando se refiere a "anillo carbocíclico " o "carbociclo" en el presente documento indica que el anillo carbocíclico puede

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estar sustituido en una o más posiciones sustituibles del anillo con uno o más grupos seleccionados independientemente entre alquilo (preferiblemente alquilo inferior), alcoxi (preferiblemente alcoxi inferior), nitro, monoalquilamino (preferiblemente un alquilamino inferior), dialquilamino (preferiblemente a di[inferior]alquilamino), ciano, halo, haloalquilo (preferiblemente trifluorometilo), alcanoilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, alquilo amido (preferiblemente alquilo amido inferior), alcoxialquilo (preferiblemente un alcoxi[inferior]alquilo inferior), alcoxicarbonilo (preferiblemente un alcoxicarbonilo inferior), alquilcarboniloxi (preferiblemente un alquilcarboniloxi inferior) y arilo (preferiblemente fenilo), estando el arilo opcionalmente sustituido con grupos halo, alquilo inferior y alcoxi.

El término "heteroátomos" incluirá oxígeno, azufre y nitrógeno.

Los compuestos de fórmula I pueden existir como una forma libre (sin ionización) o pueden formar sales que también están dentro del alcance de la presente invención. Se prefieren sales farmacéuticamente aceptables (es decir, no toxicas y fisiológicamente aceptables), aunque también son útiles otras sales, por ejemplo, en el aislamiento o la purificación de los compuestos de la presente invención.

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Los compuestos de fórmula I pueden formar sales con metales alcalinos tales como sodio, potasio y litio, con metales alcalinotérreos tales como calcio y magnesio, con bases orgánicas tales como diciclohexilamina, tributilamina, piridina y aminoácidos tales como arginina, lisina y similares. Las sales pueden formarse como se conoce por los expertos en la materia.

Los compuestos para la fórmula I pueden formar sales con una diversidad de ácidos orgánicos e inorgánicos. Las sales incluyen las formadas con cloruro ácido, bromuro ácido, ácido metanosulfónico, ácido sulfúrico, ácido acético, ácido trifluoroacético, ácido oxálico, ácido maleico, ácido bencenosulfónico, ácido toluenosulfónico y diversos otros (por ejemplo, nitratos, fosfatos, boratos, tartratos, citratos, succinatos, benzoatos, ascorbatos, salicilatos y similares). Las sales pueden formarse como se conoce por los expertos en la materia.

Además, pueden formarse zwitteriones ("sales internas").

Se contemplan todos los estereoisómeros de los compuestos de la presente invención, en forma de mezcla, pura o sustancialmente pura. La definición de compuestos de acuerdo con la invención incluye todos los estereoisómeros posibles y sus mezclas. Muy particularmente incluye las formas racémicas y los isómeros ópticos aislados que tienen

la actividad especificada. Las formas racémicas pueden resolverse por métodos físicos, tales como, por ejemplo, cristalización fraccional, separación o cristalización derivados diastereoméricos o separación por cromatografía de columna quiral. Los isómeros ópticos individuales pueden obtenerse de los racematos a partir de los procedimientos convencionales, tales como, por ejemplo, formación de sal con un ácido ópticamente activo seguido de cristalización.

La presente invención pretende incluir todos los isótopos de átomos que aparecen en los presentes compuestos. Los isótopos 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 deuterio y tritio. Los isótopos de carbono incluyen 13C y 14C. Generalmente, pueden prepararse compuestos marcados isotópicamente de la invención mediante técnicas convencionales conocidas por los expertos en la materia o por procedimientos análogos a los descritos en el presente documento, usando un reactivo marcado isotópicamente en lugar del reactivo no marcado por el contrario empleado.

Los compuestos de la fórmula I también pueden tener formas de profármacos. Ya que se conoce que los profármacos mejoran numerosas cualidades deseables de los productos farmacéuticos (por ejemplo, solubilidad, biodisponibilidad, fabricación, etc.), los compuestos de la presente invención

pueden administrarse en forma de profármaco. Por lo tanto, la presente invención pretende incluir profármacos de los compuestos indicados en el presente documento, procedimientos para administrar los mismos y composiciones que contienen los mismos. "Profármacos" pretenden incluir cualquier vehículo unido covalentemente que libera un profármaco activo de la presente invención *in vivo* cuando el profármaco se administra a un sujeto mamífero. Los profármacos de la presente invención se preparan modificando grupos funcionales presentes en el compuesto de modo que las modificaciones se escinden, en una manipulación de rutina o *in vivo*, al precursor. Los profármacos incluyen compuestos de la presente invención en los que un grupo hidroxi, amino o sulfhidrilo está unido a cualquier grupo que, cuando el profármaco de la presente invención se administra a un sujeto mamífero, se escinde para formar un grupo sin hidroxilo, sin amino o sin sulfhidrilo, respectivamente. Los ejemplos de profármacos incluyen, pero sin limitación, derivados de acetato, formiato y benzoato de grupos funcionales de alcohol y amina en los compuestos de la presente invención.

Diversas formas de profármacos son bien conocidas en la técnica. Para ejemplos de los derivados de profármacos, véase:

a) *Design of Prodrugs*, editado por H. Bundgaard, (Elsevier, 1985) y *Methods in Enzymology*, Vol. 112, págs.

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309-396, editado por K. Widder, y col. (Academic Press, 1985);

b) *A Textbook of Drug Design and Development*, editado por Krosgaard-Larsen y H. Bundgaard, Capítulo 5, "Design and Application of Prodrugs", de H. Bundgaard, págs. 113-191 (1991); y

c) H. Bundgaard, *Advanced Drug Delivery Reviews*, 8, 1-38 (1992). Además, se apreciará que los solvatos (por ejemplo, hidratos) de los compuestos de fórmula I también están dentro del ámbito de la presente invención. Los procedimientos de solvatación son generalmente conocidos en la técnica.

"Compuesto estable" y "estructura estable" pretenden indicar un compuesto que es lo suficientemente fuerte para resistir el aislamiento a un grado útil de pureza de una mezcla de reacción, y la formulación en un agente terapéutico eficaz. Se prefiere que los compuestos enumerados en el presente documento no contengan un grupo N-halo, $S(O)_2H$ o S(O)H.

Como se usa en el presente documento, "tratar" o "tratamiento" incluyen el tratamiento de una patología en un mamífero, particularmente en un ser humano, e incluyen: (a) prevenir la aparición de la patología en un mamífero, en particular, cuando el mamífero está predispuesto a la patología pero todavía no se ha diagnosticado que la tenga;

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(b) inhibir la patología, es decir, detener su desarrollo; y/o (c) aliviar la patología, es decir, causar la regresión de la patología.

"Cantidad terapéuticamente eficaz" pretende incluir una cantidad de un compuesto de la presente invención que es eficaz cuando se administra sola o en combinación. "Cantidad terapéuticamente eficaz" también pretende incluir una cantidad de la combinación de compuestos que es eficaz para el tratamiento de la enfermedad.

La presente invención incluye además composiciones que comprenden uno o más compuestos de la presente invención y un vehículo farmacéuticamente aceptable.

Un "vehículo farmacéuticamente aceptable" se refiere a los medios generalmente aceptados en la técnica para la dosificación de agentes biológicamente activos a animales, en particular, mamíferos. Los vehículos farmacéuticamente aceptables se formulan de acuerdo con varios factores que están bien dentro del ámbito de los expertos en la materia. Éstos incluye, sin limitación: el tipo y naturaleza del agente activo formulado; el sujeto al que se le va a administrar la composición que contiene al agente; la vía de administración deseada de la composición; y la indicación terapéutica que se persiga. Los vehículos farmacéuticamente aceptables incluyen medios líquidos acuosos y no acuosos, así como una diversidad de formas farmacéuticas

sólidas y semi-sólidas. Los vehículos pueden incluir varios ingredientes y aditivos distintos además del agente activo, y los ingredientes adicionales se incluyen en la formulación por una serie de razones, por ejemplo, estabilización del agente activo, aglutinantes, etc., bien conocidos por los expertos en la materia. Las descripciones de vehículos farmacéuticamente aceptables adecuados, y factores implicados en su selección, se encuentran en una diversidad de fuentes disponibles fácilmente tales como, por ejemplo, *Remington's Pharmaceutical Sciences*, 17ª ed., Mack Publishing Company, Easton, PA, 1985, que se incorpora en el presente documento por referencia en su totalidad.

UTILIDAD

La presente invención se basa en el descubrimiento de que determinados compuestos son inhibidores de proteína cinasas. Más específicamente, compuestos tales como los descritos en la presente invención inhiben la actividad de la proteína tirosina cinasa de elementos de la familia de receptores JAK. Estos inhibidores serán útiles en el tratamiento de enfermedades proliferativas que son dependientes de la señalización por uno o más de estos receptores. Las enfermedades incluyen trastornos mieloproliferativos, tumores sólidos del páncreas, próstata, pulmón, cabeza y cuello, mama, colon, ovario, así como otros tipos de tumores que incluyen mieloma múltiple, melanoma,

neuroblastoma, glioblastoma y neoplasias malignas hematológicas tales como leucemia mielógena aguda.

La invención también se refiere a una composición farmacéutica del compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente aceptable en el tratamiento de un trastorno hiperproliferativo en mamíferos. En particular, se espera que la composición farmacéutica inhiba el crecimiento y/o la metástasis de esos tumores sólidos primarios y recurrentes que están asociados con Flt-3 (cinasa 3 de tipo Fms), JAK2, JAK3 y JAK1, especialmente los tumores que son significativamente dependientes de JAK2, para su propio crecimiento y su propagación, incluyendo, por ejemplo, cánceres de la sangre, tiroides, mama, colon, páncreas o una diversidad de tipos tumorales que incluyen mieloma múltiple, melanoma, neuroblastoma y glioblastoma. Además de la actividad de JAK2, la actividad inhibidora frente a JAK3/JAK1 o TYK2 puede ser útil en el tratamiento determinados cánceres que tienen un componente inflamatorio.

Por lo tanto, de acuerdo con un aspecto más de la invención, se proporciona el uso de un compuesto de la fórmula I, o una sal farmacéuticamente aceptable del mismo en la fabricación de un medicamento para uso en la producción de un efecto antiproliferativo en un animal de sangre caliente, tal como un ser humano.

De acuerdo con una característica adicional de la invención, se proporciona un procedimiento para producir un efecto antiproliferativo en un animal de sangre caliente, tal como un ser humano, que necesita el tratamiento, que comprende administrar al animal de una cantidad eficaz de una compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo como se ha definido anteriormente en el presente documento.

En virtud de su capacidad para inhibir Flt-3, JAK2 y JAK3, cinasas, los compuestos de la presente invención pueden usarse en el tratamiento de enfermedades proliferativas, incluyendo cáncer.

Por lo tanto, la presente invención proporciona procedimientos para el tratamiento de una diversidad de cánceres, incluyendo, pero sin limitación, las siguientes:

carcinoma, incluyendo el de la vejiga (incluyendo cáncer de vejiga acelerado y metastásico), mama, colon (incluyendo cáncer colorrectal), riñón, hígado, pulmón (incluyendo cáncer microcítico y no microcítico de pulmón y adenocarcinoma de pulmón), ovario, próstata, testículos, tracto genitourinario, sistema linfático, recto, laringe, páncreas (incluyendo carcinoma pancreático exocrino), esófago, estómago, vesícula biliar, cuello uterino, tiroides y piel (incluyendo carcinoma de células escamosas);

tumores hematopoyéticos del linaje linfoide,

incluyendo leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkin, linfoma no Hodgkin, linfoma de células pilosas, linfoma histiocítico y linfoma de Burkett;

tumores hematopoyéticos del linaje mieloide, incluyendo leucemias mielógenas agudas y crónicas, síndrome mielodisplásico, leucemia mieloide y leucemia promielocítica;

tumores del sistema nervioso central y periférico, incluyendo astrocitoma, neuroblastoma, glioma y schwannomas;

tumores de origen mesenquimal, incluyendo fibrosarcoma, rabdomiosarcoma y osteosarcoma; y

otros tumores, incluyendo melanoma, xeroderma pigmentosa, queratoacantoma, seminoma, cáncer folicular de tiroides y teratocarcinoma.

La presente invención proporciona procedimientos para el tratamiento de leucemia, enfermedades mieloproliferativas tales como policitemia vera, trombocitopenia esencia y mielofibrosis, mieloma múltiple, cáncer de colon, cáncer de mama y cáncer gástrico.

El tratamiento antiproliferativo definido antes en el presente documento se puede aplicar como un terapia única o puede implicar, además de un compuesto de la invención, una o más sustancias y/o tratamientos diferentes. Los tratamientos pueden alcanzarse por medio de la administración simultánea, secuencial o por separado de los componentes

individuales del tratamiento. Los compuestos de la presente invención pueden ser útiles en combinación con agentes y tratamientos anticancerosos y citotóxicos conocidos, incluyendo radiación. Si se formula como una dosis fija, los productos de combinación emplean los compuestos de la presente invención dentro del intervalo de dosificación que se describe a continuación y el otro agente farmacéuticamente activo dentro de su intervalo de dosificación aprobado. Los compuestos de fórmula I pueden usarse secuencialmente con agentes y tratamiento anticancerosos y citotóxicos conocidos, incluyendo radiación, cuando una formulación de combinación es inapropiada.

El término agente "anticanceroso" incluye cualquier agente conocido que sea útil para el tratamiento del cáncer incluyendo los siguientes: 17α-etinilestradiol, dietilestilbestrol, testosterona, prednisona, fluoximesterona, propionato de drosmostanolona, testolactona, acetato de megestrol, metilprednisolona, metiltestosterona, prednisolona, triamcinolona, clorotrianiseno, hidroxiprogesterona, aminoglutetimida, estramustina, acetato de medroxiprogesterona, leuprolida, flutamida, toremifeno, Zoladex; inhibidores de metaloproteinasa de matriz; inhibidores VEGF, tales como anticuerpos anti-VEGF (Avastin®) y moléculas pequeñas tales como ZD6474 y SU6668; Vatalanib, BAY-43-9006, SU11248, CP-547632 y CEP-7055; inhibidores HER 1

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y HER 2 incluyendo anticuerpos anti-HER 2 (Herceptina); inhibidores de EGFR, incluyendo gefitinib, erlotinib, ABX-EGF, EMD72000, 11F8 y cetuximab; inhibidores de Eg5, tales como SB-715992, SB-743921 y MKI-833; inhibidores pan Her, tales como canertinib, EKB-569, CI-1033, AEE-788, XL-647, Acm 2C4 y GW-572016; inhibidores de cinasa, por ejemplo, Gleevec® y dasatinib (Sprycel®); Casodex® (bicalutamida, Astra Zeneca), Tamoxifeno; inhibidores de MEK-1 cinasa, inhibidores de MAPK cinasa, inhibidores de PI3 cinasa; inhibidores de PDGF, tales como imatinib; agentes antiangiogénicos y antivasculares que, mediante la interrupción del flujo sanguíneo a tumores sólidos, hacen a las células cancerosas inactivas privándolas de nutrición; castración, que hace a los carcinomas dependientes de andrógenos no proliferativos; inhibidores de tirosina cinasas receptoras o no receptoras; inhibidores de la señalización de integrina; agentes de acción de la tubulina, tales como vinblastina, vincristina, vinorelbina, vinflunina, paclitaxel, docetaxel, 7-O-metiltiometilpaclitaxel, 4-desacetil-4-metilcarbonatopaclitaxel, 3'-*terc*-butil-3'-N-*terc*-butiloxicarbonil-4-deacetil-3'-defenil-3'-N-debenzoil-4-O-metoxicarbonil-paclitaxel, C-4-metil carbonato pactlitaxel, epotilona A, epotilona B, epotilona C, epotilona D, desoxiepotilona A, desoxiepotilona B, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7-11-dihidroxi-

8,8,10,12,16-pentametil-3-[1-metil-2-(2-metil-4-tiazolil)etenil]-4-aza-17-oxabiciclo[14.1.0]heptadecano-5,9-diona (ixabepilona), [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(aminometil)-4-tiazolil]-1-metiletenil]-7,11-dihidroxi-8,8,10,12,16-pentametil-4-17-dioxabiciclo[14.1.0]-heptadecano-5,9-diona y derivados de la misma; inhibidores de CDK, inhibidores del ciclo celular antiproliferativos, epidofilotoxina, etopósido, VM-26; enzimas antineoplásicas, por ejemplo, inhibidores de topoisomerasa I, camptotecina, topotecán, SN-38; procarbazina; mitoxantrona; complejos de coordinación con platino, tales como cisplatino, carboplatino y oxaliplatino; modificadores de la respuesta biológica; inhibidores del crecimiento; agentes terapéuticos antihormonales; leucovorina; tegafur; antimetabolitos, tales como antagonistas de la purina (por ejemplo, 6-tioguanina y 6-mercaptopurina); antagonistas de la glutamina, por ejemplo, DON (AT-125; d-oxo-norleucina); inhibidores de ribonucleótido reductasa; inhibidores mTOR; y factores de crecimiento hematopoyéticos.

Los agentes citotóxicos adicionales incluyen ciclofosfamida, doxorrubucina, daunorrubicina, mitoxantrona, melfalán, hexametil melamina, tiotepa, citarabina, idatrexato, trimetraxato, dacarbazina, L-asparaginasa, bicalutamida, leuprolida, derivados de piridobenzoindol,

interferones e interleucinas.

En el campo de la oncología médica, es una práctica normal usar una combinación de formas distintas de tratamiento para tratar a cada paciente con cáncer. En la oncología médica, el otro componente o componentes del tratamiento, además del tratamiento antiproliferativo definido anteriormente en el presente documento, puede ser cirugía, radioterapia o quimioterapia. La quimioterapia puede cubrir tres categorías principales de agente terapéutico:

(i) agentes antiangiogénicos que trabajan por mecanismos distintos a los definidos anteriormente en el presente documento (por ejemplo, linomida, inhibidores de la función $\alpha v\beta 3$ integrina, angioestatina, razoxano);

(ii) agentes citostáticos tales como antiestrógenos (por ejemplo, tamoxifeno, toremifeno, raloxifeno, droloxifeno, yodoxifeno), progestágenos (por ejemplo, acetato de megestrol), inhibidores de aromatasa (por ejemplo, anastrozol, letrozol, borazol, exemestano), antihormonas, antiprogestágenos, antiandrógenos (por ejemplo, flutamida, nilutamida, bicalutamida, acetato de ciproterona), agonistas y antagonistas de LHRH (por ejemplo, acetato de goserelina, leuprolida), inhibidores de la testosterona 5α-dihidroreductasa (por ejemplo, finasterida), inhibidores de farnesiltransferasa, agentes anti-invasión (por ejemplo, inhibidores de metaloproteinasa tales como marimastat e

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inhibidores de la función del receptor activador del plasminógeno urocinasa) e inhibidores de la función de factores de crecimiento (tales factores de crecimiento incluyen, por ejemplo, EGF, FGF, factor del crecimiento derivado de plaquetas y factor de crecimiento de hepatocitos, tales inhibidores incluyen anticuerpos de factores de crecimiento, anticuerpos de receptores de factores de crecimiento tales como Avastin® (bevacizumab) y Erbitux® (cetuximab); inhibidores de tirosina cinasa e inhibidores de serina/treonina cinasa); y

(iii) fármacos antiproliferativos/antineoplásicos y combinaciones de los mismos, como se usan en la oncología médica, tales como antimetabolitos (por ejemplo, antifolatos tales como matotrexato, fluoropirimidinas tales como 5-fluorouracilo, análogos de purina y adenosina, arabinósido de citosina); antibióticos antitumorales de intercalación (por ejemplo, antaciclinas tales como doxorubicina, daunomicina, epirrubicina e idarrubicina, mitomicina-C, dactinomicina, mitramicina); derivados de platino (por ejemplo, cisplatino, carboplatino); agentes alquilantes (por ejemplo, mostaza de nitrógeno, melfalán, clorambucil, busulfán, ciclofosfamida, nitrosoureas de ifosfamida, tiotepa; agentes antimitóticos (por ejemplo, alcaloides de la vinca tales como vincristina, vinorrelbina, vinblastina y vinflunina) y taxiodes tales como

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Taxol® (paclitaxel), Taxotere® (docetaxel) y agentes de microtúbulos más nuevos tales como análogos de epotilona (ixabepilona), análogos de discodermolida y análogos de eleuterobina; inhibidores de topoisomerasa (por ejemplo, epipodofilotoxinas tales como etopósido y tenipósido, amsacrina, topotecán, irinotecán); inhibidores del ciclo celular (por ejemplo, flavopiridoles); modificadores de la respuesta biológica e inhibidores de proteasoma tales como Velcade® (bortezomib).

Como se ha indicado anteriormente, los compuestos de la fórmula I de la presente invención son de interés por sus efectos antiproliferativos. Se espera que los compuestos de la invención sean útiles en una gran diversidad de patologías incluyendo cáncer, psoriasis y artritis reumatoide.

Más específicamente, los compuestos de fórmula I son útiles en el tratamiento de una diversidad de cánceres, incluyendo (pero sin limitación) los siguientes:

- carcinoma, incluyendo el de próstata, adrenocarcinoma pancreático ductal, mama, colon, pulmón, ovario, páncreas y tiroides;

- tumores del sistema nervioso central y periférico, incluyendo neuroblastoma, glioblastoma y meduloblastoma;

- neoplasias malignas hematológicas tales como

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leucemia mielógena aguda (AML), y

- otros tumores, incluyendo melanoma y mieloma múltiple.

Debido al papel clave de las cinasas en la regulación de la proliferación celular en general, los inhibidores pueden actuar como agentes citostáticos reversibles que pueden ser útiles en el tratamiento de cualquier proceso de enfermedad que presenta una proliferación celular anormal, por ejemplo, hiperplasia benigna de próstata, poliposis adenomatosa familiar, neurofibromatosis, fibrosis pulmonar, artritis, psoriasis, glomerulonefritis, reestenosis después de una angioplastia o una cirugía vascular, formación hipertrófica de cicatrices y enfermedad inflamatoria del intestino.

Los compuestos de fórmula I son especialmente útiles en el tratamiento de tumores que tienen una alta incidencia de actividad de tirosina cinasa, tales como tumores de próstata, colon, cerebro, tiroides y pancreáticos. Mediante la administración de una composición (o una combinación) de los compuestos de la presente invención, se reduce el desarrollo de tumores en un huésped mamífero.

Los compuestos de fórmula I también pueden ser útiles en el tratamiento de otras enfermedades cancerosas (tales como leucemia mielógena aguda).

Las composiciones farmacéuticas de la presente

invención, que contienen el principio activo, pueden estar en una forma adecuada para el uso oral, por ejemplo, como comprimidos, trociscos, pastillas, suspensiones acuosas y oleosas, polvos o gránulos dispersables, emulsiones, cápsulas duras o blandas, o jarabes o elixires.

Cuando un compuesto de acuerdo con la presente invención se administra a un sujeto humano, la dosificación diaria normalmente se determinará por la prescripción del médico con una dosificación generalmente variable de acuerdo con la edad, el peso, el sexo y la respuesta individual del paciente, así como la gravedad de los síntomas del paciente.

Si se formulan como una dosis fija, los productos de combinación emplean los compuestos de la presente invención dentro del intervalo de dosificación descrito anteriormente y el otro agente o tratamiento farmacéuticamente activo dentro de su intervalo de dosificación aprobado. Los compuestos de fórmula I se pueden administrar secuencialmente con agentes anticancerosos o citotóxicos conocidos cuando una formulación de la combinación es inapropiada. La invención no está limitada en la secuencia de administración; los compuestos de fórmula I se pueden administrar antes o después de la administración del agente o agentes anticancerosos o citotóxicos conocidos.

Los compuestos se pueden administrar en un intervalo de dosificación de aproximadamente 0.05 a 200

mg/kg/día, preferentemente menos de 100 mg/kg/día, en una sola dosis o en 2 a 4 dosis divididas.

DOSIFICACIÓN Y FORMULACIÓN

Los compuestos de la presente invención se pueden administrar en formas farmacéuticas orales tales como comprimidos, cápsulas (cada una de las cuales incluye formulaciones de liberación sostenida o de liberación temporizada), píldoras, polvos, gránulos, elixires, pigmentos, suspensiones, jarabes y emulsiones. También se pueden administrar de forma intravenosa (en embolada o infusión), intraperitoneal, subcutánea o intramuscular, siendo todas las formas farmacéuticas usadas bien conocidas por los expertos en la materia de las técnicas farmacéuticas. Se pueden administrar solos, pero generalmente se administraran con un vehículo farmacéutico seleccionado basándose en la vía de administración elegida y en la práctica farmacéutica habitual.

El régimen de dosificación para los compuestos de la presente invención variará, por supuesto, dependiendo de factores conocidos, tales como las características farmacodinámicas del agente particular y su modo y vía de administración; la especie, edad, sexo, salud, condición médica y peso del destinatario; la naturaleza y la duración de los síntomas; el tipo de tratamiento concurrente; la frecuencia de tratamiento; la vía de administración, la

función renal y hepática del paciente y el efecto deseado. Un médico o veterinario puede determinar y prescribir la cantidad eficaz del fármaco requerido para tratar el cáncer.

A modo de directriz general, la dosificación oral diaria de cada principio activo, cuando se usa para los efectos indicados, variará entre aproximadamente 0.001 a 1000 mg/kg de peso corporal, preferentemente entre aproximadamente 0.001 a 100 mg/kg de peso corporal por día, y lo más preferentemente entre aproximadamente 0.001 a 20 mg/kg/día. Por vía intravenosa, las dosis más preferidas variarán entre aproximadamente 0.1 y aproximadamente 10 mg/kg. Los compuestos de la presente invención se pueden administrar en una sola dosis diaria o la dosificación diaria total puede administrarse en dosis divididas de dos, tres o cuatro veces diarias.

Los compuestos de la presente invención se pueden administrar de forma intranasal, mediante el uso tópico de vehículos intranasales adecuados, o por rutas transdérmicas, usando parches cutáneos transdérmicos. Cuando se administra en forma de un sistema de liberación transdérmica, la administración de la dosificación será, por supuesto, continua mejor que intermitente, a lo largo del régimen de dosificación.

Los compuestos se administran típicamente en combinación con diluyentes farmacéuticos adecuados,

excipientes o vehículos (denominados colectivamente en el presente documento como vehículos farmacéuticos) seleccionados adecuadamente con respecto a la forma de administración pretendida, es decir, comprimidos orales, cápsulas, elixires, jarabes y similares y de forma coherente con las prácticas farmacéuticas convencionales.

Por ejemplo, para la administración oral en forma de un comprimido o cápsula, el componente del fármaco activo puede combinarse con un vehículo oral, no tóxico, farmacéuticamente aceptable e inerte, tal como lactosa, almidón, sacarosa, glucosa, metil celulosa, estearato de magnesio, fosfato dicálcico, manitol, sorbitol y similares; para la administración oral en forma líquida, los componentes del fármaco oral se pueden combinar con cualquier vehículo no tóxico, inerte, farmacéuticamente aceptable, tal como etanol, glicerol, agua y similares. Además, cuando es deseado o necesario, también se pueden incorporar a la mezcla aglutinantes, lubricantes, agentes disgregantes y agentes colorantes. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales, tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas naturales o sintéticas, tales como goma arábiga, tragacanto, o alginato sódico, carboximetilcelulosa, polietilenglicol, ceras y similares. Los lubricantes usados en estas formas farmacéuticas incluyen oleato sódico, estearato sódico, estearato de magnesio,

benzoato sódico, acetato sódico, cloruro sódico y similares. Los disgregantes incluyen, sin limitación, almidón, metil celulosa, goma de agar, bentonita, goma xantana y similares.

Los compuestos de la presente invención pueden también administrarse en forma de sistemas de liberación liposomal, tales como vesículas unilamelares pequeñas, vesículas unilamelares grandes y vesículas multilamelares. Los liposomas se pueden formar a partir de una diversidad de fosfolípidos, tales como colesterol, estearilamina o fosfatidilcolinas.

Los compuestos de la presente invención también pueden acoplarse con polímeros solubles tales como vehículos de fármacos dirigibles. Los polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamida-fenol, polihidroxietilaspartamidafenol u óxido de polietileno-polilisina sustituido con residuos de palmitoilo. Además, los compuestos de la presente invención pueden acoplarse a una clase de polímeros biodegradables útiles para conseguir una liberación controlada de un fármaco, por ejemplo, ácido poliláctico, ácido poliglicólico, copolímeros de ácidos poliláctico y poliglicólico, poliepsilón caprolactona, ácido polihidroxibutírico, poliortoésteres, poliacetales, polihidropiranos, policianoacilatos y copolímeros de bloques reticulados o anfipáticos de hidrogeles.

Las formas farmacéuticas (composiciones farmacéuticas) adecuadas para la administración pueden contener de aproximadamente 1 miligramo a aproximadamente 1000 miligramos de principio activo por unidad de dosificación. En estas composiciones farmacéuticas, el principio activo estará presente normalmente en una cantidad de aproximadamente el 0.1-95% en peso basándose en el peso total de la composición.

Las cápsulas de gelatina pueden contener un principio activo y vehículos en polvo, tales como lactosa, almidón, derivados de celulosa, estearato de magnesio, ácido esteárico y similares. Se pueden usar diluyentes similares para fabricar comprimidos. Tanto los comprimidos como las cápsulas se pueden fabricar como productos de liberación sostenida para proporcionar una liberación continua de la medicación durante un periodo de horas. Los comprimidos prensados pueden estar recubiertos con azúcares o recubiertos con películas para enmascarar cualquier sabor indeseable y proteger al comprimido de la atmósfera, o pueden tener un recubrimiento entérico para la disgregación selectiva en el tracto intestinal.

Las formas farmacéuticas líquidas para la administración oral pueden contener colorantes y saporíferos para aumentar la aceptación del paciente.

En general, son vehículos adecuados para soluciones

parenterales agua, un aceite adecuado, solución salina, dextrosa acuosa (glucosa) y soluciones de azúcares relacionadas y glicoles tales como propilenglicol o polietilenglicoles. Las soluciones para la administración parenteral contienen preferentemente una sal soluble en agua de un principio activo, agentes estabilizantes adecuados y, si es necesario, sustancias amortiguadoras. Son agentes estabilizantes adecuados agentes antioxidantes, tales como bisulfito sódico, sulfito sódico o ácido ascórbico, solos o combinados. También se usan ácido cítrico y sus sales y EDTA sódico. Además, las soluciones parenterales pueden contener conservantes, tales como cloruro de benzalconio, metil- o propil-parabeno y clorobutanol.

Se describen vehículos farmacéuticos adecuados en *Remington's Pharmaceutical Sciences,* Mack Publishing Company, un texto de referencia convencional en este campo.

ENSAYOS BIOLÓGICOS

Ensayo de Tirosina Cinasa JAK2

Los ensayos se llevaron a cabo en placas de 384 cavidades con fondo en V. El volumen final de ensayo fue de 30 µl preparado a partir de adiciones de 15 µl de enzima y sustratos (péptido fluoresceinado y ATP) y compuestos de ensayo en amortiguador de ensayo (HEPES 100 mM pH 7.4, $MgCl_2$ 10 mM, Beta-Glicerolfosfato 25 mM, 0.015% de Brij35 y DDT 4 mM). La reacción se inició por la combinación de JAK2 con

sustratos y compuestos de ensayo. La reacción se incubó a temperatura ambiente durante 60 min y se terminó añadiendo 45 µl de EDTA 35 mM a cada muestra. La mezcla de reacción se analizó en el Caliper LabChip 3000 por separación electroforética del sustrato fluorescente y el producto fosforilado. Se calcularon los datos de inhibición por comparación con reacciones de control sin enzima para una inhibición del 100% y reacciones sólo con vehículo para una inhibición del 0%. La concentración final de reactivos en los ensayos es ATP, 30 µM; péptido fluorescente JAK2, 1.5 µM; JAK2, 1 nM; y DMSO, 1.6%. Se generaron curvas de respuesta a la dosis para determinar la concentración requerida para inhibir el 50% de la actividad cinasa (CI_{50}). Los compuestos se disolvieron a 10 mM en dimetilsulfóxido (DMSO) y se evaluaron a once concentraciones, cada una por duplicado. Los valores de CI_{50} se obtuvieron por análisis de regresión no lineal.

Ensayo de Tirosina Cinasa JAK3

Los ensayos se llevaron a cabo en placas de 384 cavidades con fondo en V. El volumen final de ensayo fue de 30 µl preparado a partir de adiciones de 15 µl de enzima y sustratos (péptido fluoresceinado y ATP) y compuestos de prueba en amortiguador de ensayo (HEPES 100 mM pH 7.4, $MgCl_2$ 10 mM, Beta-Glicerolfosfato 25 mM, 0.015% de Brij35 y DDT 4

mM). La reacción se inició por la combinación de JAK3 con sustratos y compuestos de ensayo. La reacción se incubó a temperatura ambiente durante 60 min y se terminó añadiendo 45 µl de EDTA 35 mM a cada muestra. La mezcla de reacción se analizó en el Caliper LabChip 3000 por separación electroforética del sustrato fluorescente y el producto fosforilado. Los datos de inhibición se calcularon por comparación con reacciones de control sin enzima para una inhibición del 100% y reacciones sólo con vehículo para una inhibición del 0%. La concentración final de reactivos en los ensayos es ATP, 8 µM; péptido fluorescente JAK3, 1.5 µM; JAK3, 2.5 nM; y DMSO, 1.6%. Se generaron curvas de respuesta a la dosis para determinar la concentración requerida para inhibir el 50% de la actividad cinasa (CI_{50}). Los compuestos se disolvieron a 10 mM en dimetilsulfóxido (DMSO) y se evaluaron a once concentraciones, cada una por duplicado. Los valores de CI_{50} se obtuvieron por análisis de regresión no lineal.

Ensayo de Inhibición de la Proliferación Celular

Los compuestos se evaluaron para determinar su capacidad de inhibir la proliferación celular, usando un ensayo que mide la incorporación de timidina en el ADN de la célula en división, que se correlaciona directamente con el número de células. Se sembraron células SET-2 en placas de 96 cavidades a 10000 células/cavidad y se cultivaron durante 24

h en RPMI-1640 suplementado con suero bovino fetal al 20%, antes de que se añadieran los compuestos de ensayo. Los compuestos se diluyeron en medio de cultivo de tal forma que la concentración de dimetilsulfóxido nunca superase el 0,1%. Tras la adición de los compuestos, las células se cultivaron durante 72 h más antes de que se determinara la proliferación celular por medición de la síntesis de ADN con la incorporación de 3H-timidina.

Los compuestos descritos en el presente documento se ensayaron en los ensayos de JAK2 y de Inhibición de la Proliferación Celular descritos anteriormente. Se obtuvieron los siguientes resultados.

TABLA 1

Ejemplo N°	JAK2 (CI_{50}, uM)	SET-2 (CI_{50}, uM)
3	1.50E-03	0.01
4	0.03	2.53

Ejemplo N°	JAK2 (CI_{50}, uM)	SET-2 (CI_{50}, uM)
15	1.52E-03	0.49
29	0.01	10.00
33	6.37E-04	0.01
34	1.50E-03	0.24
35	5.36E-04	2.85
38	0.04	0.06
49	0.05	3.93
53	1.47E-03	0.10
55	7.48E-04	4.30E-03
61	7.51E-04	
70	7.33E-04	0.33
73	1.00E-03	0.06
81	0.01523	0.339
98	0.000695	0.007365
101	7.43E-04	10.00
109	1.52E-03	4.15
116	1.49E-03	0.17
125	0.05	1.27

Los compuestos descritos en el presente documento se ensayaron en uno o más de los ensayos identificados anteriormente y se encontró que eran activos.

C. Ensayo *in vivo*

El compuesto formulado en vehículo adecuado se administró a ratones en forma de un bolo oral o inyectado por vía intraperitoneal o subcutánea a ratones Balb/C. Se recolectaron muestras sanguíneas a través del sangrado orbital o punción cardiaca en varios puntos temporales después de la administración del compuesto. Se colocaron alícuotas sanguíneas (90 µl) en placas de 96 cavidades. Se repartió en cada cavidad solución diluida (5 ul) de trombopoyetina (mTPO; Peprotech) (diluida 1:1000 en dPBS/BSA, 2 ul en 2 ml de dPBS/BSA) para la estimulación de la ruta. Las placas se incubaron a 37°C en un baño de agua durante 10 minutos. A cada cavidad se le añadieron 1.5 ml de solución de fijación/lisis (de BD Biosciences). Después, las muestras se incubaron a 37°C durante 15 minutos para asegurar la lisis de los glóbulos rojos (GR). Las placas se centrifugaron a 2000 rpm durante 5 minutos y se aspiraron usando un aspirador de V&P de 96 cavidades. Las células se lavaron con dPBS, se recentrifugaron, se resuspendieron y se transfirieron a una placa regular de 96 cavidades. Las células se lavaron

dos veces con dPBS seguido de la adición de CD61 FITC (de eBiosciences) para la tinción del recetor de superficie durante 45 min en la oscuridad a temperatura ambiente. después, las células se lavaron en dPBS y se permeabilizaron para la tinción con pSTAT5 como se indica a continuación: se añadieron 200 µl de amortiguador de permeabilización III (de BD Bioscience), las muestras se incubaron en hielo durante 30 minutos y después las muestras se lavaron dos veces con dPBS/BSA al 1% y se resuspendieron en 100 µl de dPBS/BSA que contenía anticuerpos Stat5 (pY695) Alexa 647. Las muestras se incubaron a temperatura ambiente en la oscuridad durante 45 minutos, se lavaron dos veces y se resuspendieron en 10 µl de los anticuerpos Stat5 (pY695) Alexa 647 usados que se añadieron a la muestra. Las muestras se resuspendieron en 200 µl de dPBS/BSA, se pasaron por el FACSCanto en imágenes de muestra y se procesaron usando el software de análisis Diva 6 y FlowJo 8.5.3.

ABREVIATURAS

Las siguientes abreviaturas se pueden utilizar en los procedimientos de preparación y en los Ejemplos:

h = horas

DCM = diclorometano

THF = tetrahidrofurano

HPLC = cromatografía líquida de alto rendimiento

DIEA = diisopropiletilamina

i-PrOH = alcohol isopropílico

TFA = ácido trifluoroacético

min = minutos

DMF = dimetilformamida

EDC = *N*-(3-dimetilaminopropil)-*N'*-etilcarbodiimida

HOBt = hidroxibenzotriazol

NMP = *N*-metilpirolidinona

EtOAc = acetato de etilo

AcOH = ácido acético

Reactivo de BOP = hexafluorurofosfato de benzotriazol-1-il-oxi-tris-(dimetilamino)-fosfonio

salmuera = solución acuosa saturada de cloruro sódico

Et_3N = trietilamina

t_R = tiempo de retención

ta = temperatura ambiente

NCS = *N*-clorosuccinamida

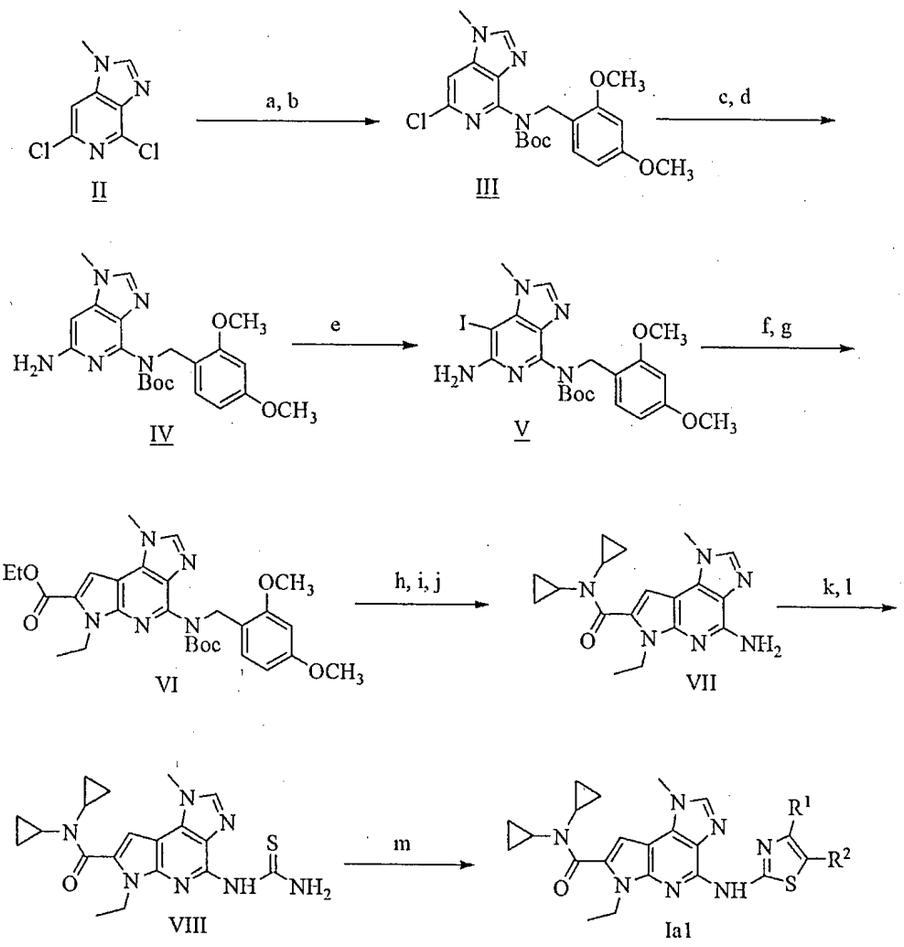
NBS = *N*-bromosuccinamida

NIS = *N*-yodosuccinamida

Procedimientos de Preparación

Los compuestos de fórmula general I en la que el grupo R es tiazol (como en Ia1) y R^1 y R^2 son grupos CF_3 o

alquilo o cicloalquilo o se combinan para formar un anillo carbocíclico o heterocíclico saturado o en el que el grupo R2 es $COOR^b$ pueden prepararse usando el procedimiento general representado en el Esquema de reacción 1. El intermediario de dicloro II (preparado usando el procedimiento indicado en el documento WO200612237) puede combinarse con un 2,4-dimetoxibencilo y la amina secundaria resultante se protege con un grupo protector adecuado (Boc) (III). El segundo átomo de cloro puede convertirse en la correspondiente amina (IV) a través del intermediario de benzofenona imina. El compuesto amino puede halogenarse para dar intermediario V. V puede someterse a la formación de anillo indol mediada por metales de transición y el nitrógeno del indol resultante protegerse con yoduro de etilo para proporcionar VI. La hidrólisis del éster seguida de la formación del enlace amida y de la escisión de los grupos protectores con tratamiento ácido producirá la amina VII. La amina VII puede convertirse en la tiourea VIII primero mediante la unión con isotiocianato de benzoilo seguido de tratamiento con una base acuosa. La formación de tiazol puede lograrse mediante la condensación con un derivado de α-bromocetona ($R^1CHBrCOR^2$).

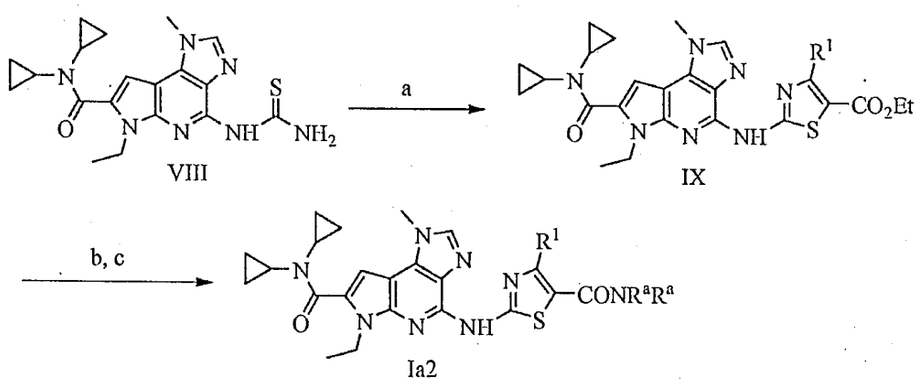


a) 2,4-dimetoxibencilamina, calor; b) NaHMDS, Boc_2O; c) $(Ph)_2$=NH; d) HCl; e) NIS; f) $Pd_2(dba)_3$, piruvato de etilo; g) EtI, Cs_2CO_3; h) NaOH (ac.); i) HCl diciclopropilamina, HATU, DIPEA; j) TFA; k) isotiocianato de benzoilo; l) NaOH (ac.); m) $R^2CHBrCOR^1$

Esquema de reacción 1

Los compuestos de fórmula general Ia2 en la que el grupo R^1 es $CONR^aR^a$ pueden prepararse usando el Esquema de reacción 2. El intermediario de tiourea (VIII) puede

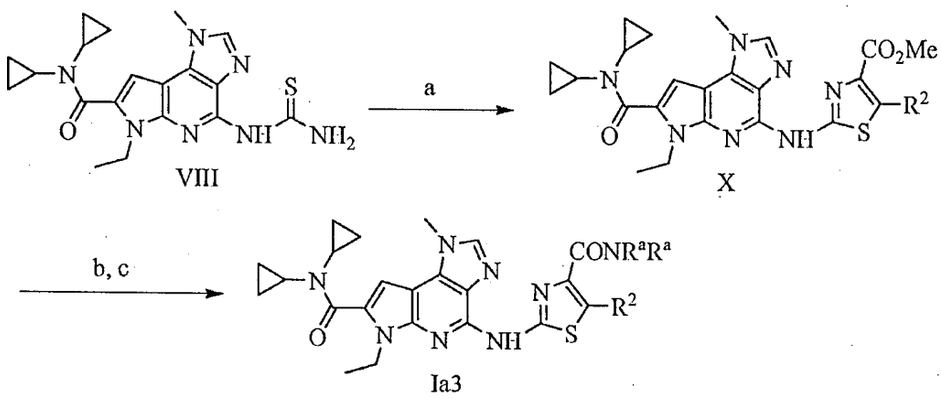
combinarse con $EtO_2CCHBrCOR^1$ para proporcionar el éster de tiazol (IX). El éster puede hidrolizarse y el ácido puede acoplarse con la amina para proporcionar el derivado de tiazol amida (Ia)



a) $EtO_2CCHBrCOR^1$; b) NaOH (ac.); c) HNR^aR^a, HATU, DIPEA

Esquema de reacción 2

De forma similar, los compuestos de fórmula general Ia3 en la que el grupo R^1 es $CONR^aR^a$ pueden prepararse usando el protocolo representado en el Esquema de reacción 3.

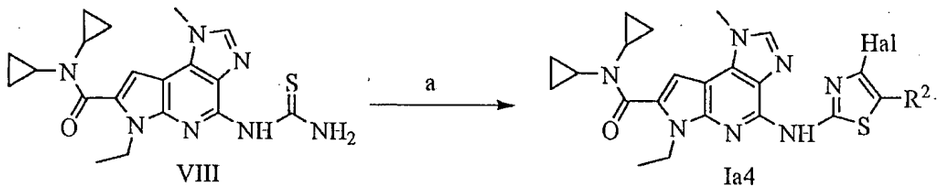


a) $R^2CHBrCOCO_2Me$; b) NaOH (ac.); c) HNR^aR^a, HATU, DIPEA

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Esquema de reacción 3

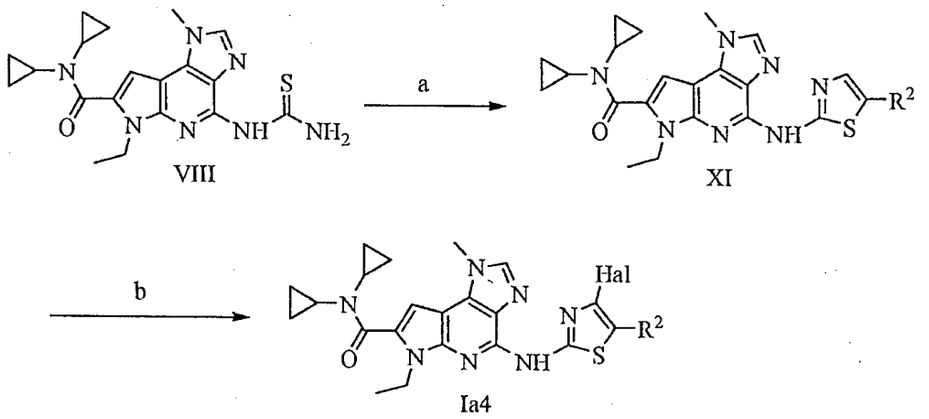
Los compuestos de fórmula general Ia en la que R^1 es halógeno (Cl, Br o I) pueden prepararse mediante condensación de una a,a'-dihalocetona como se representa en el Esquema de reacción 4.



a) $R^2COCH(Hal)_2$

Esquema de reacción 4

Como alternativa, el derivado de tiourea VIII puede convertirse a la temperatura ambiente en el tiazol XI sin sustituir en C-5 y después directamente halogenarse usando una fuente halógena electrófila o a través de metalación seguido de inactivación con un agente halogenante electrófilo (Esquema de reacción 5).

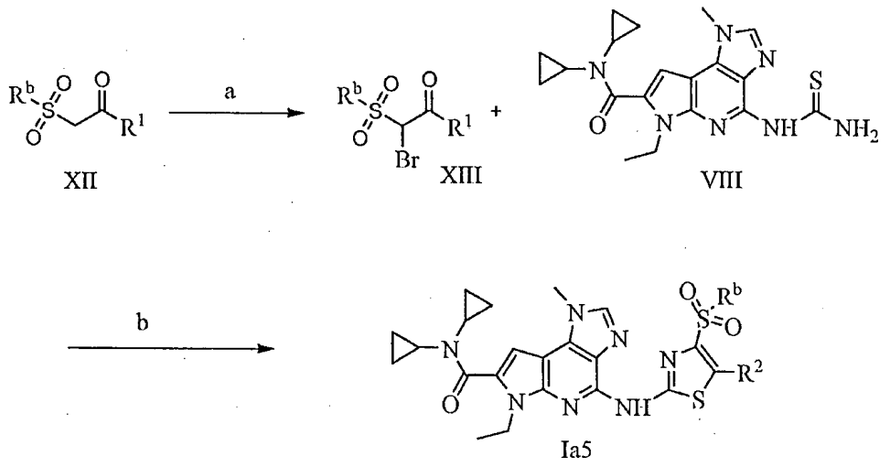


a) $BrCH_2COR^2$; b) Selectfluor o NCS o NBS o NIS o tBuLi

seguido de Selectfluor o NBS o NCS

Esquema de reacción 5

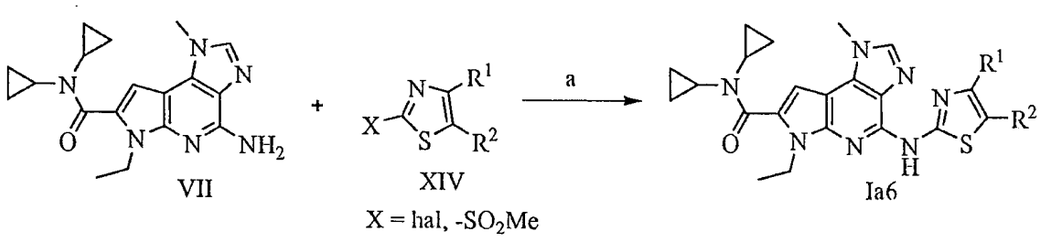
Los compuestos de fórmula general Ia5 en la que R^1 es SO_2R^b pueden sintetizarse usando la estrategia sintética general que se muestra en el Esquema de reacción 6.



a) Ácido Br_2-acético; b) EtOH, calor

Esquema de reacción 6

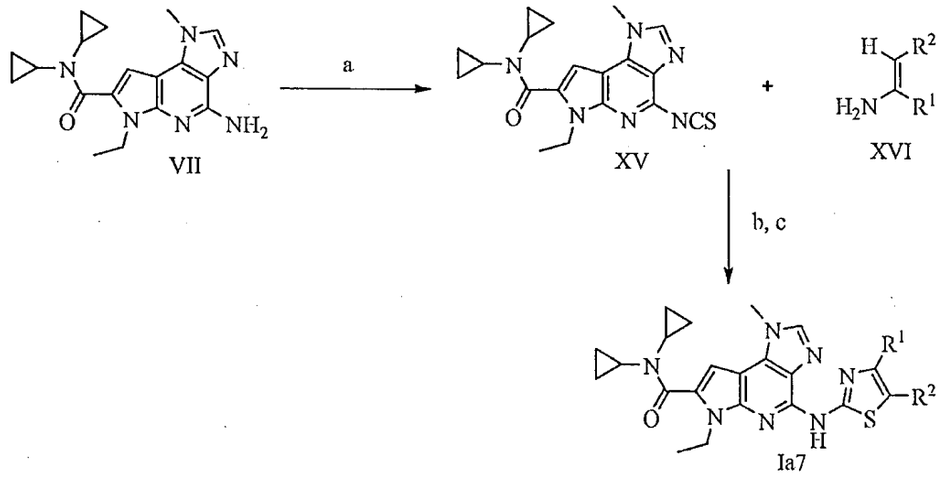
Los compuestos con fórmula general Ia en la que R^1 y R^2 se combinan para formar un anillo aromático o heteroaromático pueden prepararse usando el Esquema de reacción 7.



a) catalizador de Pd(0), NaOtBu, ligando de fosfina, calor

Esquema de reacción 7

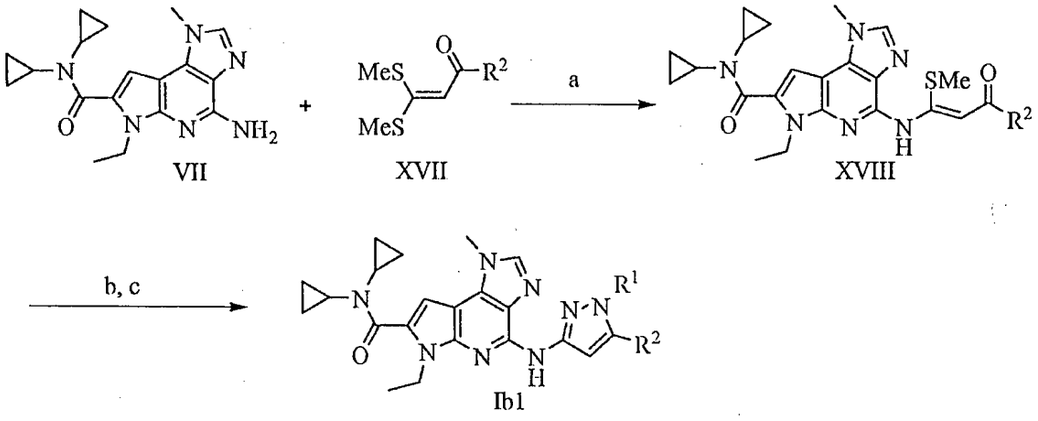
Como alternativa, estos compuestos pueden prepararse primero mediante el acoplamiento de anilina o heteroanilina (XVI) con el isotiocianato (XV) seguido de ciclilación oxidativa (Esquema de reacción 8).



a) 1,1'-Tiocarbonildi-2(1*H*)-piridona; b) NaH; c) NIS

Esquema de reacción 8

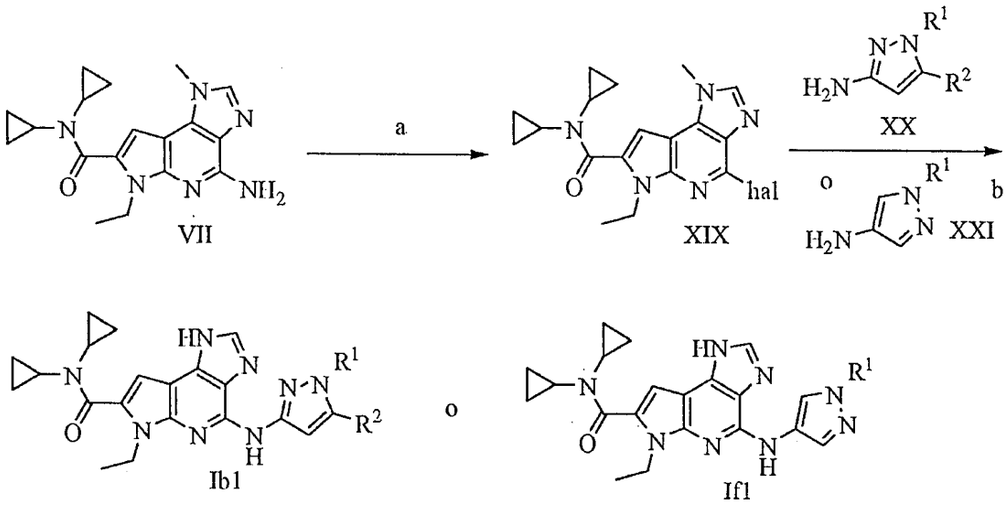
Los compuestos de fórmula general Ib1 pueden prepararse usando la estrategia sintética general representada en el Esquema de reacción 9. La anilina VII puede combinarse con el compuesto de γ-ditiometilcetona XVII, (preparado usando el procedimiento a la temperatura ambiente indicado en *Synlett,* p 2331 (2008)) en condiciones básicas para proporcionar XVIII. Una condensación gradual de los derivados de hidrazina Boc-protegida dará el pirazol Ib1 requerido.



a) NaH, THF; b) $R^1N(Boc)NH_2$, AcOH, 35-40°C; c) HCO_2H o TFA, 60°C

Esquema de reacción 9

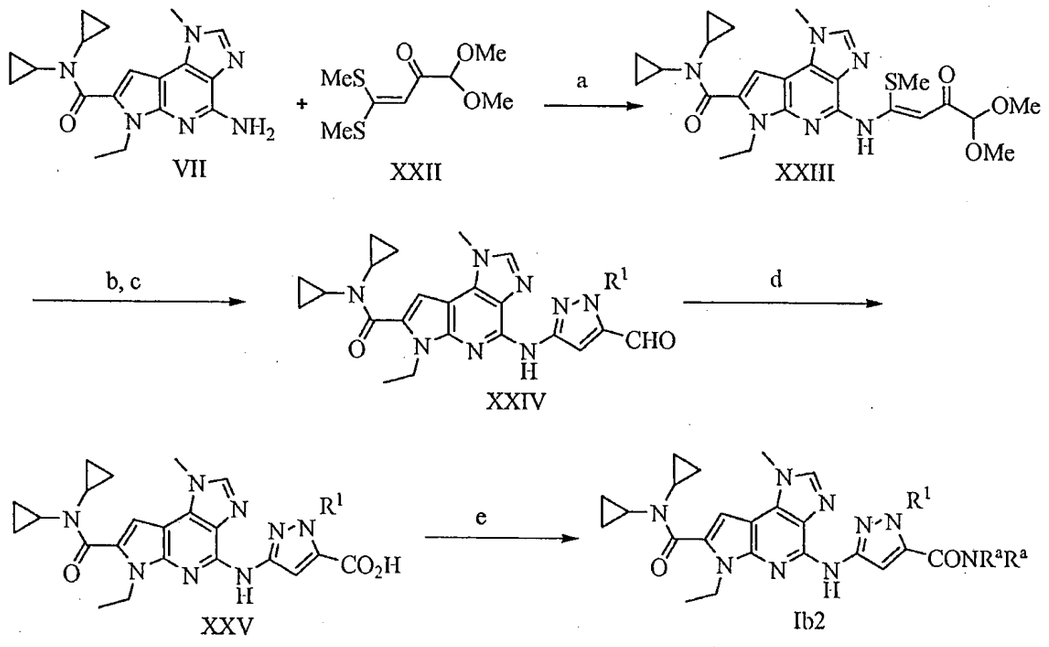
Los compuestos de fórmula general Ib1 o If1 y 1f también pueden prepararse mediante el acoplamiento de un derivado de halo C-4 (XIX) con un derivado de 2-aminopirazol apropiadamente sustituido (XX) usando una reacción catalizada por un metal de transición (Esquema de reacción 10).



a) nitrito de isoamilo, CH_2I_2 o nitrito de isoamilo, CH_2Br_2; b) $Pd_2(dba)_3$, Xanphos, Cs_2CO_3

Esquema de reacción 10

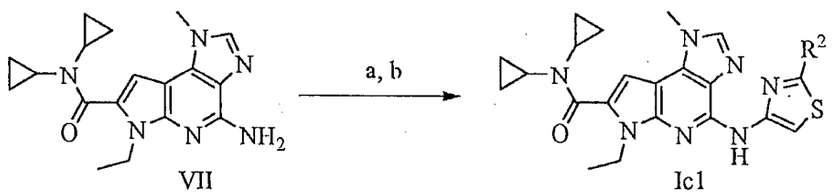
Los compuestos de fórmula general Ib2 en la que el grupo R^2 es $CONR^aR^a$ pueden sintetizarse usando el Esquema de reacción 11. La anilina VII puede combinarse con el derivado de γ-ditiometilcetona XXII, (preparado usando el procedimiento de *Tetrahedron*, p 2631 (2003)) para proporcionar el intermediario XXIII. La condensación gradual del derivado de hidrazina Boc-protegida dará el pirazol aldehído XXIV requerido. El aldehído puede oxidarse usando oxone o hipoclorito sódico para formar el ácido carboxílico XXV. El acoplamiento del ácido XXV con amina dará la pirazol amida Ib2.



a) NaH, THF, calor; b) $R^1N(Boc)NH2$, AcOH; c) TFA; d) oxone o hipoclorito sódico; e) HNR^aR^a, HATU, DIPEA

Esquema de reacción 11

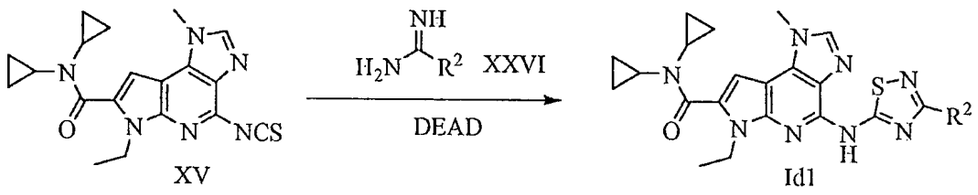
Los compuestos de fórmula general Ic1 pueden prepararse usando el protocolo general que se muestra en el Esquema de reacción 12. La anilina VII puede acoplarse con cloruro cloroacetilo y la amida resultante puede tratarse con tioamida (R^2CSNH_2) para proporcionar el tiazol Ic1.



a) cloruro de cloroacetilo, base; b) R^2CSNH_2

Esquema de reacción 12

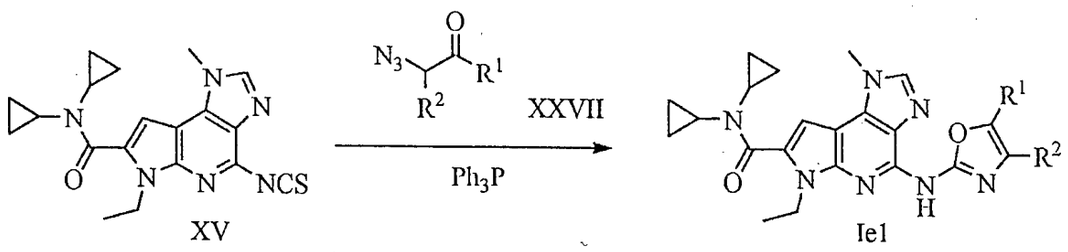
Los compuestos de fórmula general 1d1 pueden prepararse como para el Esquema de reacción 13. Los derivados de isotiocianato XV descritos previamente pueden combinarse con la amidina XXV en condiciones de reacción deshidratación para dar el 1,2,4-tiadiazol (Id1).



Esquema de reacción 13

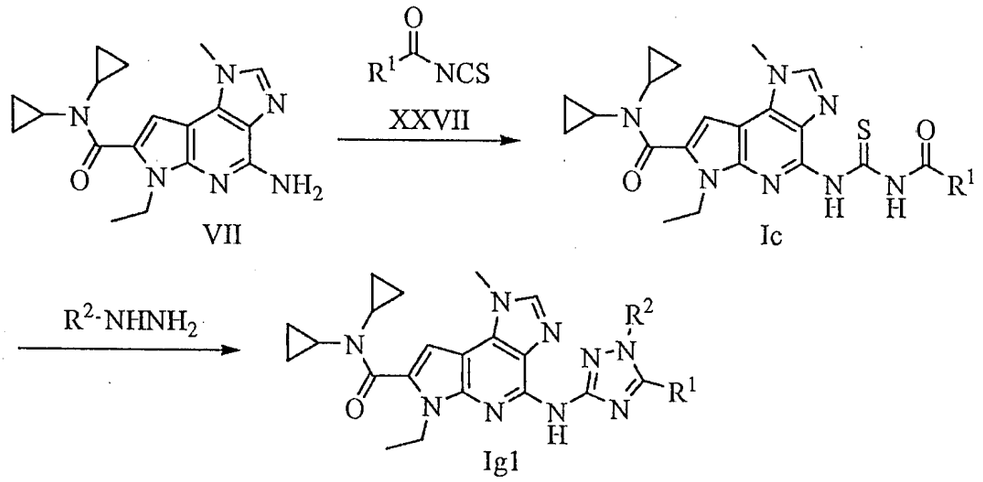
Los compuestos de fórmula general 1e1 pueden prepararse usando una estrategia sintética como se muestra en el Esquema de reacción 14. El isotiocianato XV puede

combinarse con la azida XXVI en presencia de fosfina para producir el 1,3-oxazol Ie1.



Esquema de reacción 14

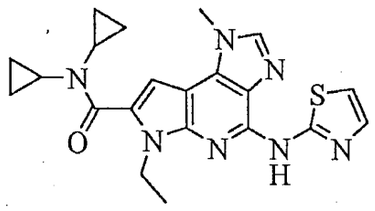
Los compuestos de fórmula general 1g1 pueden prepararse usando una estrategia sintética como se muestra en el Esquema de reacción 15. La amina VII puede combinarse con el isotiocianato de acilo XXVII. El aciltioureaido puede condensarse con un derivado de hidrazina para producir el derivado de 1,2,4-triazol 1g1.



Esquema de reacción 15

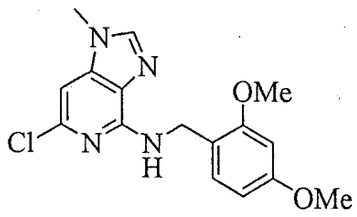
EJEMPLOS

Ejemplo 1



***N,N*-Diciclopropil-6-etil-1-metil-4-(tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

1A Preparación de 6-cloro-*N*-(2,4-dimetoxibencil)-1-metil-1*H*-imidazo[4,5-c]piridin-4-amina



En un matraz de fondo redondo de 200 ml se disolvió 4,6-dicloro-1-metil-1*H*-imidazo[4,5-*c*]piridina (15 g, 74.2 mmol) (preparada como para el ejemplo **A1.5** del documento WO2006122137) en 2,4-dimetoxibencilamina (25 ml, 166 mmol). La mezcla de reacción se calentó a 110°C durante 3 h y se enfrió a la temperatura ambiente. Se añadió agua y precipitó un sólido de color castaño. La filtración al vacío produjo un sólido de color castaño. El sólido se lavó con acetato de etilo y hexano, produciendo 6-cloro-*N*-(2,4-dimetoxibencil)-1-

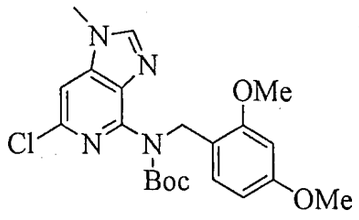
000245

metil-1*H*-imidazo[4,5-*c*]piridin-4-amina (23.459 g, rendimiento del 95%) en forma de un sólido de color crema.

MS (ESI) m/z 333.0 (M+H)

RMN ^{1}H (500 MHz, DMSO-d_6) δ ppm 8.05 (s, 1H), 7.17 (t, 1H, J = 6.19 Hz), 7.06 (d, 1H, J = 8.25 Hz), 6.87 (s, 1H), 6.55 (d, 1H, J = 2.47 Hz), 6.42 (dd, 1H, J = 8.52, 2.47 Hz), 4.54 (d, 2H, J = 5.77 Hz), 3.82 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H).

1B Preparación de 6-cloro-1-metil-1*H*-imidazo[4,5-c]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo



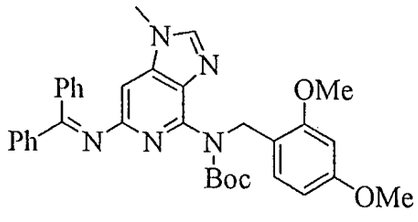
A una solución a -78°C de 6-cloro-*N*-(2,4-dimetoxibencil)-1-metil-1*H*-imidazo[4,5-c]piridin-4-amina (ejemplo **1A**, 0.63 g, 1.893 mmol) en tetrahidrofurano (38 ml) enfriada se le añadió lentamente NaHMDS (1.0 M THF, 2.366 ml, 2.366 mmol). Después de agitar a -78°C durante 30 min, se añadió BOC_2O (0.483 ml, 2.082 mmol). El baño frío se retiró y la reacción se dejó calentar a la ta durante una noche. Mediante el análisis por HPLC, se observó una conversión de ~50%. La solución se volvió a enfriar a -78°C. Se añadió NaHMDS (THF 1.0 M, 2.366 ml, 2.366 mmol) y la mezcla se agitó

durante 30 min antes de la adición de BOC_2O (0.483 ml, 2.082 mmol). El baño frío se retiró y la reacción se calentó a la temperatura ambiente durante 5 h. El solvente se retiró a presión reducida y el residuo se repartió entre acetato de etilo y agua. La fase orgánica se lavó dos veces con agua, se secó sobre sulfato de magnesio anhidro, se filtró y se concentró al vacío. El residuo en bruto se purificó por cromatografía ultrarrápida usando una columna Isco de 40 g eluyendo con acetato de etilo al 50-100%/hexano, produciendo 6-cloro-1-metil-1*H*-imidazo[4,5-c]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo (0.638 g, rendimiento del 78%) en forma de un sólido espumoso de color blanco.

MS (ESI) m/z 433.0 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.91 (s, 1H), 7.47 (d, 1H, *J* = 8.31 Hz), 7.19 (s, 1H), 6.38 (dd, 1H, *J* = 8.31, 2.52 Hz), 6.32 (d, 1H, *J* = 2.52 Hz), 5.13 (s, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.59 (s, 3H), 1.40 (s, 9H).

1C Preparación de 2,4-dimetoxibencil(6-(difenilmetilenoamino)-1-metil-1*H*-imidazo[4,5-c]piridin-4-il)carbamato de *terc*-butilo



Se añadió dioxano anhidro (4 ml) a una mezcla de

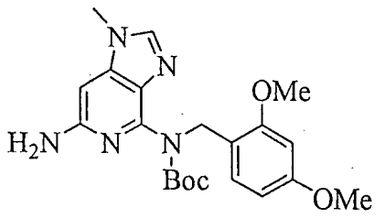
000247

6-cloro-1-metil-1*H*-imidazo[4,5-c]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo (ejemplo **1B**, 0.638 g, 1.474 mmol), benzofenona imina (0.297 ml, 1.769 mmol), $Pd_2(dba)_3$ (0.270 g, 0.295 mmol), 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (0.256 g, 0.442 mmol) y carbonato de cesio (0.672 g, 2.063 mmol). La mezcla de reacción se calentó a 90°C durante una noche. Después de la refrigeración a la ta, el solvente se retiró al vacío. El residuo se repartió entre acetato de etilo y agua. La fase orgánica se lavó dos veces con agua, se secó sobre sulfato de magnesio anhidro, se filtró y se concentró al vacío. El residuo en bruto se purificó por cromatografía ultrarrápida usando una columna Isco de 40 g eluyendo con acetato de etilo al 50-100%/hexano, proporcionando 2,4-dimetoxibencil(6-(difenilmetilenoamino)-1-metil-1*H*-imidazo[4,5-c]piridin-4-il)carbamato de *terc*-butilo (0.757 g, rendimiento del 89%) en forma de un sólido de color amarillo claro.

MS (ESI) m/z 414.0 ($M-CPh_2+2H$)

RMN ^1H (400 MHz, DMSO-d_6) δ ppm 8.16 (s, 1H), 7.67 (dd, 2H, *J* = 8.56, 1.51 Hz), 7.44-7.60 (m, 3H), 7.25 (d, 1H, *J* = 8.31 Hz), 6.96-7.11 (m, 4H), 6.87 (s, 1H), 6.46 (d, 1H, *J* = 2.52 Hz), 6.33 (dd, 1H, *J* = 8.56, 2.27 Hz), 4.52 (s, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 1.25 (s, 9H).

1D Preparación de 6-amino-1-metil-1*H*-imidazo[4,5-c]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo



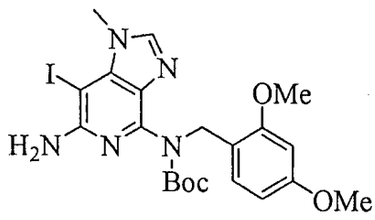
En un matraz de fondo redondo de 1000 ml, se agitó 2,4-dimetoxibencil(6-(difenilmetilenoamino)-1-metil-1*H*-imidazo[4,5-c]piridin-4-il)carbamato de *terc*-butilo (ejemplo **1C**, 9.2 g, 15,93 mmol) en THF (50 ml). Se añadió HCl 1 N (33 ml). Después de 2 min, la reacción se interrumpió con NaOH 1 N (65 ml) y acetato de etilo (100 ml). La fase orgánica se separó, se secó sobre sulfato sódico anhidro, se filtró y se concentró al vacío. El residuo se secó al vacío durante 1 h y se trituró con éter (4 x). Se aisló 6-amino-1-metil-1*H*-imidazo[4,5-c]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo (6.587 g, 15.93 mmol, rendimiento del 100%) en forma de un sólido de color crema. El material se llevó a la siguiente etapa sin purificación adicional.

MS (ESI) m/z 413.0 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 7.93 (s, 1H), 7.44 (d, 1H, J = 8.31 Hz), 6.44 (d, 1H, J = 2.27 Hz), 6.35 (dd, 1H, J = 8.56, 2.27 Hz), 6.25 (s, 1H), 5.58 (s, 2H), 4.87 (s, 2H), 3.67 (s, 6H), 3.63 (s, 3H), 1.30 (s, 9H).

000249

1E Preparación de 6-amino-7-yodo-1-metil-1*H*-imidazo[4,5-c]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo



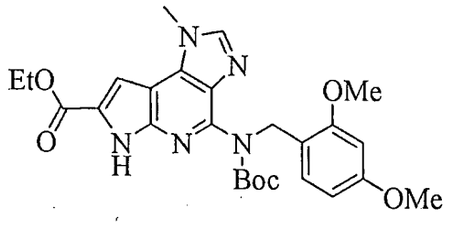
En un matraz de fondo redondo se disolvió 6-amino-1-metil-1*H*-imidazo[4,5-c]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo (ejemplo **1D**, 7.887 g, 19.08 mmol) en MeCN (200 ml) y se enfrió a 0°C. Se disolvió *N*-yodosuccinimida (4.51 g, 20.03 mmol) en el MeCN restante (50 ml) y se añadió gota a gota a la mezcla de reacción durante 40 min. La mezcla de reacción se agitó a 0°C durante 10 min más y se inactivó con sulfito ácido sódico 2 M (125 ml). La agitación y la temperatura se mantuvieron durante 50 min. La mezcla se transfirió a un embudo decantación. La fase acuosa se extrajo con CH_2Cl_2 (3 x 100 ml). Las fases orgánicas combinadas se lavaron con agua y salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío. El residuo en bruto se purificó por cromatografía ultrarrápida usando una columna Isco de 120 g eluyendo con acetato de etilo al 20-100%/CH_2Cl_2, proporcionando 6-amino-7-yodo-1-metil-1*H*-imidazo[4,5-c]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo (8.436 g, rendimiento del 82%) en forma de un sólido de color amarillo claro.

000250

MS (ESI) m/z 539.0 (M)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.00 (s, 1H), 7.40 (d, 1H, *J* = 8.06 Hz), 6.43 (d, 1H, *J* = 2.52 Hz), 6.31-6.39 (m, 1H), 5.73 (s, 2H), 4.86 (s, 2H), 3.95 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 1.30 (s, 9H).

1F Preparación de 4-(*terc*-butoxicarbonil(2,4-dimetoxibencil)amino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxilato de etilo



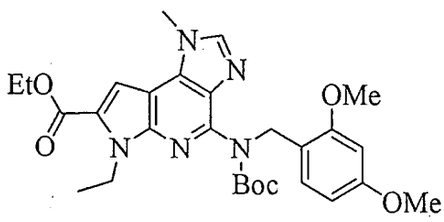
A un matraz de fondo redondo cargado con 6-amino-7-yodo-1-metil-1*H*-imidazo[4,5-c]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo (ejemplo **1E**, 3.49 g, 6.47 mmol) en DMA (43.1 ml) se le añadieron $Pd_2(dba)_3$ (0.474 g, 0.518 mmol), piruvato de etilo (7.22 ml, 64.7 mmol) y N-metildiciclohexilamina (2.77 ml, 12.94 mmol). La mezcla de reacción se roció con argón durante 10 min y se calentó a 60°C durante 6 h. La reacción se completó mediante CLEM. Después de la refrigeración a la temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y $NaHCO_3$ acuoso saturado. La emulsión resultante se filtró al vacío a través de una capa de Celite y se transfirió a un embudo decantación. La fase acuosa se extrajo con acetato de etilo.

Las fases orgánicas combinadas se lavaron con solución acuosa de LiCl al 10% (2 x). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró al vacío. El residuo de color pardo se purificó por cromatografía ultrarrápida usando una columna Isco de 120 g eluyendo con acetato de etilo al 40-80%/hexano, produciendo 4-(*terc*-butoxicarbonil(2,4-dimetoxibencil)amino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxilato de etilo (2.830 g, rendimiento del 86%).

MS (ESI) m/z 510.0 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.83 (s, 1H), 7.57 (d, 1H, *J* = 8.31 Hz), 7.39 (d, 1H, *J* = 2.27 Hz), 6.40 (dd, 1H, *J* = 8.44, 2.39 Hz), 6.32 (d, 1H, *J* = 2.52 Hz), 5.16 (s, 2H), 4.43 (c, 2H, *J* = 7.05 Hz), 4.09 (s, 3H), 3.74 (s, 3H), 3.56 (s, 3H), 1.43 (t, 3H, *J* = 7.18 Hz), 1.40 (s, 9H).

1G Preparación de 4-(*terc*-butoxicarbonil(2,4-dimetoxibencil)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxilato de etilo



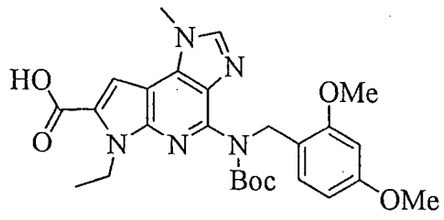
A una solución de 4-(*terc*-butoxicarbonil(2,4-dimetoxibencil)amino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxilato de etilo (ejemplo **1F**, 5.046 g, 9.90 mmol) en DMF (49.5 ml) se le añadieron yoduro

de etilo (1.601 ml, 19.81 mmol) y carbonato de cesio (6.45 g, 19.81 mmol). La mezcla de reacción se calentó a 60°C durante 60 min y se enfrió a la temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo y se filtró al vacío para retirar el carbonato de cesio. Se añadió bicarbonato sódico acuoso saturado y la fase acuosa se extrajo con acetato de etilo (2 x). Las fases orgánicas combinadas se lavaron con cloruro de litio al 10% (3 x), se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron al vacío. El producto en bruto se llevó a la siguiente etapa.

MS (ESI) m/z 538.1 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.79 (s, 1H), 7.62 (d, 1H *J* = 8.28 Hz), 7.43 (s, 1H), 6.39 (dd, 1H, *J* = 8.41, 2.38 Hz), 6.32 (d, 1H, *J* = 2.26 Hz), 5.20 (s, 2H), 4.79 (c, 2H, *J* = 7.03 Hz), 4.41 (c, 2H, *J* = 7.28 Hz), 4.07 (s, 3H), 3.74 (s, 3H), 3.61 (s, 3H), 1.44 (t, 3H, *J* = 7.15 Hz), 1.41 (s, 9H), 1.37 (t, 3H, *J* = 7.03 Hz).

1H Preparación de ácido 4-(*terc*-butoxicarbonil(2,4-dimetoxibencil)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxílico

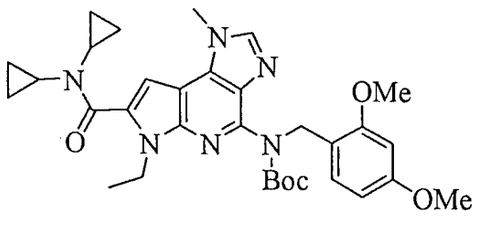


A una solución de 4-(*terc*-butoxicarbonil(2,4-

dimetoxibencil)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxilato de etilo (ejemplo **1G**, 5.32 g, 9.9 mmol) en etanol (49.5 ml) se le añadió una solución acuosa de NaOH 1 N (49.5 ml). La mezcla de reacción se calentó a 60°C durante 3 h y se enfrió a la ta. El etanol se retiró por concentración al vacío. El residuo se acidificó con HCl 1 N y el producto se recogió por filtración al vacío. Después del secado al vacío, se aisló ácido 4-(*terc*-butoxicarbonil(2,4-dimetoxibencil)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxílico (4.3 g, 8.44 mmol, rendimiento del 85% en dos etapas) en forma de un sólido de color blanco.

MS (ESI) m/z 510.0 (M+H)

1I Preparación de 7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo



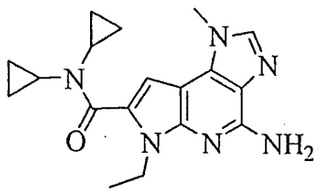
A una mezcla de ácido 4-(*terc*-butoxicarbonil(2,4-dimetoxibencil)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxílico (ejemplo **1H**, 0.89 g, 1.747 mmol) en acetonitrilo (17.47 ml) se le añadieron clorhidrato de diciclopropilamina

(0.303 g, 2.271 mmol), *N*-metilmorfolina (0.499 ml, 4.54 mmol), DMAP (0.021 g, 0.175 mmol) y HATU (0.797 g, 2.096 mmol). La mezcla de reacción se agitó a la ta durante 5 h y se calentó a 50°C durante 45 min. La reacción se enfrió a la temperatura ambiente. El acetonitrilo se retiró al vacío y el residuo se repartió entre bicarbonato sódico acuoso saturado y diclorometano. La fase acuosa se extrajo con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. El producto en bruto se purificó por cromatografía ultrarrápida usando una columna Isco de 80 g eluyendo con MeOH al 1-4%/CH_2Cl_2, produciendo 7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo (0.8 g, rendimiento del 78%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 589.0 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.78 (s, 1H), 7.67 (d, 1H, *J* = 8.28 Hz), 6.85 (s, 1H), 6.40 (dd, 1H, *J* = 8.41, 2.38 Hz), 6.33 (d, 1H, *J* = 2.51 Hz), 5.20 (s, 2H), 4.58 (c, 2H, *J* = 7.03 Hz), 4.02 (s, 3H), 3.74 (s, 3H), 3.62 (s, 3H), 2.77-2.85 (m, 2H), 1.42 (s, 9H), 1.39 (t, 3H, *J* = 7.40 Hz), 0.80-0.89 (m, 4H), 0.72-0.78 (m, 4H).

1J Preparación de 4-amino-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



A una solución de 7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-il(2,4-dimetoxibencil)carbamato de *terc*-butilo (ejemplo **1I**, 2.66 g, 4.51 mmol) en diclorometano (33.8 ml) se le añadió TFA (11.28 ml). La mezcla de reacción se agitó a la ta durante 45 min y se concentró al vacío. El residuo en bruto se repartió entre acetato de etilo y bicarbonato sódico acuoso saturado. La fase acuosa se extrajo con acetato de etilo (2 x) y los extractos orgánicos combinados se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. El producto en bruto se purificó por cromatografía ultrarrápida usando una columna Isco de 40 g eluyendo con MeOH al 4-10%/CH_2Cl_2, produciendo 4-amino-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (1.2 g, 3.55 mmol, rendimiento del 79%) en forma de un sólido de color amarillo claro.

MS (ESI) m/z 339.2 (M+H)

RMN ^{1}H (400 MHz, MeOD) δ ppm 7.95 (s, 1H), 7.15 (s, 1H), 4.51 (c, 2H *J* = 7.13 Hz), 4.04 (s, 3H), 2.89-2.98 (m, 2H), 1.35 (t, 3H), 0.82-0.91 (m, 4H), 0.70-0.81 (m, 4H).

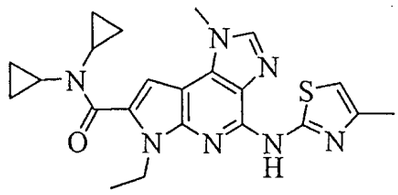
1 Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

A una mezcla de 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 30 mg, 0.089 mmol), 2-bromotiazol (11.98 µl, 0.133 mmol), $Pd_2(dba)_3$ (12.18 mg, 0.013 mmol), BINAP (24.84 mg, 0.040 mmol) y *terc*-butóxido sódico (13.63 mg, 0.142 mmol) se le añadió PhMe (887 µl). La mezcla se roció con gas argón durante 5 min y se calentó a 85°C durante 5.5 h. La mezcla de reacción se filtró a través de un lecho de Celite y se concentró. El residuo en bruto se purificó por HPLC preparativa, proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (4 mg, rendimiento del 10.49%) junto con algo de material de partida recuperado.

MS (ESI) m/z 423.0 (M+H)

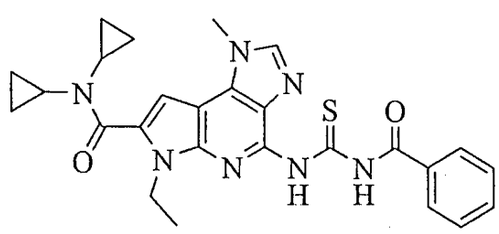
RMN ^{1}H (500 MHz, DMSO-d_6) δ ppm 8.14 (s, 1H), 7.47 (d, 1H, *J* = 3.57 Hz), 7.24 (s, 1H), 7.14 (d, 1H, *J* = 3.57 Hz), 4.63 (c, 2H, *J* = 6.87 Hz), 4.05 (s, 3H), 2.88-2.99 (m, 2H), 1.39 (t, 3H, *J* = 7.01 Hz), 0.73-0.81 (m, 4H), 0.64-0.70 (m, 4H).

Ejemplo 2



***N,N*-Diciclopropil-6-etil-1-metil-4-(4-metiltiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

2A Preparación de 4-(3-benzoiltioureido)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

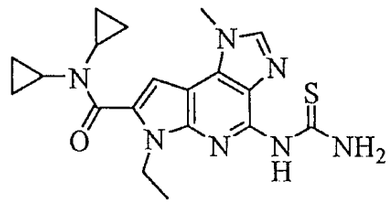


Una solución de 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 234 mg, 0.69 mmol) e isotiocianato de benzoilo (0.1 ml, 0.83 mmol) en acetona (3 ml) se agitó a la temperatura ambiente durante 3 h. La mezcla de reacción se enfrió a 0°C y se añadió agua. El sólido de color pardo resultante se recogió por filtración y se secó al aire, dando 4-(3-benzoiltioureido)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (306 mg, rendimiento del 88%).

MS (ESI) tr = 1.86 min, m/z 502 (M+H).

RMN ^1H (400 MHz, DMSO-d_6) δ ppm 8.44 (s a, 1H) 7.99-8.07 (m, 2H) 7.64-7.74 (m, 1H) 7.58 (t, J = 7.65 Hz, 2H) 7.34 (s, 1H) 4.47 (s a, 2H) 4,11 (s, 3H) 2.90-2.99 (m, 2H) 2.08 (s, 1H) 1.28 (s a, 3H) 0.64-0.81 (m, 8H).

2B Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



Se calentaron 4-(3-benzoiltioureido)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **2A**, 306 mg, 0.61 mmol) y NaOH 1 N (10 ml, 10.00 mmol) en 10 ml de EtOH a 60°C durante 1 h. La reacción se enfrió a la temperatura ambiente y se concentró. La solución acuosa restante se extrajo (3 x) con acetato de etilo. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por cromatografía sobre gel de sílice (diclorometano/metanol al 0-4%) dio *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida en forma de un sólido de color amarillo (199 mg, rendimiento del 82%).

MS (ESI) m/z 398 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 11.02 (s a, 1H) 9.27 (s, 2H) 7.75 (s, 1H) 6.89 (s, 1H) 4.52 (c, *J* = 7.12 Hz, 2H) 4.06 (s, 3H) 2.77-2.90 (m, 2H) 1.45 (t, *J* = 7.15 Hz, 3H) 0.73-0.97 (m, 8H).

2 Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(4-metiltiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

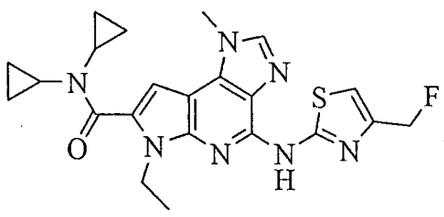
Se calentaron *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **2B**, 40 mg, 0.10 mmol) y cloroacetona (62.4 mg, 0.40 mmol) en EtOH (2 ml) a 80°C durante 20 min. La reacción se enfrió a la temperatura ambiente y el solvente se retiró al vacío. Se añadió una solución saturada de $NaHCO_3$ y la fase acuosa se extrajo (3 x) con diclorometano. Las fases orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material en bruto se purificó por cromatografía sobre gel de sílice (diclorometano/metanol al 0-7%), proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(4-metiltiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (9 mg, rendimiento del 12%) en forma de un sólido de color blanco.

EM (CI) m/z 436.1 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 10.70 (s a, 1H), 8.12 (s, 1H), 7.23 (s, 1H), 6.69 (s, 1H), 4.61 (c, 2H, *J* = 7.19 Hz), 4.04 (s, 3H), 2.88-2.98 (m, 2H), 2.29 (s, 3H), 1.38

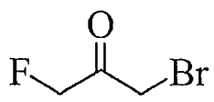
(t, 3H, J = 7.15 Hz), 0.72-0.81 (m, 4H), 0.62-0.70 (m, 4H).

Ejemplo 3



***N,N*-Diciclopropil-6-etil-4-(4-(fluorometil)tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

3A Preparación de 1-bromo-3-fluoropropan-2-ona



Se añadió gota a gota bromo (0.36 ml, 7.02 mmol) a una solución de 1-fluoropropan-2-ona (0.51 ml, 7.02 mmol) en tetracloruro de carbono (25 ml). La solución se calentó a 45°C durante 3 h. La reacción se enfrió a la temperatura ambiente y se interrumpió con agua. Después de la extracción con diclorometano (3 x), las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por cromatografía sobre gel de sílice (EtOAc al 0-20%/Hexanos) dio 1-bromo-3-fluoropropan-2-ona en forma de un aceite de color amarillo (118 mg, 65%).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 5.14 (s, 1H) 5.02 (s, 1H) 4.10 (d, J = 2.86 Hz, 2H).

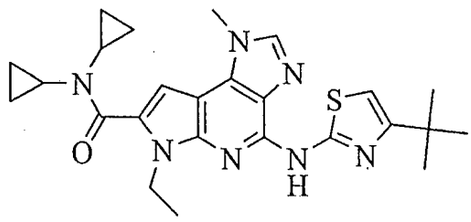
3 Preparación de *N,N*-diciclopropil-6-etil-4-(4-(fluorometil)tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Se preparó a partir de *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **2B**) y 1-bromo-3-fluoropropan-2-ona (ejemplo **3A**) usando el mismo procedimiento que para **2**.

MS (ESI) tr = 1.94 min, m/z 454 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 9.34 (s a, 1H) 7.75 (s, 1H) 6.96 (d, *J* = 3.52 Hz, 1H) 6.90 (s, 1H) 5.27-5.53 (m, 2H) 4.75 (c, *J* = 7.12 Hz, 2H) 3.98-4.11 (m, 3H) 2.76-2.91 (m, 2H) 1.54 (t, *J* = 7.04 Hz, 3H) 0.70-0.94 (m, 8H).

Ejemplo 4



4-(4-*terc*-Butiltiazol-2-ilamino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

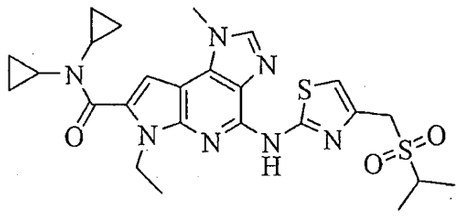
Se preparó a partir de *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **2B**) y 1-cloro-3,3-dimetilbutan-2-ona usando el mismo procedimiento que se ha indicado para **2**.

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MS (ESI) tr = 1.99 min, m/z 478 (M+H).

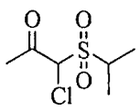
RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.74 (s, 1H) 6.90 (s, 1H) 6.48 (s, 1H) 4.74 (c, *J* = 7.03 Hz, 1H) 4.04 (s, 3H) 2.77-2.90 (m, 2H) 1.53 (t, *J* = 7.03 Hz, 3H) 1.37 (s, 9H) 0.70-0.96 (m, 8H).

Ejemplo 5



***N,N*-Diciclopropil-6-etil-4-(4-(isopropilsulfonilmetil)tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

5A Preparación de 1-cloro-1-(isopropilsulfonil)propan-2-ona



Se añadió gota a gota cloruro de sulfurilo (0.248 ml, 3.05 mmol) a una solución de 1-(isopropilsulfonil)propan-2-ona (418 mg, 2.55 mmol) en 1:1 de AcOH/DCM (16 ml) a 0°C. La reacción se agitó a la ta durante 4 h. El solvente se retiró al vacío y después se diluyó con diclorometano. La fase orgánica se lavó (2 x) con una solución saturada de $NaHCO_3$, se secó sobre Na_2SO_4, se filtró y se concentró, dejando 800 mg en forma de un aceite transparente. El

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material se usó sin purificación adicional.

RMN ^{1}H (500 MHz, CLOROFORMO-*d*) δ ppm 5.19 (s, 1H) 3.65 (dt, *J* = 13.66, 6.90 Hz, 1H) 2.56 (s, 3H) 1.45 (dd, *J* = 6.94, 3.05 Hz, 6H).

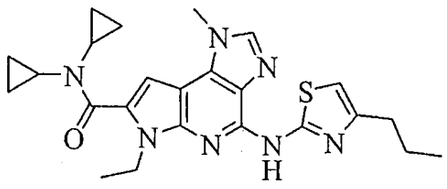
5 Preparación de *N,N*-diciclopropil-6-etil-4-(4-(isopropilsulfonilmetil)tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Se preparó a partir de *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo 2B) y 1-cloro-1-(isopropilsulfonil)propan-2-ona (ejemplo 5) usando el mismo procedimiento que se ha indicado para **2**.

MS (ESI) tr = 1.84 min, m/z 542 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 7.82 (s, 1H) 7.01 (s, 1H) 6.90 (s, 1H) 4.73 (c, *J* = 7.04 Hz, 2H) 4.35 (s, 2H) 4.06 (s, 3H) 3.36 (quint., *J* = 6.88 Hz, 1H) 2.79-2.91 (m, 2H) 1.53 (t, *J* = 7.04 Hz, 3H) 1.43 (d, *J* = 6.82 Hz, 6H) 0.74-0.92 (m, 8H).

Ejemplo 6



***N,N*-Diciclopropil-6-etil-1-metil-4-(4-propiltiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

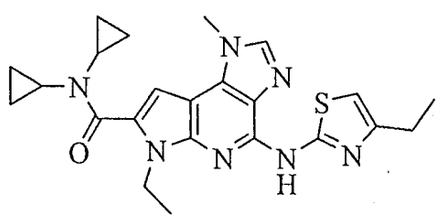
Se preparó a partir de *N,N*-diciclopropil-6-etil-1-

metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo 2B) y 1-bromopentan-2-ona usando el mismo procedimiento que se ha indicado para **2**.

MS (ESI) tr = 1.94 min, m/z 464 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 8.43-9.78 (m, 1H) 7.71 (s, 1H) 6.89 (s, 1H) 6.48 (s, 1H) 4.75 (c, *J* = 7.04 Hz, 2H) 4.04 (s, 3H) 2.76-2.92 (m, 2H) 2.68 (t, *J* = 737 Hz, 2H) 1.76 (dc, *J* = 14.94, 7.42 Hz, 2H) 1.53 (t, *J* = 7.04 Hz, 3H) 1.01 (t, *J* = 7.26 Hz, 3H) 0.69-0.94 (m, 8H).

Ejemplo 7



***N,N*-Diciclopropil-6-etil-4-(4-etiltiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

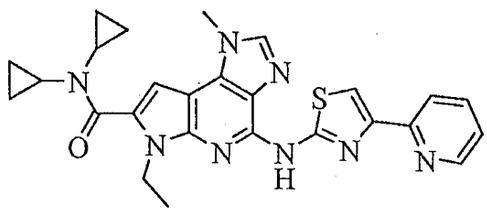
Se preparó a partir de *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **2B**) y 1-bromobutan-2-ona usando el mismo procedimiento que se ha indicado para 2.

MS (ESI) m/z 450 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 7.71 (s, 1H) 6.89 (s, 1H) 6.49 (s, 1H) 4.75 (c, *J* = 7.03 Hz, 2H) 4.04 (s, 3H) 2.80-2.88 (m, 2H) 2.75 (c, *J* = 7.45 Hz, 1H) 1.54 (t, *J* =

7.15 Hz, 2H) 1.33 (t, J = 7.40 Hz, 2H) 0.82 (s a, 8H).

Ejemplo 8



***N,N*-Diciclopropil-6-etil-1-metil-4-(4-(piridin-2-il)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

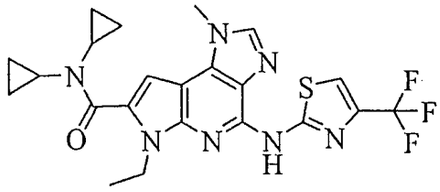
Una solución de 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 70 mg, 0.21 mmol) e isotiocianato de benzoilo (36 µl, 0.27 mmol) en acetona (1 ml) se agitó a la temperatura ambiente durante 1.5 h. El solvente se retiró al vacío, el residuo se recogió en EtOH (1.5 ml) y se añadió K_2CO_3 (40 mg, 0.290 mmol). La reacción se calentó a 60°C durante 3 h. Después de la refrigeración a la temperatura ambiente, se añadió 2-bromo-1-(piridin-2-il)etanona, bromhidrato (139.4 mg, 0.50 mmol) y la reacción se calentó a 80°C durante 24 h. La mezcla de reacción se enfrió a la temperatura ambiente y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (MeOH al 0-7%/diclorometano). La repurificación por HPLC preparativa proporcionó 10.2 mg (rendimiento del 10%) de *N,N*-diciclopropil-6-etil-1-

metil-4-(4-(piridin-2-il)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida en forma de un sólido de color pardo.

MS (ESI) tr = 1.78 min, m/z 499 (M+H).

RMN ^{1}H (DMSO-d6) δ ppm 10.9 (s, 1H), 8.2 (s a, 1H), 7.81 (d, 1H), 7.75 (s, 1H), 3.92 (m, 4H), 3.77 (c, 2H, *J* = 7.8 Hz), 2.52-2.81 (m, 7H).

Ejemplo 9



Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(4-(trifluorometil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

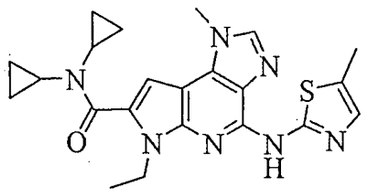
Este compuesto se preparó de acuerdo con el ejemplo **2** usando 3-bromo-1,1,1-trifluoroacetona, proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(4-(trifluorometil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida.

MS (ESI) m/z 490.0 (M+H)

RMN ^{1}H (500 MHz, DMSO-d_6) δ ppm 11.71 (s, 1H), 8.16 (s, 1H), 7.86 (s, 1H), 7.27 (s, 1H), 4.63 (c, 2H), 4.05 (s, 3H), 2.89-2.98 (m, 2H), 1.40 (t, 3H, *J* = 6.87 Hz), 0.74-0.80 (m, 4H), 0.64-0.71 (m, 4H).

000267

Ejemplo 10



Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(5-metiltiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Se disolvió 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 86.3 mg, 0.255 mmol) en acetona y se añadió isotiocianato de benzoilo (37.8 µl, 0.281 mmol). La reacción se agitó a la temperatura ambiente durante 2 h. El solvente se retiró al vacío. El residuo se recogió en etanol (1500 µl) y se añadió K_2CO_3 (49.3 mg, 0.357 mmol). La mezcla de reacción se calentó a 60°C durante 3 h. Se añadió 2-bromopropanal (45.4 mg, 0.332 mmol). Después de 3 h, se añadió más 2-bromopropanal (~100 mg). Se agitó a 60°C durante 16 h. Se añadió 2-bromopropanal y la mezcla de reacción se agitó a 60°C durante 3 h. El etanol se retiró mediante concentración al vacío. El residuo en bruto se purificó por cromatografía ultrarrápida usando una columna Isco de 12 g eluyendo con MeOH al 2-10%/CH_2Cl_2. Se realizó purificación adicional mediante HPLC preparativa. Se aisló *N,N*-diciclopropil-6-etil-1-metil-4-(5-metiltiazol-2-ilamino)-1,6-

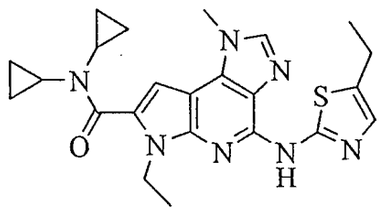
000268

dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (20 mg, rendimiento del 17.47%) en forma de un sólido de color blanco.

MS (ESI) m/z 436,0 (M+H)

RMN ^{1}H (500 MHz, DMSO-d_6) δ ppm 10.56 (s a, 1H), 8.12 (s, 1H), 7.23 (s, 1H), 7.12 (s, 1H), 4.62 (c, 2H, *J* = 6,78 Hz), 4.04 (s, 3H), 2.87-2.99 (m, 2H), 2.39 (s, 3H), 1.35-1.46 (m, 3H), 0.72-0.81 (m, 4H), 0.59-0.71 (m, 4H).

Ejemplo 11



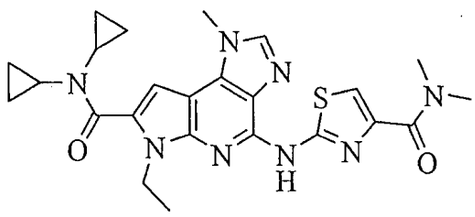
***N,N*-Diciclopropil-6-etil-4-(5-etiltiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Se preparó a partir de 2-bromobutanal y 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo 1J) usando el mismo procedimiento que el del ejemplo **8**.

MS (ESI) tr = 1.86 min, m/z 450 (M+H).

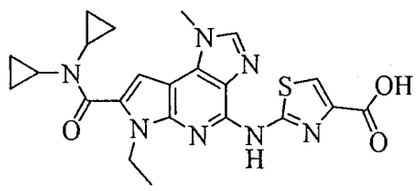
RMN ^{1}H (500 MHz, CLOROFORMO-*d*) δ ppm 8.91-9.22 (m, 1H) 7.71 (s, 1H) 7.14 (s, 1H) 6.89 (s, 1H) 4.75 (c, *J* = 6.94 Hz, 2H) 4.05 (s, 3H) 2.80-2.89 (m, 4H) 1.55 (t, *J* = 5.00 Hz, 3H) 1.37 (t, *J* = 7.49 Hz, 3H) 0.73-0.92 (m, 8H).

Ejemplo 12



2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N,N*-dimetiltiazol-4-carboxamida

12A Preparación de ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-4-carboxílico



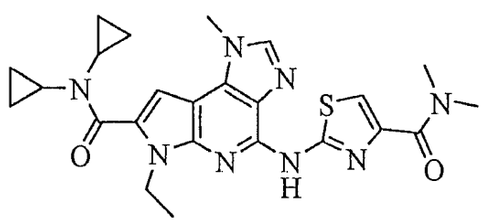
Se agitaron 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (**1J**, 300 mg, 0.89 mmol) e isotiocianato de benzoilo (0.16 ml, 1.15 mmol) en acetona (4 ml) a la ta durante 1.5 h. El solvente se retiró al vacío y el residuo se recogió en EtOH (6 ml). Se añadió K_2CO_3 (172 mg, 1.241 mmol) y la reacción se calentó a 60°C durante 3 h. La reacción se enfrió a la ta y se añadió 3-bromo-2-oxopropanoato de etilo (692 mg, 3.55 mmol). La reacción se calentó a 70°C durante una noche. Después de que se completara la etapa de

ciclación, se añadió NaOH 1 N (6.3 ml, 6.30 mmol) a la mezcla de reacción y se calentó a 60°C durante 4 h. La reacción se enfrió a la temperatura ambiente y el solvente se retiró al vacío. La solución acuosa resultante se acidificó hasta alcanzar un valor de pH de 1 y el precipitado se retiró por filtración al vacío, lavándolo con agua, EtOAc y después con diclorometano, proporcionando ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-4-carboxílico (325 mg, rendimiento del 79%) en forma de un sólido de color pardo.

MS (ESI) tr = 1.85 min, m/z 466 (M+H).

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.16 (s, 1H) 7.94 (s, 1H) 7.26 (s, 1H) 4.63 (c, *J* = 6.94 Hz, 2H) 4.05 (s, 3H) 3.36 (s a, 1H) 2.89-2.99 (m, 2H) 1.40 (t, *J* = 7.03 Hz, 3H) 0.61-0.83 (m, 8H).

12 Preparación de 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*-dimetiltiazol-4-carboxamida



A ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-

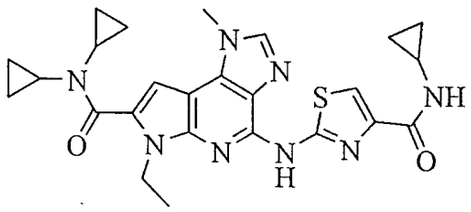
ilamino)tiazol-4-carboxílico (ejemplo **12A**, 44 mg, 0.095 mmol) en DMF (2 ml) se le añadieron HATU (108 mg, 0.284 mmol), DIPEA (0.066 ml, 0.378 mmol) y dimetilamina (0.013 ml, 0.189 mmol). La reacción se agitó a la ta durante 3 h y después el solvente se retiró al vacío. El residuo se purificó por HPLC preparativa, dando 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*-dimetiltiazol-4-carboxamida (10 mg, rendimiento del 21%) en forma de un sólido de color pardo.

MS (ESI) m/z 493 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 9.45 (s a, 1H) 7.81 (s, 1H) 7.43 (s, 1H) 6.90 (s, 1H) 4.74 (c, *J* = 7.03 Hz, 2H) 4.05 (s, 3H) 3.31 (s a, 3H) 3.13 (s a, 3H) 2.75-2.90 (m, 2H) 1.54 (t, *J* = 7.15 Hz, 3H) 0.65-0.96 (m, 8H).

Los ejemplos **13-17** se prepararon usando el procedimiento que se ha descrito para el ejemplo **12**.

Ejemplo 13



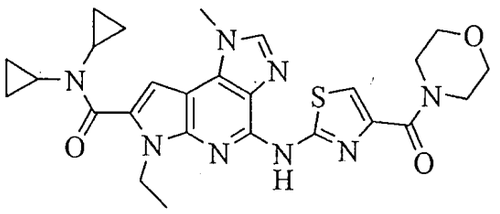
***N*-Ciclopropil-2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-4-carboxamida**

MS (ESI) tr = 1.99 min, m/z 505 (M+H).

000272

RMN ^{1}H (400 MHz, MeOD) δ ppm 8.07 (s, 1H) 7.74 (s, 1H) 7.26 (s, 1H) 4.73 (c, *J* = 7.03 Hz, 1H) 4.13 (s, 3H) 2.94-3.04 (m, 2H) 2.85-2.93 (m, 1H) 1.51 (t, *J* = 7.03Hz, 2H) 0.67-0.95 (m, 12H).

Ejemplo 14

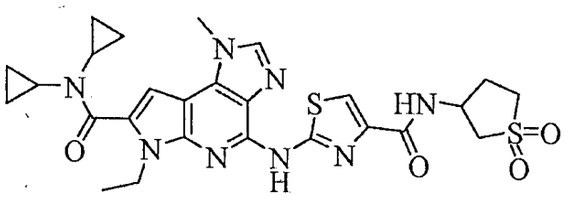


***N,N*-Diciclopropil-6-etil-1-metil-4-(4-(morfolin-4-carbonil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

MS (ESI) tr = 1.87 min, m/z 535 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 9.21 (s a, 1H) 7.76 (s, 1H) 7.56 (s, 1H) 6.81-6.94 (m, 1H) 4.74 (c, *J* = 7.11 Hz, 2H) 4.07 (s, 3H) 3.79 (s a, 4H) 3.50 (d, *J* = 4.52 Hz, 2H) 2.74-2.90 (m, 2H) 1.60 (s, 2H) 1.54 (t, *J* = 7.03 Hz, 3H) 0.70-0.94 (m, 8H).

Ejemplo 15

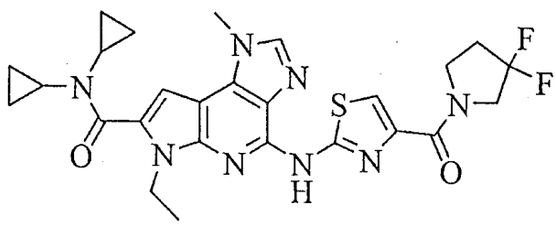


***N,N*-Diciclopropil-4-((4-((1,1-dioxidotetrahidro-3-tiofenil)carbamoil)-1,3-tiazol-2-il)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

MS (ESI) tr = 1.88 min, m/z 583 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 9.31 (s a, 1H) 7.77 (s, 1H) 7.69-7.75 (m, 1H) 6.91 (s, 1H) 4.85-4.99 (m, 1H) 4.64-4.81 (m, 2H) 4.07 (s, 3H) 3.45-3.61 (m, 2H) 3.35 (s a, 1H) 3.19 (dt, *J* = 13.36, 8.12 Hz, 2H) 2.75-2.91 (m, 2H) 2.57-2.72 (m, 1H) 2.42 (ddd, *J* = 14.49, 7.53, 7.34 Hz, 1H) 1.54 (t, *J* = 6.90 Hz, 3H) 0.69-0.94 (m, 8H).

Ejemplo 16

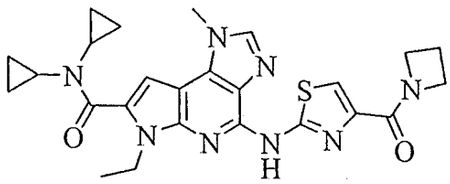


***N,N*-Diciclopropil-4-(4-(3,3-difluoropirrolidin-1-carbonil)tiazol-2-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

MS (ESI) tr = 2.05 min, m/z 555 (M+H).

RMN ^{1}H (400 MHz, MeOD) δ ppm 8.00 (s, 1H) 7.73 (s, 1H) 7.70 (s, 1H) 7.19 (s, 1H) 4.68 (c, *J* = 7.03 Hz, 2H) 4.51 (t, *J* = 12.80 Hz, 1H) 4.34 (t, *J* = 7.40 Hz, 1H) 4.06 (s, 3H) 3.96 (t, *J* = 13.18 Hz, 1H) 3.86 (t, *J* = 7.65 Hz, 1H) 2.87-3.02 (m, 2H) 2.34-2.59 (m, 2H) 1.45 (t, *J* = 6.90 Hz, 3H) 0.72-0.95 (m, 8H).

Ejemplo 17

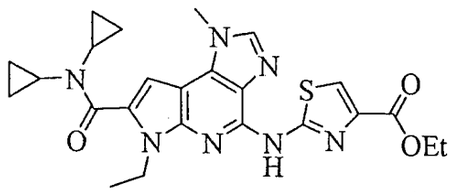


(4-(Azetidin-1-carbonil)tiazol-2-ilamino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

MS (ESI) tr = 1.95 min, m/z 505 (M+H).

RMN ^{1}H (400 MHz, MeOD) δ ppm 8.03 (s, 1H) 7.70 (s, 1H) 7.21 (s, 1H) 4.78 (t, *J* = 7.53 Hz, 2H) 4.69 (c, *J* = 7.03 Hz, 2H) 4.19 (t, *J* = 7.78 Hz, 2H) 4.08 (s, 3H) 2.95 (ddd, *J* = 7.22, 3.45, 3.14 Hz, 2H) 2.27-2.48 (m, 2H) 1.47 (t, *J* = 7.03 Hz, 3H) 0.69-0.93 (m, 8H).

Ejemplo 18



2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-4-carboxilato de etilo

Este compuesto se preparó de acuerdo con el ejemplo **2** usando bromopiruvato de etilo y *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **2B**), produciendo 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-

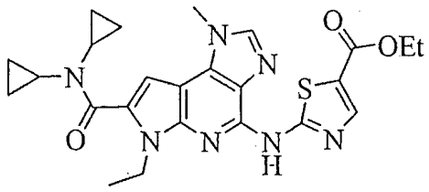
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dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-4-carboxilato de etilo en forma de un sólido de color amarillo.

MS (ESI) m/z 494.1 (M+H)

RMN ^{1}H (500 MHz, DMSO-d_6) δ ppm 11.42 (s a, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.25 (s, 1H), 4.62 (c, 2H), 4.30 (c, 2H, *J* = 7.15 Hz), 4.05 (s, 3H), 2.89-2.97 (m, 2H), 1.39 (t, 3H, *J* = 7.01 Hz), 1.32 (t, 3H, *J* = 7.15 Hz), 0.74-0.80 (m, 4H), 0.64-0.70 (m, 4H).

Ejemplo 19



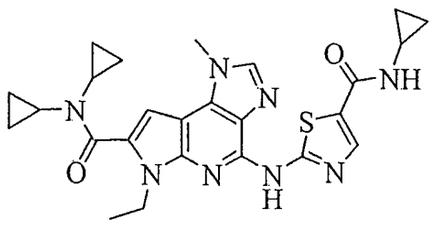
2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxilato de etilo

Este compuesto se preparó de acuerdo con el ejemplo 2 usando 2-cloro-2-formilacetato de etilo y *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **2B**), proporcionando 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxilato de etilo (18.5 mg, rendimiento del 17%) en forma de un sólido de color amarillo claro.

MS (ESI) m/z 494.0 (M+H)

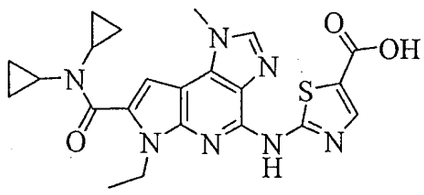
RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 11.95 (s, 1H), 8.20 (s, 1H), 8.14 (s, 1H), 7.28 (s, 1H), 4.63 (c, 2H, *J* = 7.19 Hz), 4.28 (c, 2H, *J* = 7.19 Hz), 4.06 (s, 3H), 2.88-3.00 (m, 2H), 1.44 (t, 3H, *J* = 7.03 Hz), 1.32 (t, 3H, *J* = 7.15 Hz), 0.73-0.81 (m, 4H), 0.63-0.70 (m, 4H).

Ejemplo 20



***N*-Ciclopropil-2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxamida**

20A Preparación de ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxílico



A una solución de 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxilato de etilo (**ejemplo 19**, 14.6 mg, 0.030 mmol) en EtOH (296 µl) se le añadió una solución acuosa NaOH 1 N (296 µl). La mezcla de reacción se agitó a la ta

durante 3 h y se agitó a 50°C durante 18 h. Después de la refrigeración a la temperatura ambiente, el etanol se retiró mediante concentración al vacío. El residuo se acidificó con HCl 1 N y el producto sólido se recogió por filtración. Se aisló ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxílico en forma de un sólido de color amarillo claro que se usó en bruto en la siguiente reacción.

MS (ESI) m/z 465.9 (M+H)

20 Preparación de *N*-ciclopropil-2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxamida

A una mezcla de ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxílico (ejemplo **20A**, 13.97 mg, 0.030 mmol) en DMF (300 µl) se le añadieron ciclopropilamina (4.16 µl, 0.060 mmol), HATU (14.83 mg, 0.039 mmol) y base de Hünig (15.72 µl, 0.090 mmol). La mezcla de reacción se agitó a la ta durante 1 h y se concentró al vacío. El residuo se recogió en MeOH y se purificó por HPLC preparativa. Se aisló *N*-ciclopropil-2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxamida (3 mg, rendimiento del 19.82%) en forma de un

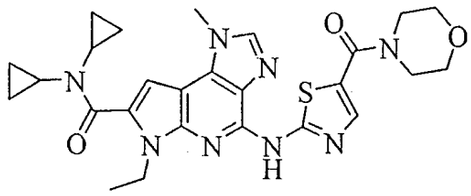
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sólido de color blanco.

MS (ESI) m/z 505.0 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.36 (s a, 1H), 8.15 (s, 1H), 8.02 (s, 1H), 7.25 (s, 1H), 4.63 (c, 2H, J = 7.11 Hz), 4.05 (s, 3H), 2.89-3.00 (m, 2H), 2.76 (tc, 1H, J = 7.25, 3.70 Hz), 1.41 (t, 3H, J = 7.03 Hz), 0.74-0.81 (m, 4H), 0.64-0.72 (m, 6H), 0.51-0.59 (m, 2H).

Ejemplo 21



***N,N*-Diciclopropil-6-etil-1-metil-4-(5-(morfolin-4-carbonil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

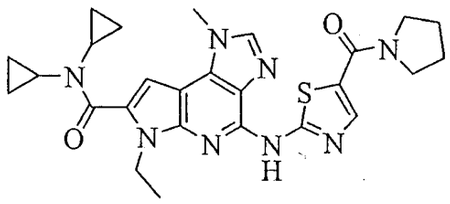
Este compuesto se preparó de acuerdo con el Ejemplo **20** usando morfolina y ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxílico (ejemplo **20A)**, proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(5-(morfolin-4-carbonil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida en forma de un sólido de color blanco.

MS (ESI) m/z 535.1 (M+H)

RMN ^{1}H (400 MHz, MeOD) δ ppm 8.08 (s, 1H), 7.79-7.93

(m, 1H), 7.26 (s, 1H), 4.74 (c, 2H, J = 7.28 Hz), 4.12 (s, 3H), 3.81-3.88 (m, 2H), 3.72-3.80 (m, 2H), 2.91-3.02 (m, 2H), 1.52 (t, 3H, J = 7.15 Hz), 0.83-0.93 (m, 4H), 0.72-0.84 (m, 4H).

Ejemplo 22



***N,N*-Diciclopropil-6-etil-1-metil-4-(5-(pirrolidin-1-carbonil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

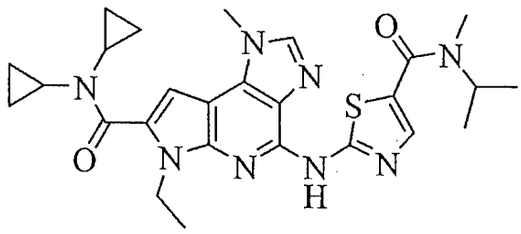
Este compuesto se preparó de acuerdo con el Ejemplo **20** usando pirrolidina y ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxílico (ejemplo **20A**), proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(5-(pirrolidin-1-carbonil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

MS (ESI) m/z 519,1. (M+H).

RMN ^{1}H (400 MHz, METANOL-d_4) δ 8.58 (s, 1H), 7.97 (s, 1H), 7.28 (s, 1H), 4.71 (c, J = 6.7 Hz, 2H), 4.20 (s, 3H), 3.87 (t, J = 6.5 Hz, 2H), 3.67 (t, J = 6.7 Hz, 2H), 2.97-3.05 (m, 2H), 2.10-2.19 (m, 2H), 1.98-2.07 (m, 2H), 1.51 (t, J = 7.2 Hz, 3H), 0.88-0.95 (m, 4H), 0.80-0.86 (m, 4H).

000280

Ejemplo 23



2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*-isopropil-*N*-metiltiazol-5-carboxamida

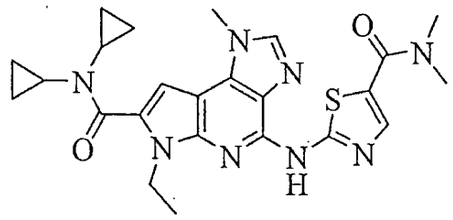
Este compuesto se preparó de acuerdo con el Ejemplo **20** usando *N*-metilpropan-2-amina y ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxílico (ejemplo **20A**), proporcionando 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*-isopropil-*N*-metiltiazol-5-carboxamida

MS (ESI) m/z 521.1 (M+H).

RMN ^{1}H (400 MHz, METANOL-d_4) δ: 8.68 (s, 1H), 7.87 (s., 1H), 7.32 (s, 1H), 4.74 (c, *J* = 7.0 Hz, 2H), 4.24 (s, 3H), 3.18 (s a, 3H), 2.99-3.06 (m, 2H), 1.53 (t, *J* = 7.0 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 6H), 0.89-0.96 (m, 4H), 0.81-0.88 (m, 4H)

C00281

Ejemplo 24



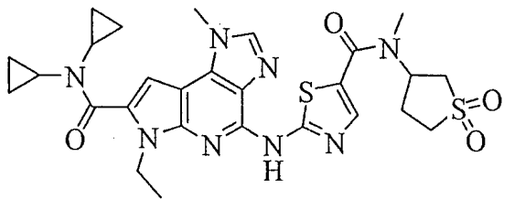
2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*-dimetiltiazol-5-carboxamida

Este compuesto se preparó de acuerdo con el Ejemplo **20** usando *N*,*N*-dimetilamina y ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)tiazol-5-carboxílico (ejemplo **20A**), dando 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*-dimetiltiazol-5-carboxamida.

MS (ESI) m/z 493.1 (M+H).

RMN ^{1}H (400 MHz, METANOL-d_4) δ: 8.56 (s, 1H), 7.91 (s, 1H), 7.31 (s, 1H), 4.72 (c, *J* = 7.0 Hz, 1H), 4.22 (s, 3H), 3.15-3.45 (br. S, 6H), 2.97-3.05 (m, 2H), 2.91 (s, 1H), 1.54 (t, *J* = 7.0 Hz, 3H), 0.88-0.95 (m, 4H), 0.80-0.86 (m, 4H).

Ejemplo 25



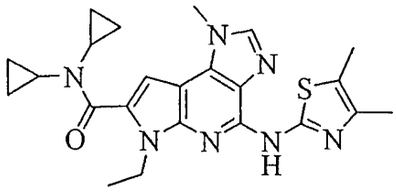
2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*-(1,1-dioxo-tetrahidrotiofen-3-il)-*N*-metiltiazol-5-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo 20.

MS (ESI) m/z 597.0 (M+H).

RMN ^{1}H (400 MHz, METANOL-d_4) δ: 8,74 (s, 1H), 7.99 (s, 1H), 7.37 (s, 1H), 5.34-5.45 (m, 1H), 4.78 (c, *J* = 6.9 Hz, 2H), 4.28 (s, 3H), 4.05 (s, 3H), 3.49-3.59 (m, 1H), 3.22-3.33 (m, 1H), 3.00-3.10 (m, 2H), 2.94 (s, 1H), 2.47-2.66 (m, 2H), 1.57 (t, *J* = 6.9 Hz, 3H), 1.34-1.45 (M, 1H), 0.91-0.99 (m, *J* = 6.5 Hz, 4H), 0.83-0.90 (m, 4H).

Ejemplo 26



***N,N*-Diciclopropil-4-(4,5-dimetiltiazol-2-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

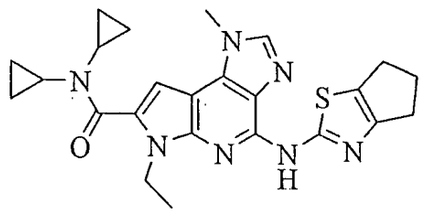
Este compuesto se preparó de acuerdo con el ejemplo

2 usando 3-bromo-2-butanona (0.034 ml, 0.323 mmol), proporcionando *N,N*-diciclopropil-4-(4,5-dimetiltiazol-2-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (59.17 mg, rendimiento del 44.3%) en forma de un sólido de color amarillo claro.

MS (ESI) m/z 450.1 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.15 (s, 1H), 7.23 (s, 1H), 4.61 (c, 2H, *J* = 7.03 Hz), 4.04 (s, 3H), 2.88-2.98 (m, 2H), 2.29 (s, 3H), 2.19 (s, 3H), 1.38 (t, 3H, *J* = 7.03 Hz), 0.73-0.80 (m, 4H), 0.62-0.71 (m, 4H).

Ejemplo 27



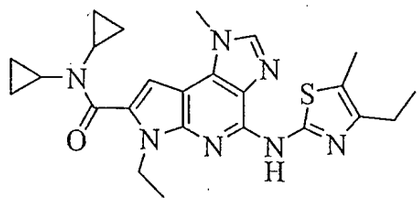
***N,N*-Diciclopropil-4-(5,6-dihidro-4H-ciclopenta[d]tiazol-2-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Se preparó usando el mismo procedimiento que el del ejemplo **2**.

MS (ESI) tr = 1.95 min, m/z 462 (M+H).

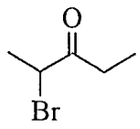
RMN ^{1}H (500 MHz, MeOD) δ ppm 8.12 (s, 1H) 7.22 (s, 1H) 4.68 (c, *J* = 7.12 Hz, 2H) 4.10 (s, 3H) 2.86-3.02 (m, 4H) 2.80 (t, *J* = 7.07 Hz, 2H) 2.43-2.61 (m, 2H) 1.46 (t, *J* = 7.07 Hz, 3H) 0.70-0.90 (m, 8H).

Ejemplo 28



***N,N*-Diciclopropil-6-etil-4-(4-etil-5-metiltiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

28A Preparación de 2-bromopentan-3-ona



Se preparó de acuerdo con el procedimiento descrito en *Chem. Comm.* **2004**, 470-471.

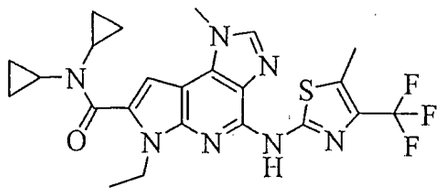
28 Preparación de *N,N*-diciclopropil-6-etil-4-(4-etil-5-metiltiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Se preparó a partir del ejemplo **26A** usando un procedimiento similar al del ejemplo **2**.

MS (ESI) m/z 464 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 8,81-9.19 (m, 1H) 7.69 (s, 1H) 6.89 (s, 1H) 4.75 (c, *J* = 7.12 Hz, 2H) 4.03 (s, 3H) 2.78-2.93 (m, 2H) 2.63 (c, *J* = 7.48 Hz, 2H) 2.37 (s, 3H) 1.53 (t, *J* = 7.04 Hz, 3H) 1.26 (t, *J* = 7.48 Hz, 3H) 0.73-0.95 (m, 8H).

Ejemplo 29



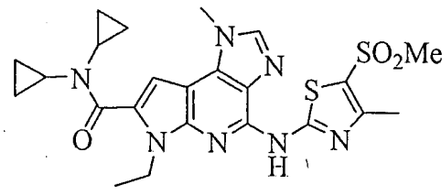
Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(5-metil-4-(trifluorometil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo 2 usando 3-bromo-1,1,1-trifluorobutan-2-ona, proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(5-metil-4-(trifluorometil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida en forma de un sólido de color blanco.

MS (ESI) m/z 504.0 (M+H)

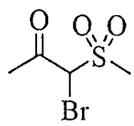
RMN ^{1}H (500 MHz, DMSO-d_6) δ ppm 8.14 (s, 1H), 7.25 (s, 1H), 4.62 (c, 2H, *J* = 6.97 Hz), 4.04 (s, 3H), 2.89-2.98 (m, 2H), 1.40 (t, 3H, *J* = 6.87 Hz), 0.73-0.80 (m, 4H), 0.65-0.71 (m, 4H).

Ejemplo 30



Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(4-metil-5-(metilsulfonil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

30A Preparación de 1-bromo-1-(metilsulfonil)propan-2-ona



A una solución de metanosulfonilacetona (0.5 g, 3.67 mmol) en AcOH (7.34 ml) y diclorometano (11.02 ml) en un matraz de fondo redondo se le añadió gota a gota bromo (0.189 ml, 3.67 mmol). La mezcla de reacción se agitó a la ta durante 90 min. El solvente se retiró al vacío. El residuo se recogió en éter y se lavó con bicarbonato sódico acuosos saturado (2 x). Los extractos orgánicos se concentraron al vacío. Se aisló 1-bromo-1-(metilsulfonil)propan-2-ona (0.332 g, rendimiento del 42%) en forma de un aceite.

EM (CI) m/z 215.0 (M+H)

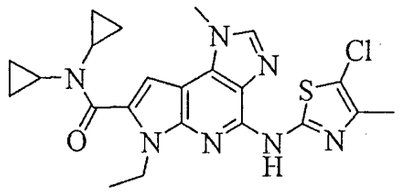
30 Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(4-metil-5-(metilsulfonil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo **1** usando 1-bromo-1-(metilsulfonil)propan-2-ona (**28A**, 32.5 mg, 0.151 mmol), proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(4-metil-5-(metilsulfonil)tiazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (12.5 mg, 0.023 mmol, rendimiento del 30.6%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 514.1 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 12.00 (s a, 1H), 8.18 (s, 1H), 7.27 (s, 1H), 4.59 (c, 2H, J = 6.78 Hz), 4.06 (s, 3H), 3.29 (s, 3H), 2.88-2.98 (m, 2H), 2.53 (s, 3H), 1.41 (t, 3H, J = 6.90 Hz), 0.72-0.81 (m, 4H), 0.62-0.71 (m, 4H).

Ejemplo 31



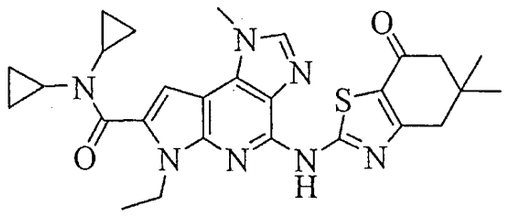
Preparación de 4-(5-cloro-4-metiltiazol-2-ilamino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo **2** usando 1,1-dicloropropan-2-ona (14.26 µl, 0.147 mmol), proporcionando 4-(5-cloro-4-metiltiazol-2-ilamino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (4.35 mg, rendimiento del 18.9%) en forma de un sólido de color verde claro.

MS (ESI) m/z 470.1 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 11.34 (s, 1H), 8.14 (s, 1H), 7.25 (s, 1H), 4.58 (c, 2H, J = 7.28 Hz), 4.04 (s, 3H), 2.88-2.98 (m, 2H), 2.25 (s, 3H), 1.40 (t, 3H, J = 6.90 Hz), 0.73-0.81 (m, 4H), 0.63-0.70 (m, 4H).

Ejemplo 32



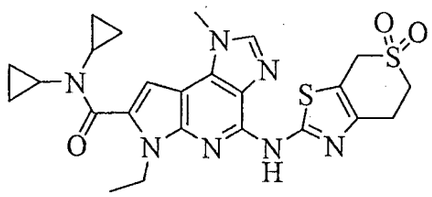
Preparación de *N,N*-diciclopropil-4-(5,5-dimetil-7-oxo-4,5,6,7-tetrahidrobenzo[d]tiazol-2-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo **2** usando 2-cloro-5,5-dimetilciclohexano-1,3-diona (34.9 mg, 0.200 mmol), proporcionando *N,N*-diciclopropil-4-(5,5-dimetil-7-oxo-4,5,6,7-tetrahidrobenzo[d]tiazol-2-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (11.24 mg, rendimiento del 21.7%) en forma de un sólido de color amarillo claro.

MS (ESI) m/z 518.2 (M+H)

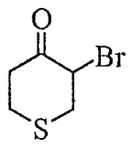
RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 11.93 (s, 1H), 8.19 (s, 1H), 7.28 (s, 1H), 4.62 (c, 2H), 4.06 (s, 3H), 2.89-2.98 (m, 2H), 2.80 (s, 2H), 2.40 (s, 2H), 1.41 (t, 3H, *J* = 7.03 Hz), 1.09 (s, 6H), 0.73-0.80 (m, 4H), 0.63-0.71 (m, 4H).

Ejemplo 33



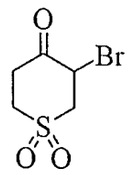
Preparación de diciclopropilamida del ácido 4-(5,5-dioxo-4,5,6,7-tetrahidro-5λ⁶-tiopirano[4,3-d]tiazol-2-ilamino)-6-etil-1-metil-1,6-dihidro-1,3,5,6-tetraaza-as-indaceno-7-carboxilico

33A Preparación de 3-bromodihidro-2*H*-tiopiran-4(3*H*)-ona



A una mezcla de tetrahidrotiopiran-4-ona (0.5 g, 4.30 mmol) en diclorometano (51.2 ml) y metanol (20.49 ml) se le añadió tribromuro de *tetra-n*-butilamonio (2.283 g, 4.73 mmol). La mezcla de reacción se agitó a la ta durante 2.5 h. El solvente se retiró al vacío. El producto en bruto se trituró con éter (3 x). Las fases de éter combinadas se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron al vacío. El producto se aisló en forma de un aceite de color naranja claro. El material se usó inmediatamente en la siguiente reacción.

33B Preparación de 3-bromo-1,1-dioxo-tetrahidro-1λ^6-tiopiran-4-ona



A una solución enfriada (0°C) de 3-bromodihidro-2*H*-tiopiran-4(3*H*)-ona (ejemplo **33A**, 0.791 g, 4.05 mmol) en diclorometano (20.27 ml) se le añadió lentamente mCPBA (1.749 g, 10.14 mmol). La mezcla de reacción se dejó calentar a la temperatura ambiente. La mezcla de reacción se inactivó con bicarbonato sódico acuoso saturado. La fase acuosa se extrajo con diclorometano (2 x). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron al vacío, proporcionando 3-bromo-1,1-dioxo-tetrahidro-1λ^6-tiopiran-4-ona en forma de un sólido de color blanco que se usó inmediatamente en la siguiente reacción.

33 Preparación de diciclopropilamida del ácido 4-(5,5-dioxo-4,5,6,7-tetrahidro-5λ^6-tiopirano[4,3-d]tiazol-2-ilamino)-6-etil-1-metil-1,6-dihidro-1,3,5,6-tetraaza-as-indaceno-7-carboxílico

Este compuesto se preparó de acuerdo con el ejemplo **1** usando 3-bromo-1,1-dioxo-tetrahidro-λ^6-tiopiran-4-ona (ejemplo **33B**, 32.5 mg, 0.151 mmol), proporcionando diciclopropilamida del ácido 4-(5,5-dioxo-4,5,6,7-tetrahidro-

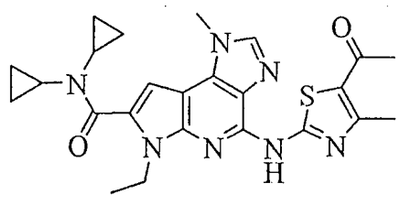
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5λ^6-tiopirano[4,3-d]tiazol-2-ilamino)-6-etil-1-metil-1,6-dihidro-1,3,5,6-tetraaza-as-indaceno-7-carboxílico (9 mg, rendimiento del 17.56%) en forma de un sólido de color castaño claro.

MS (ESI) m/z 526.2 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.16 (s, 1H), 7.25 (s, 1H), 4.61 (c, 2H, *J* = 6.78 Hz), 4.54 (s, 2H), 4.04 (s, 3H), 3.49, (7, 2H, *J* = 6.02 Hz), 3.16 (t, 2H, *J* = 8.16 Hz), 2.89-2.97 (m, 2H), 1.38 (t, 3H, *J* = 7.03 Hz), 0.73-0.79 (m, 4H), 0.61-0.70 (m, 4H)

Ejemplo 34



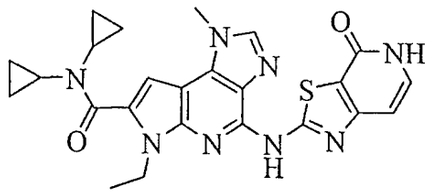
Preparación de 4-(5-acetil-4-metiltiazol-2-ilamino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo **2** usando 3-cloro-2,4-pentanodiona (36.0 µl, 0.302 mmol), proporcionando 4-(5-acetil-4-metiltiazol-2-ilamino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (76 mg, rendimiento del 100%) en forma de un sólido de color amarillo claro.

MS (ESI) m/z 478.2 (M+H)

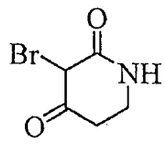
RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.31 (s, 1H), 7.28 (s, 1H), 4.62 (c, 2H, *J* = 6.94 Hz), 4.08 (s, 3H), 2.89-2.99 (m, 2H), 2.61 (s, 3H), 1.44 (t, 3H, *J* = 7.03 Hz), 0.72-0.81 (m, 4H), 0.64-0.72 (m, 4H).

Ejemplo 35



Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(4-oxo-4,5-dihidrotiazolo[5,4-c]piridin-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

35A Preparación de 3-bromopiperidin-2,4-diona



A una mezcla de piperidin-2,4-diona (0.072 g, 0.637 mmol) en ácido acético (1.591 ml) se le añadió gota a gota bromo (0.033 ml, 0.637 mmol). La mezcla de reacción se agitó a la ta 70 min. Se añadió diclorometano y la mezcla turbia se concentró al vacío. La solución residual se trató con éter etílico. Se formó un sólido de color blanco y el AcOH/éter se decantó. El sólido blanco, que se supone que era el producto, se llevó a la siguiente etapa. El sólido de color blanco empezó a hacerse líquido y a volverse rojo rápidamente después de su exposición a la luz y del reposo.

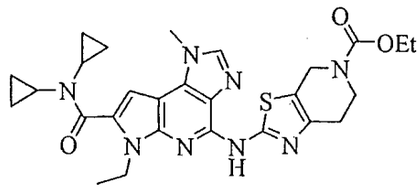
35 Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(4-oxo-4,5-dihidrotiazolo[5,4-c]piridin-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo **2** usando 3-bromopiperidin-2,4-diona (ejemplo **35A**), proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(4-oxo-4,5-dihidrotiazolo[5,4-c]piridin-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (4.51 mg, rendimiento del 12.3%) en forma de un sólido de color blanco que contenía *N,N*-diciclopropil-6-etil-1-metil-4-(4-oxo-4,5,6,7-tetrahidrotiazolo[5,4-c]piridin-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida al 10%.

MS (ESI) m/z 489.1 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.20 (s, 1H), 7.32-7.47 (m, 1H), 7.29 (s, 1H), 6.62 (d, 1H, *J* = 7.03 Hz), 4.66 (c, 2H, *J* = 7.19 Hz), 4.07 (s, 3H), 2.88-3.06 (m, 2H), 1.44 (t, 3H, *J* = 7.03 Hz), 0.72-0.85 (m, 4H), 0.60-0.72 (m, 4H).

Ejemplo 36



Preparación de 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-6,7-dihidrotiazolo[5,4-c]piridin-5(4*H*)-carboxilato de etilo

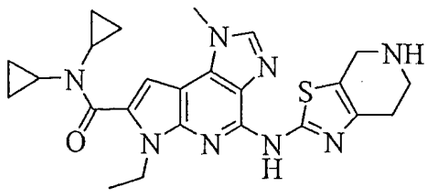
Este compuesto se preparó de acuerdo con el ejemplo

2 usando éster etílico del ácido 3-bromo-4-oxo-piperidin-1-carboxílico, proporcionando 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-6,7-dihidrotiazolo[5,4-c]piridin-5(4*H*)-carboxilato de etilo (5 mg, rendimiento del 15.36%) en forma de un sólido de color blanco.

MS (ESI) m/z 549.2 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 10.83 (s a, 1H), 8.12 (s, 1H), 7.23 (s, 1H), 4.56-4.67 (m, 4H), 4.10 (c, 2H, *J* = 7.19 Hz), 4.04 (s, 3H), 3.72 (t, 2H, *J* = 5.52 Hz), 2.87-2.98 (m, 2H), 2.64-2.73 (m, 2H), 1.38 (t, 3H, *J* = 7.03 Hz), 1.22 (t, 3H, *J* = 7.15 Hz), 0.71-0.81 (m, 4H), 0.60-0.71 (m, 4H).

Ejemplo 37



Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(4,5,6,7-tetrahidrotiazolo[5,4-c]piridin-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo 2 usando 3-bromopiperidin-4-ona, bromhidrato (33.8 mg, 0.130 mmol), proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(4,5,6,7-tetrahidrotiazolo[5,4-c]piridin-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (30 mg, rendimiento del 60%)

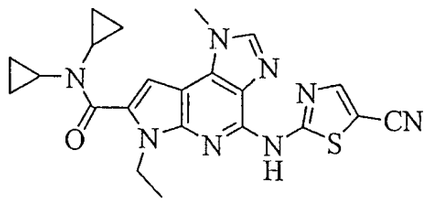
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en forma de un sólido de color amarillo claro.

MS (ESI) m/z 477.3 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 9.08 (s a, 2H), 8.25 (s, 1H), 7.27 (s, 1H), 4.63 (c, 2H, *J* = 6.78 Hz), 4.38 (s a, 2H), 4.06 (s, 3H), 2.85-2.98 (m, 4H), 1.38 (t, 3H, *J* = 7.03 Hz), 0.73-0.81 (m, 4H), 0.62-0.71 (m, 4H).

Ejemplo 38



4-(5-cianotiazol-2-ilamino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

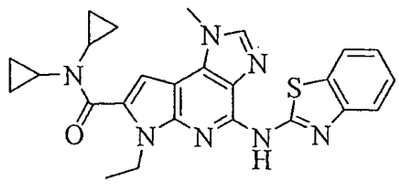
A una mezcla de 4-amino-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 60 mg, 0.177 mmol), 2-clorotiazol-5-carbonitrilo (38.5 mg, 0.266 mmol), Pd2(dba)3 (24.4 mg, 0.027 mmol), BINAP (49.7 mg, 0.080 mmol) y *terc*-butóxido sódico (27.3 mg, 0.284 mmol) se le añadió DME (1 ml). La mezcla se purgó con gas argón durante 5 min y se calentó a 85°C durante 3 h. La mezcla de reacción mostró una conversión de ~60% mediante HPLC, se filtró a través de un lecho de Celite y se concentró. El producto en bruto se purificó por HPLC preparativa, proporcionando 4-(5-cianotiazol-2-ilamino)-*N*,*N*-

diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida en forma de un sólido de color blanquecino.

MS (ESI) m/z 447.2 (M+H).

RMN ^{1}H (500 MHz, CD3OD-$CDCl_3$) δ: 8.60 (s, 1H), 8.04 (s, 1H), 7.56 (s, 4H), 7.13 (s, 1H), 4.71 (c, *J* = 7.1 Hz, 2H), 4.20 (s, 3H), 2.84-2.91 (m, 2H), 1.52 (t, *J* = 7.1 Hz, 3H), 0.83-0.90 (m, 5H), 0.74-0.80 (m, 4H).

Ejemplo 39



4-(benzo[d]tiazol-2-ilamino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

A una solución de 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 21.2 mg, 0.063 mmol) en DMF (626 µl) se le añadió en una porción hidruro sódico (10.02 mg, 0.251 mmol). Después de 20 min, se añadió 2-bromo-1,3-benzotiazol (53.6 mg, 0.251 mmol). La mezcla de reacción se agitó a la temperatura ambiente durante 16 h. La mezcla de reacción se inactivó con agua y se diluyó con acetato de etilo. La fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos combinados se lavaron con LiCl. al 10%, se secaron sobre sulfato sódico anhidro, se filtraron y se

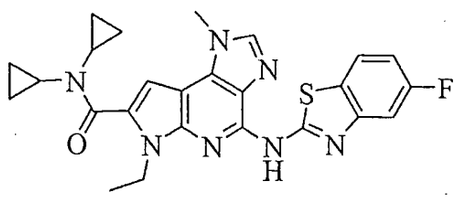
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concentraron al vacío. El residuo en bruto se purificó por cromatografía ultrarrápida usando una columna Isco de 4 g eluyendo con MeOH al 0-5%/CH_2Cl_2, produciendo 4-(benzo[d]tiazol-2-ilamino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (6.8 mg, rendimiento del 21.87%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 472.2 (M+H)

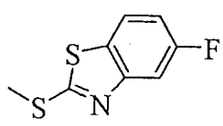
RMN ^{1}H (500 MHz, DMSO-d6) δ ppm 8.17 (s, 1H), 7.95 (d, 1H, *J* = 7.97 Hz), 7.67 (d, 1H, *J* = 8.25 Hz), 7.39 (t, 1H, *J* = 7.97 Hz), 7.27 (s, 1H), 7.22 (t, 1H, *J* = 8.52 Hz), 4.70 (c, 2H, *J* = 7.06 Hz), 4.06 (s, 3H), 2.88-2.99 (m, 2H), 1.65 (s a, 1H), 1.45 (t, 3H, *J* = 7.01 Hz), 0.74-0.84 (m, 4H), 0.64-0.73 (m, 4H).

Ejemplo 40



Preparación de *N*,*N*-diciclopropil-6-etil-4-(5-fluorobenzo[d]tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

40A Preparación de 5-fluoro-2-(metiltio)benzo[d]tiazol



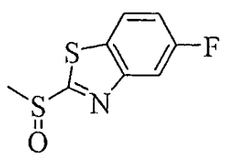
A una solución de 5-fluoro-2-mercaptobenzotiazol

(0.15 g, 0.810 mmol) en THF (8.10 ml) enfriada a 0°C se le añadió hidruro sódico (0.036 g, 0.891 mmol). Después de agitar 10 min, se añadió yodometano (0.076 ml, 1.215 mmol) y la mezcla de reacción se calentó lentamente a la temperatura ambiente durante 2 h. La reacción se diluyó con acetato de etilo y se interrumpió con bicarbonato sódico acuoso saturado. La fase orgánica se lavó con salmuera, se secó sobre sulfato sódico anhidro, se filtró y se concentró al vacío. Se aisló 5-fluoro-2-(metiltio)benzo[d]tiazol (0.178 g, rendimiento del 110%) en forma de un sólido de color blanco. El material se usó sin ninguna purificación adicional.

MS (ESI) m/z 200.0 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.68 (dd, 1H, *J* = 8.81, 5.04 Hz), 7.56 (dd, 1H, *J* = 9.57, 2.52 Hz), 7.07 (td, 1H, *J* = 8.81, 2.52 Hz), 2.80 (s, 3H)

40B Preparación de 5-fluoro-2-(metilsulfinil)benzo[d]tiazol



Se disolvió 5-fluoro-2-(metiltio)benzo[d]tiazol (ejemplo **40A**, 0.178 g, 0.893 mmol) en CH_2Cl_2 (5.96 ml). Se añadió en una porción mCPBA (0.154 g, 0.893 mmol) y la mezcla de reacción se agitó a la temperatura ambiente. La reacción se interrumpió con bicarbonato sódico acuoso

saturado y se diluyó con diclorometano. La fase acuosa se extrajo con diclorometano (2 x). El extracto orgánico combinado se lavó con salmuera, se secó sobre sulfato de magnesio anhidro, se filtró y se concentró al vacío. Se aisló 5-fluoro-2-(metilsulfinil)benzo[d]tiazol (0.180 g, rendimiento del 94%) en forma de un sólido de color blanco y se usó sin purificación adicional.

MS (ESI) m/z 216.0 (M+H)

RMN ^{1}H (500 MHz, CLOROFORMO-d) δ ppm 7.97 (dd, 1H, *J* = 9.07, 4.95 Hz), 7.76 (dd, 1H, *J* = 9.07, 2.47 Hz), 7.27-7.34 (m, 1H), 3.10 (s, 3H)

40 Preparación de *N,N*-diciclopropil-6-etil-4-(5-fluorobenzo[d]tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

A una solución de 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 50 mg, 0.148 mmol) en DMF (1.5 ml) se le añadió hidruro sódico (17.73 mg, 0.443 mmol). Después de 20 min, se añadió en una porción 5-fluoro-2-(metilsulfinil)benzo[d]tiazol (ejemplo **40B**, 95 mg, 0.443 mmol). La mezcla de reacción se agitó a la temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo y se inactivó con agua. La fase acuosa se extrajo con acetato de etilo (2 x). Las fases orgánicas combinadas se lavaron con solución de cloruro

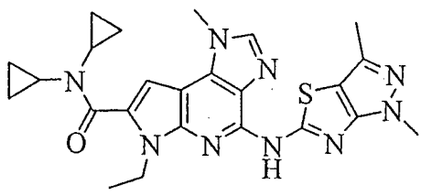
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de litio al 10% (2 x), se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. El residuo en bruto se purificó por cromatografía ultrarrápida usando una columna Isco de 12 g eluyendo con MeOH al 0-5%/CH_2Cl_2, proporcionando *N,N*-diciclopropil-6-etil-4-(5-fluorobenzo[d]tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (13 mg, rendimiento al 17.07%).

EM (CI) m/z 490.2 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 11.53 (s a, 1H), 8.19 (s, 1H), 7.95-8.02 (m, 1H), 7.47 (d, 1H, *J* = 9.82 Hz), 7.28 (s, 1H), 7.09 (t, 1H, *J* = 8.18 Hz), 4.69 (c, 2H, *J* = 7.13 Hz), 4.06 (s, 3H), 2.89-3.02 (m, 2H), 1.45 (t, 3H, *J* = 7.05 Hz), 0.74-0.81 (m, 4H), 0.63-0.71 (m, 4H).

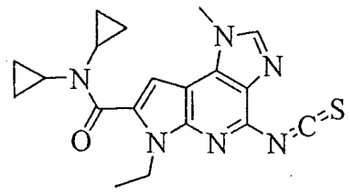
Ejemplo 41



Preparación de *N,N*-diciclopropil-4-(1,3-dimetil-1*H*-pirazolo[3,4-d]tiazol-5-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

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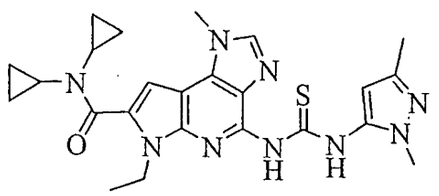
41A Preparación de *N,N*-diciclopropil-6-etil-4-isotiocianato-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



A una mezcla de 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (194.5 mg, 0.575 mmol) en diclorometano (2874 µl) en un matraz de fondo redondo en una atmósfera de nitrógeno se le añadió 1,1'-tiocarbonildi-2(1H)-piridona (133 mg, 0.575 mmol). La mezcla de reacción se agitó a la temperatura ambiente durante 16 h. La mezcla de reacción se concentró a presión reducida. Se aisló *N,N*-diciclopropil-6-etil-4-isotiocianato-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida en forma de un sólido pegajoso de color amarillo. El material se usó tal cual en las reacciones posteriores.

MS (ESI) m/z 381.1 (M+H)

41B Preparación de *N,N*-diciclopropil-4-(3-(1,3-dimetil-1*H*-pirazol-5-il)tioureido)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



A un matraz cargado con *N,N*-diciclopropil-6-etil-4-

000302

isotiocianato-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **41A**, 0.0342 g, 0.090 mmol) se le añadió THF (0.449 ml). Se añadió 5-amino-1,3-dimetilpirazol (0.012 g, 0.108 mmol) seguido de hidruro sódico (3.60 mg, 0.090 mmol). La mezcla de reacción se agitó a la temperatura ambiente durante 16 h. La mezcla de reacción se diluyó con acetato de etilo y se inactivó con bicarbonato sódico acuoso saturado. La fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos combinados se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. El material en bruto se usó sin purificación adicional.

MS (ESI) m/z 492.2 (M+H)

41 Preparación de *N,N*-diciclopropil-4-(1,3-dimetil-1*H*-pirazolo[3,4-d]tiazol-5-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Se disolvió *N,N*-diciclopropil-4-(3-(1,3-dimetil-1*H*-pirazol-5-il)tioureido)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **41B**, 41 mg, 0.083 mmol) en cloroformo (2780 µl) y se enfrió a 0°C. Se añadió lentamente NIS (18.76 mg, 0.083 mmol) y la reacción se calentó a la temperatura ambiente. La mezcla de reacción se concentró. Se añadieron metanol y éter y la mezcla se filtró. Después de un periodo de reposo de una semana, el producto precipitó de la solución. El producto se

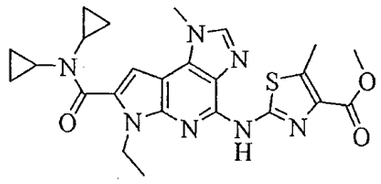
000303

trituró con metanol. Se aisló *N,N*-diciclopropil-4-(1,3-dimetil-1*H*-pirazolo[3,4-d]tiazol-5-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida en forma de un sólido de color amarillo claro (8.1 mg, rendimiento del 20%).

MS (ESI) m/z 490.3 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 11.39 (s, 1H), 8.17 (s, 1H), 7.26 (s, 1H), 4.66 (c, 2H, *J* = 7.03 Hz), 4.05 (s, 3H), 3.85 (s, 3H) 2.88-3.00 (m, 2H), 2.33 (s, 3H), 1.43 (t, 3H, *J* = 7.03 Hz), 0.72-0.82 (m, 4H), 0.61-0.73 (m, 4H).

Ejemplo 42



2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-5-metiltiazol-4-carboxilato de metilo

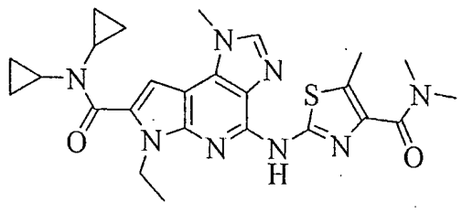
Se añadió 3-bromo-2-oxobutanoato de metilo (320 mg, 1.642 mmol) a una suspensión de *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **2B**, 435 mg, 1.094 mmol) en EtOH (10 ml) y la mezcla de reacción se calentó a 65°C durante 2 h. El solvente se retiró al vacío y el residuo se purificó por cromatografía sobre gel de sílice (MeOH al 2-10%/diclorometano), dando 2-(7-(diciclopropilcarbamoil)-6-

etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-5-metiltiazol-4-carboxilato de metilo (380 mg, rendimiento del 70%) en forma de un sólido de color amarillo.

MS (ESI) tr = 0.87 min, m/z 494 (M+H)

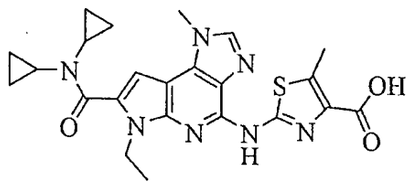
RMN ^{1}H (CLOROFORMO-d) δ: 9.41 (s a, 1H), 7.78 (s, 1H), 6.89 (s, 1H), 4.73 (c, *J* = 7.0 Hz, 2H), 4.03 (s, 3H), 3.95 (s, 3H), 2.80-2.87 (m, 2H), 2.77 (s, 3H), 1.54 (t, *J* = 7.0 Hz, 3H), 0.83-0.90 (m, 4H), 0.73-0.80 (m, 4H).

Ejemplo 43



2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*,5-trimetiltiazol-4-carboxamida

43A Preparación de ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-5-metiltiazol-4-carboxílico



Se añadió NaOH acuoso 1 N (0.962 ml, 0.962 mmol) a

una suspensión de 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-5-metiltiazol-4-carboxilato de metilo (ejemplo **41**, 0.19 g, 0.385 mmol) en etanol (2 ml) y la mezcla se calentó a 60°C durante 2 h. La reacción se enfrió a la temperatura ambiente y se acidificó con HCl 1 N hasta alcanzar un valor de pH de 4. La mezcla de reacción se concentró y el residuo se trituró 5 veces con metanol. Los lavados de metanol combinados se concentraron y el sólido restante se lavó 3 veces con 2:1 de éter/diclorometano y proporcionó ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-5-metiltiazol-4-carboxílico (105 mg, rendimiento del 57%).

MS (ESI) tr = 0.79 min, m/z 480 (M+H)

43 Preparación de 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*,5-trimetiltiazol-4-carboxamida

Una mezcla de ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-5-metiltiazol-4-carboxílico (**43A**, 30 mg, 0.063 mmol), dimetilamina acuosa al 40% (0.016 ml, 0.125 mmol) y HATU (35.7 mg, 0.094 mmol) en DMF (1 ml) se agitó a la temperatura ambiente durante 3 h. El solvente se evaporó y el residuo se purificó por cromatografía sobre gel de sílice (MeOH al 2-10%/diclorometano). El material se purificó

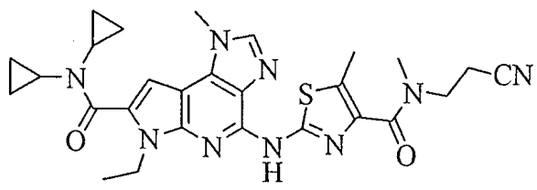
adicionalmente por HPLC preparativa, dando 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*,5-trimetiltiazol-4-carboxamida (20 mg , rendimiento del 62.5%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 507 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ: 7.79 (s, 1H), 6.90 (s, 1H), 4.73 (c, *J* = 7.0 Hz, 2H), 4.05 (s, 3H), 3.12 (s., 3H), 3.11 (s, 3H), 2.80-2.87 (m, 2H), 2.53 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H), 0.83-0.91 (m, 4H), 0.74-0.80 (m, 4H)

Los Ejemplos **44-49** se prepararon usando el mismo protocolo que se ha descrito para el ejemplo **42**

Ejemplo 44

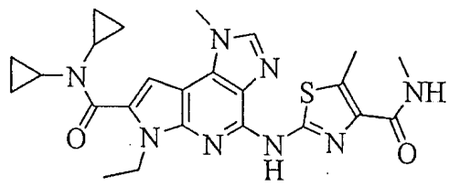


N-(2-Cianoetil)-2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-N,5-dimetiltiazol-4-carboxamida

MS (ESI) m/z 546 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 9.34 (s a, 1H) 7.75 (d, *J* = 5.94 Hz, 1H) 6.90 (s, 1H) 4.74 (c, *J* = 7.04 Hz, 2H) 4.06 (s, 3H) 3.80 (t, *J* = 6.71 Hz, 2H) 3.11-3.32 (m, 3H) 2.95 (t, *J* = 6.71 Hz, 2H) 2.78-2.91 (m, 2H) 2.58 (d, *J* = 15.85 Hz, 3H) 1.54 (t, *J* = 7.04 Hz, 3H) 0.70-0.94 (m, 8H).

Ejemplo 45

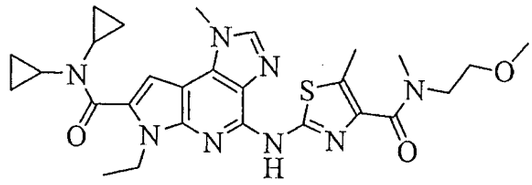


2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,5-dimetiltiazol-4-carboxamida

MS (ESI) m/z 493 (M+H).

RMN ^{1}H (500 MHz, CLOROFORMO-d) δ ppm 7.84 (s, 1H) 7.40 (d, *J* = 4.99 Hz, 1H) 6.90 (s, 1H) 4.73 (c, *J* = 6.94 Hz, 2H) 4.08 (s, 3H) 2.99 (d, *J* = 4.99 Hz, 3H) 2.73-2.91 (m, 5 H) 2.14 (s, 1H) 1.53 (t, *J* = 7.07 Hz, 3H) 0.66-0.97 (m, 8H).

Ejemplo 46



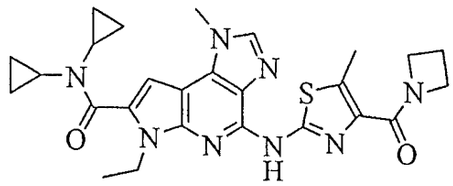
2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*-(2-metoxietil)-*N*,5-dimetiltiazol-4-carboxamida

MS (ESI) m/z 551 (M+H).

RMN ^{1}H (500 MHz, CLOROFORMO-d) δ ppm 7.73 (d, *J* = 3.05 Hz, 1H) 6.90 (s, 1H) 4.74 (c, *J* = 7.21 Hz, 2H) 4.05 (s, 3H) 3.72 (dd, *J* = 13.73, 4.58 Hz, 2H) 3.61-3.68 (m, 1H) 3.57 (t, *J* = 5.41 Hz, 1H) 3.27-3.45 (m, 3H) 3.17 (d, *J* = 8.32 Hz, 3H) 2.79-2.88 (m, 2H) 2.54 (d, *J* = 5.83 Hz, 3H) 1.54 (t, *J* =

7.07 Hz, 3H) 0.73-0.92 (m, 8H).

Ejemplo 47

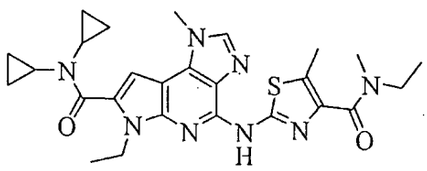


4-(4-(Azetidin-1-carbonil)-5-metiltiazol-2-ilamino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

MS (ESI) m/z 519 (M+H).

RMN ^{1}H (500 MHz, CLOROFORMO-d) δ ppm 8.50-9.65 (m, 1H) 8.00 (s, 1H) 6.88 (s, 1H) 4.68 (c, *J* = 7.21 Hz, 2H) 4.59 (t, *J* = 7.63 Hz, 2H) 4.18 (t, *J* = 7.77 Hz, 2H) 4.09 (s, 3H) 2.78-2.89 (m, 2H) 2.72 (s, 3H) 2.30 (quint., *J* = 7.70 Hz, 2H) 1.49 (t, *J* = 7.07 Hz, 3H) 0.72-0.92 (m, 8H).

Ejemplo 48



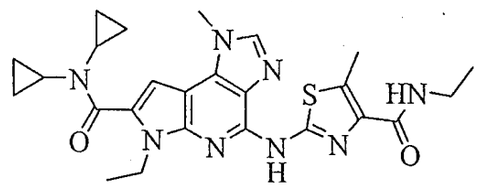
2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*-etil-*N*,5-dimetiltiazol-4-carboxamida

MS (ESI) m/z 521 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.77 (s, 1H) 6.89 (s, 1H) 4.74 (c, *J* = 7.04 Hz, 2H) 4.04 (s, 3H) 3.36-3.66 (m, 2H) 3.07 (d, *J* = 14.09 Hz, 3H) 2.72-2.90 (m, 2H) 2.51 (s,

3H) 2.11 (s, 1H) 1.54 (t, *J* = 7.04 Hz, 3H) 1.13-1.35 (m, 3H) 0.66-0.90 (m, 8H).

Ejemplo 49

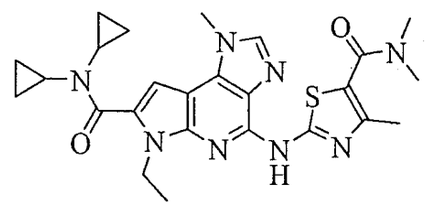


2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*-etil-5-metiltiazol-4-carboxamida

MS (ESI) m/z 508 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.78 (s, 1H) 6.89 (s, 1H) 4.73 (c, *J* = 7.04 Hz, 2H) 4.42 (c, *J* = 7.12 Hz, 2H) 4.04 (s, 3H) 2.78-2.91 (m, 2H) 2.75 (s, 3H) 2.15 (s, 1H) 1.54 (t, *J* = 7.04 Hz, 3H) 1.44 (t, *J* = 7.04 Hz, 3H) 0.68-0.91 (m, 8H).

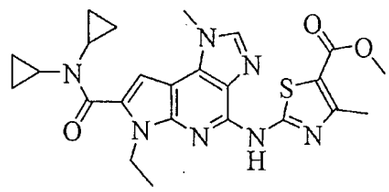
Ejemplo 50



2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*,4-trimetiltiazol-5-carboxamida

000310

50A Preparación de 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-metiltiazol-5-carboxilato metilo

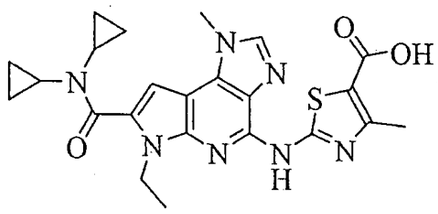


Se añadió 2-bromo-3-oxobutanoato de metilo (213 mg, 1.094 mmol, preparado siguiendo el procedimiento descrito por Abu T. Khan et al., en *Tetrahedron Letters* **2006**, *47*, 2751-2754) a una suspensión de *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **2B**, 290 mg, 0.730 mmol) en etanol (5 ml) y la mezcla de reacción se calentó a 65°C durante 2 h. El análisis por LC/MS mostró que se había completado la reacción (la reacción se mantuvo en forma de suspensión todo el tiempo). La mezcla de reacción se concentró para retirar el etanol y se recogió en diclorometano. La solución se lavó con bicarbonato sódico saturado y la fase acuosa se extrajo de nuevo con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron al vacío. El producto en bruto se purificó por cromatografía ultrarrápida usando un sistema ISCO automatizado (columna de 40 g, eluyendo con metanol al 0-5%/diclorometano), proporcionando 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-metiltiazol-5-carboxilato de metilo (301 mg, 0.610 mmol, rendimiento del 84%) en forma de un sólido de color blanco.

MS (ESI) m/z 494.4 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ: 7.75 (s, 1H), 6.92 (s, 1H), 4.76 (c, *J* = 7.0 Hz, 2H), 4.08 (s, 3H), 3.92 (s, 3H), 2.82-2.89 (m, 2H), 2.71 (s, 3H), 1.59 (t, *J* = 7.0 Hz, 3H), 0.85-0.93 (m, 4H), 0.75-0.82 (m, 4H).

50B Preparación de ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-metiltiazol-5-carboxílico



Una mezcla de 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-metiltiazol-5-carboxilato de metilo (ejemplo **50A**, 288 mg, 0.583 mmol) y NaOH 1 N (5.83 ml, 5.830 mmol) en metanol (5 ml) se calentó a 65°C durante 18 h. El metanol se evaporó metanol y la solución acuosa se acidificó hasta alcanzar un valor de pH de 4 con HCl 1 N, precipitaron sólidos de la solución y se retuvieron después de la filtración, proporcionando el ácido deseado en forma pura. Después, la mezcla acuosa se extrajo con diclorometano. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto se purificó por cromatografía ultrarrápida usando un sistema ISCO automatizado (columna de 40 g, eluyendo con metanol al 0-8%/diclorometano). Se obtuvieron un total de 260 mg de ácido 2-(7-

(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-metiltiazol-5-carboxílico (rendimiento del 93%) en forma de un sólido de color amarillo.

MS (ESI) m/z 480.2 (M+H).

RMN ^{1}H (500 MHz, DMSO-d_6) δ: 8.03 (s a, 1H), 7.06 (s, 1H), 4.40 (c, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 2.96 (s, 1H), 2.69-2.76 (m, 2H), 2.36 (s, 3H), 1.20 (t, *J* = 6.9 Hz, 3H), 0.56 (d, *J* = 5.5 Hz, 4H), 0.45-0.50 (m, 4H).

50 Preparación de 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*,4-trimetiltiazol-5-carboxamida

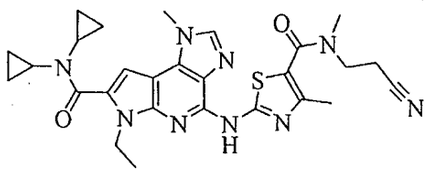
Una mezcla de ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-metiltiazol-5-carboxílico (ejemplo **50B**, 51 mg, 0.106 mmol), dimetilamina (al 40% en agua, 0.027 ml, 0.213 mmol), HATU (52.6 mg, 0.138 mmol) y 2,6-lutidina (0.025 ml, 0.213 mmol) en DMF (1 ml) se agitó a la temperatura ambiente durante 2 h. El solvente se evaporó y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO automatizado (columna de 24 g, eluyendo con metanol al 2-8%/diclorometano). El producto se purificó adicionalmente por HPLC preparativa. Se obtuvo 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,*N*,4-trimetiltiazol-5-carboxamida (17 mg, 0.032 mmol, rendimiento del 30.0%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 507.1 (M+H).

RMN ^{1}H (400 MHz, METANOL-d_4) δ: 8.75 (s, 1H), 7.27 (s, 1H), 4.66 (c, J = 7.0 Hz, 2H), 4.21 (s, 3H), 3.19 (s, 6H), 2.95-3.02 (m, 2H), 2.39 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H), 0.86-0.93 (m, 4H), 0.78-0.84 (m, 4H)

Los Ejemplos **51-55** se sintetizaron usando el mismo procedimiento que se ha usado para el 5**0**.

Ejemplo 51

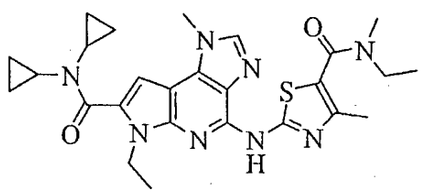


***N*-(2-Cianoetil)-2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,4-dimetiltiazol-5-carboxamida**

MS (ESI) m/z 546.1 (M+H).

RMN ^{1}H ($CDCl_3$) δ: 7.77 (s, 1H), 6.89 (s, 1H), 4.71 (c, J = 6.9 Hz, 2H), 4.05 (s, 3H), 3.81 (t, J = 6.6 Hz, 2H), 3.31 (s, 3H), 2.78-2.86 (m, 4H), 2.44 (s, 3H), 1.53 (t, J = 7.0 Hz, 3H), 0.83-0.90 (m, 4H), 0.73-0.79 (m, 4H).

Ejemplo 52



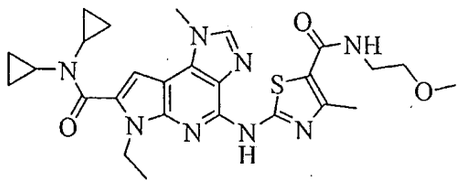
2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-

dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*-etil-*N*,4-dimetiltiazol-5-carboxamida

MS (ESI) m/z 521.1 (M+H).

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 7.74 (s, 1H), 6.88 (s, 1H), 4.72 (c, J = 7.0 Hz, 2H), 4.04 (s, 3H), 3.57 (c, J = 7.2 Hz, 2H), 3.11 (s, 3H), 2.79-2.86 (m, 2H), 2.40 (s, 3H), 1.51 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 0.82-0.90 (m, 4H), 0.73-0.79 (m, 4H).

Ejemplo 53

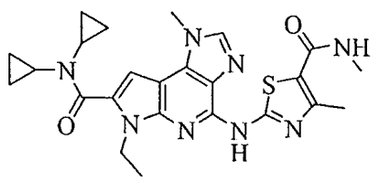


2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*-(2-metoxietil)-4-metiltiazol-5-carboxamida

MS (ESI) m/z 537.1 (M+H).

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 7.74 (s, 1H), 6.89 (s, 1H), 6.13 (t, J = 4.7 Hz, 1H), 4.74 (c, J = 7.0 Hz, 2H), 4.05 (s, 3H), 3.65 (c, J = 5.1 Hz, 2H), 3.58 (t, J = 4.8 Hz, 2H), 3.42 (s, 3H), 2.79-2.87 (m, 2H), 2.65 (s, 3H), 1.58 (t, J = 7.0 Hz, 3H), 0.83-0.90 (m, 4H), 0.73-0.80 (m, 4H).

Ejemplo 54



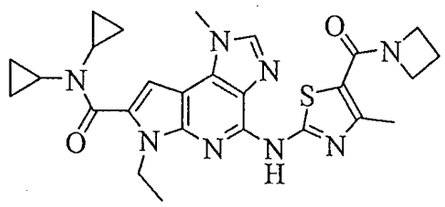
2-(7-(Diciclopropilcarbamoil)-6-etil-1-metil-1,6-

dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-*N*,4-dimetiltiazol-5-carboxamida

MS (ESI) m/z 493.1 (M+H).

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 7.77 (s, 1H), 6.86 (s, 1H), 5.87-5.94 (m, *J* = 4.6 Hz, 1H), 4.66 (c, *J* = 7.1 Hz, 2H), 4.04 (s, 3H), 3.04 (d, *J* = 4.6 Hz, 3H), 2.79-2.87 (m, 2H), 2.62 (s, 3H), 1.51 (t, *J* = 7.0 Hz, 3H), 0.83-0.90 (m, 4H), 0.73-0.80 (m, 4H).

Ejemplo 55

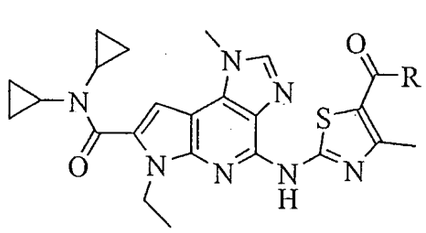


4-(5-(Azetidin-1-carbonil)-4-metiltiazol-2-ilamino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

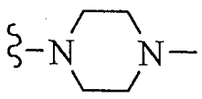
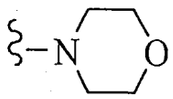
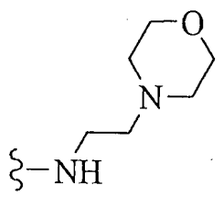
MS (ESI) m/z 519.1 (M+H).

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 7.73 (s, 1H), 6.90 (s, 1H), 4.73 (c, *J* = 7.0 Hz, 2H), 4.33 (s a, 4H), 4.05 (s, 3H), 2.80-2.87 (m, 2H), 2.66 (s, 3H), 2.33-2.43 (m, 2H), 1.55 (t, *J* = 7.2 Hz, 3H), 0.83-0.90 (m, 4H), 0.73-0.80 (m, 4H).

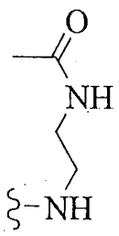
Los Ejemplos **56-70** se sintetizaron usando el mismo procedimiento que se ha usado para **50**.

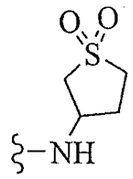
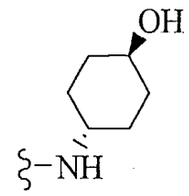
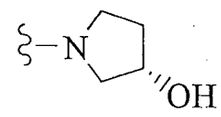


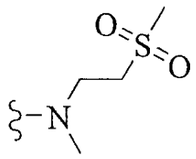
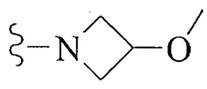
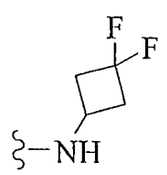
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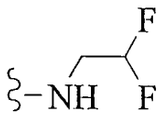
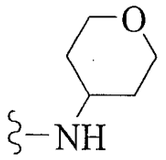
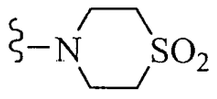
Ej. N°	R	Nombre	Tiempo de retención (min)	EM (IEN) m/z
56		*N,N*-diciclopropil-6-etil-1-metil-4-((4-metil-5-((4-metil-1-piperazinil)carbonil)-1,3-tiazol-2-il)amino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.43	562.31
57		*N,N*-diciclopropil-6-etil-1-metil-4-((4-metil-5-(4-morfolinilcarbonil)-1,3-tiazol-2-il)amino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.70	549.25
58		N,N-diciclopropil-6-etil-1-metil-4-((4-metil-5-((2-(4-morfolinil)etil)carbamoil)-1,3-tiazol-2-il)amino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.46	592.3

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Ej. N°	R	Nombre	Tiempo de retención (min)	EM (IEN) m/z
59		4-((5-((2-acetamidoetil) carbamoil)-4-metil-1,3-tiazol-2-il)amino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.51	564.27
60		4-((5-((cianometil)(metil) carbamoil)-4-metil-1,3-tiazol-2-il)amino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.78	532.25
61		4-((5-((cianometil) carbamoil)-4-metil-1,3-tiazol-2-il)amino)-N,N-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.72	518.24

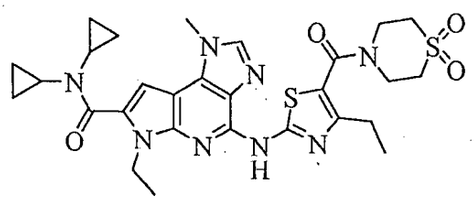
Ej. N°	R	Nombre	Tiempo de retención (min)	EM (IEN) m/z
62		N,N-diciclopropil-4-((5-((1,1-dioxidotetrahidro-3-tiofenil)carbamoil)-4-metil-1,3-tiazol-2-il)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.68	597.24
63		N,N-diciclopropil-6-etil-4-((5-((trans-4-hidroxiciclohexil)carbamoil)-4-metil-1,3-tiazol-2-il)amino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.60	577.3
64		N,N-diciclopropil-6-etil-4-((5-(((3S)-3-hidroxi-1-pirrolidinil)carbonil)-4-metil-1,3-tiazol-2-il)amino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.51	549.28

Ej. N°	R	Nombre	Tiempo de retención (min)	EM (IEN) m/z
65		*N,N*-diciclopropil-6-etil-1-metil-4-((4-metil-5-(metil(2-(metilsulfonil)etil)carbamoil)-1,3-tiazol-2-il)amino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.59	599.26
66		N,N-diciclopropil-6-etil-4-((5-((3-metoxi-1-azetidinil)carbonil)-4-metil-1,3-tiazol-2-il)amino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.80	549.28
67		N,N-diciclopropil-4-((5-((3,3-difluorociclobutil)carbamoil)-4-metil-1,3-tiazol-2-il)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	2.06	569.27

Ej. N°	R	Nombre	Tiempo de retención (min)	EM (IEN) m/z
68		*N,N*-diciclopropil-4-((5-((2,2-difluoroetil) carbamoil)-4-metil-1,3-tiazol-2-il)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.88	543.23
69		*N,N*-diciclopropil-6-etil-1-metil-4-((4-metil-5-(tetrahidro-2H-piran-4-ilcarbamoil)-1,3-tiazol-2-il)amino)-1,6-dihidroimidazo [4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.87	563.26
70		N,N-diciclopropil-4-((5-((1,1-dioxido-4-tiomorfolinil) carbonil)-4-metil-1,3-tiazol-2-il)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida	1.66	597.26

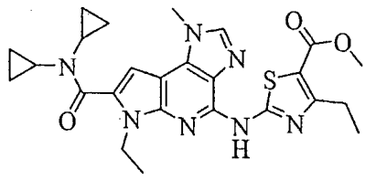
Condiciones de análisis - Columna - Mac-Mod Halo 4.6 x 50 mm 2.7 um; Gradiente de 4 min del 0% de B al 100% de B; Caudal - 4 ml/min; Solvente A = 5:95 de acetonitrilo:agua; B = 90:5 de acetonitrilo:agua; Modificador = NH_4OAc 10 mM.

Ejemplo 71



***N,N*-Diciclopropil-6-etil-4-(4-etil-5-(1,1-dioxotiomorfolin-4-carbonil)tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

71A Preparación de 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-etiltiazol-5-carboxilato de metilo



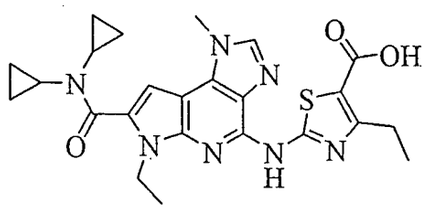
A una suspensión agitada de *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (103 mg, 0.259 mmol) en EtOH (5 ml) se le añadió 2-bromo-3-oxopentanoato[1] de metilo recién preparado (81 mg, 0.389 mmol) a la temperatura ambiente. Después, la suspensión se agitó a 65°C durante 2 h. Después, la mezcla de reacción se enfrió a la temperatura ambiente y se concentró al vacío, proporcionando un sólido de

color amarillo. Después, el sólido se recogió en cloruro de metileno y se lavó con una solución acuosa saturada de bicarbonato sódico. La fase orgánica se secó sobre sulfato de magnesio anhidro y se concentró al vacío. Después, el residuo en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando una columna Isco de 40 g eluyendo en metanol al 0-5%/cloruro de metileno, proporcionando 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-etiltiazol-5-carboxilato de metilo (37.5 mg, rendimiento del 28.5%) en forma de un sólido de color blanco.

MS (ESI) m/z 508.4 (M+H)

RMN ^{1}H (CDCl3) δ ppm 9.38 (s a, 1H), 7.75 (s, 1H), 6.92 (s, 1H), 4.76 (c, 2H, *J* = 6.94 Hz), 4.08 (s, 3H), 3.92 (s, 3H), 3.14 (c, 2H, *J* = 7.68 Hz), 2.85 (m, 2H), 1.59 (t, 3H, *J* = 6.94 Hz), 1.34 (t, 3H, *J* = 7.49 Hz), 0.78-0.91 (m, 8H)

71B Preparación de ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-etiltiazol-5-carboxílico



A una solución agitada de 2-(7-

(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-etiltiazol-5-carboxilato de metilo (ejemplo **71A**, 103 mg, 0.203 mmol) en MeOH (2 ml) se le añadió NaOH (1.420 ml, 1.420 mmol). Después, la solución se agitó a 65°C durante 18 h. Después, la mezcla de reacción se enfrió a la temperatura ambiente y se concentró al vacío, proporcionando una suspensión de color amarillo. Después, la mezcla se diluyó con agua, se llevó a un valor de pH de 4 con HCl 1 N y el precipitado se recogió por filtración al vacío. Después, el filtrado se extrajo con CH_2Cl_2; la fase orgánica se secó sobre sulfato de magnesio anhidro y se concentró al vacío. Después, el residuo en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando una columna Isco de 40 g eluyendo en MeOH al 0-8%/CH_2Cl_2. Las fracciones deseadas se combinaron con el precipitado recolectado y se concentraron, proporcionando ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-etiltiazol-5-carboxílico (126 mg, rendimiento del 126%) en forma de un sólido de color naranja/amarillo.

MS (ESI) m/z 494.2 (M+H)

RMN ^{1}H (CDCl3) δ ppm 8.23 (s, 1H), 7.28 (s, 1H), 4.62 (c, 2H, *J* = 6.94 Hz), 4.07 (s, 3H), 3.04 (c, 2H, *J* = 7.49 Hz), 3.00 (m, 2H), 1.42 (t, 3H, *J* = 7.07 Hz), 1.23 (t,

3H, *J* = 7.63 Hz), 0.67-0.79 (m, 8H).

71 Preparación de *N,N*-diciclopropil-6-etil-4-(4-etil-5-(1,1-dioxotiomorfolin-4-carbonil)tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

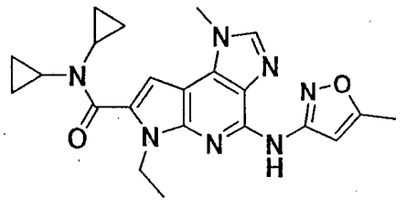
A una solución agitada de ácido 2-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4-etiltiazol-5-carboxílico (ejemplo **69B**, 33 mg, 0.067 mmol), HATU (50.8 mg, 0.134 mmol), 2,6-lutidina (0.020 ml, 0.174 mmol) y DMF (1 ml) se le añadió 1,1-dioxido de tiomorfolina (27.1 mg, 0.201 mmol). Después, la solución se agitó a 50°C durante 1.5 h. Después, la reacción se enfrió a la temperatura ambiente y se diluyó con cloruro de metileno. Después, la solución se lavó con bicarbonato sódico acuoso saturado, LiCl al 10% en H_2O y de nuevo con bicarbonato sódico acuosos saturado. La fase orgánica se secó sobre sulfato de magnesio anhidro y se concentró al vacío. Después, el residuo en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando una columna Isco de 40 g eluyendo en MeOH al 0-6%/CH_2Cl_2, dando *N,N*-diciclopropil-6-etil-4-(4-etil-5-(1,1-dioxotiomorfolin-4-carbonil)tiazol-2-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (21.7 mg, rendimiento del 52.6%) en forma de un sólido de color amarillo claro.

000325

MS (ESI) m/z 611.3 (M+H)

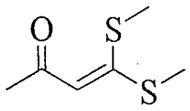
RMN ^{1}H (CDCl3) δ ppm 7.68 (s, 1H), 6.83 (s, 1H), 4.65 (c, 2H, *J* = 7.04), 4.13 (m, 4H), 3.99 (s, 3H), 3.05 (m, 4H), 2.76 (m, 2H), 2.68 (c, 2H, *J* = 7.56 Hz), 1.46 (t, 3H, *J* = 7.04 Hz), 1.25 (t, 3H, *J* = 7.59 Hz), 0.68-0.80 (m, 8H).

Ejemplo 72



N,N-diciclopropil-6-etil-1-metil-4-(5-metilisoxazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

72A Preparación de 4,4-bis(metiltio)but-3-en-2-ona

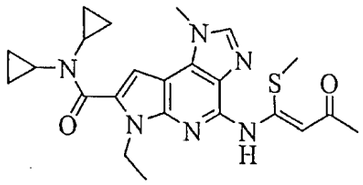


A una suspensión de *terc*-butóxido sódico (5.76 g, 60.0 mmol) en benceno (30 ml) se le añadió una solución de acetona (2.205 ml, 30.0 mmol) en disulfuro de carbono (1.81 ml, 30.0 mmol) mientras se mantenía la temperatura de reacción sin exceder de 10°C. La mezcla de reacción se agitó a la temperatura ambiente durante 3 h y se añadió yodometano (3.75 ml, 60.0 mmol) a 10°C. La mezcla de reacción resultante se agitó a la temperatura ambiente durante una noche. La mezcla de reacción se diluyó con acetato de etilo y se lavó

dos veces con agua. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO automatizado (columna de 80 g, eluyendo con acetato de etilo al 10-35%/hexanos), dando 4,4-bis(metiltio)but-3-en-2-ona (3.456 g, rendimiento del 71.0%) en forma de un sólido de color amarillo.

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 6.04 (s, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 2.20 (s, 3H).

72B Preparación de (*Z*)-*N*,*N*-diciclopropil-6-etil-1-metil-4-(1-(metiltio)-3-oxobut-1-enilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



Se añadió hidruro sódico (2.84 g, 71.1 mmol) a una solución de 4-amino-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 8.02 g, 23.70 mmol) en DMF (60 ml) y la mezcla de reacción se agitó a la temperatura ambiente durante 1 h. Se añadió 4,4-bis(metiltio)but-3-en-2-ona (ejemplo **70A**, 5.77 g, 35.5 mmol) en DMF (10 ml) y se continuó la agitación durante tres días. El análisis por LC/MS mostró que se había completado aproximadamente al 75%. La mezcla de reacción se diluyó con acetato de etilo y se añadió agua. Se formó un

precipitado blanquecino y se recogió por filtración, dando 5.1 g de producto. El filtrado se transfirió a un embudo decantación. Las fases se separaron y la fase acuosa se extrajo con diclorometano (3 x 50 ml), las fases orgánicas combinadas se lavaron con bicarbonato sódico saturado y se secaron sobre sulfato de magnesio, se filtraron y se concentraron al vacío. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO (columna de 220 g, eluyendo con metanol al 2-8%/diclorometano), dando (*Z*)-*N*,*N*-diciclopropil-6-etil-1-metil-4-(1-(metiltio)-3-oxobut-1-enilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (6.6 g, rendimiento del 61.5%) junto con 2.2 g de **1J** recuperado.

MS (ESI) m/z 453.3 (M+H).

RMN ^{1}H (400 MHz, DMSO-d_6) δ: 14.42 (s, 1H), 8.16 (s, 1H), 7.24 (s, 1H), 5.54 (s, 1H), 4.52 (c, *J* = 7.0 Hz, 2H), 4.05 (s, 3H), 2.89-2.97 (m, 2H), 2.43 (s, 3H), 2.14 (s, 3H), 1.34 (t, *J* = 7.0 Hz, 3H), 0.71-0.80 (m, 4H), 0.63-0.70 (m, 4H).

72 Preparación de *N*,*N*-diciclopropil-6-etil-1-metil-4-(5-metilisoxazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

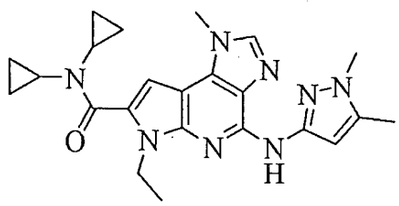
Una mezcla de (*Z*)-*N*,*N*-diciclopropil-6-etil-1-metil-4-(1-(metiltio)-3-oxobut-1-enilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (22 mg, 0.049 mmol) e hidroxilamina (solución acuosa al 50%, 3.13 µl, 0.051 mmol) en

etanol (1 ml) se calentó a reflujo durante 3 h y el análisis por LC/MS mostró que se había completado la reacción. La mezcla de reacción se diluyó con metanol y se purificó por HPLC preparativa, formando *N,N*-diciclopropil-6-etil-1-metil-4-(5-metilisoxazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (9 mg, rendimiento del 43.3%) en forma de un sólido de color blanco.

MS (ESI) m/z 420.1 (M+H).

RMN ^{1}H (400 MHz, METANOL-d_4) δ: 8.45 (s, 1H), 7.26 (s, 1H), 6.58 (s, 1H), 4.63 (c, *J* = 7.2 Hz, 2H), 4.17 (s, 3H), 2.94-3.02 (m, 2H), 2.33 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H), 0.85-0.92 (m, 4H), 0.77-0.84 (m, 4H).

Ejemplo 73



***N,N*-Diciclopropil-4-(1,5-dimetil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Una mezcla de (*Z*)-*N,N*-diciclopropil-6-etil-1-metil-4-(1-(metiltio)-3-oxobut-1-enilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **72B**, 70 mg, 0.155 mmol) y 1-metilhidrazinacarboxilato de *terc*-butilo (0.046 ml, 0.309 mmol) en ácido acético (1 ml) se agitó a

000329

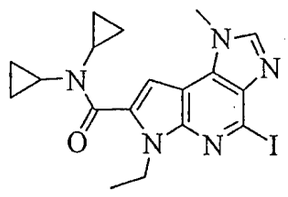
35°C durante 4 h (controlada por análisis LC/MS hasta que no quedó material de partida). Se añadió ácido fórmico (0.5 ml) y se agitó a 60°C durante 6 h. El solvente se evaporó y el producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO automatizado (columna de 12 g, eluyendo con metanol al 2-10%/diclorometano). El producto impuro se purificó adicionalmente por HPLC preparativa, dando *N,N*-diciclopropil-4-(1,5-dimetil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (45 mg, rendimiento del 63.9%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 433.2 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 7.63 (s, 1H), 6.94 (s, 1H), 6.85 (s, 1H), 4.65 (c, *J* = 7.0 Hz, 2H), 3.99 (s, 3H), 3.71 (s, 3H), 2.79-2.85 (m, 2H), 2.33 (s, 3H), 1.49 (t, *J* = 7.2 Hz, 3H), 0.82-0.87 (m, 4H), 0.72-0.78 (m, 4H).

Síntesis alternativa del ejemplo 73

73A Preparación de 4-yodo-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



A una suspensión agitada de 4-amino-*N,N*-

diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (34.4 mg, 0.102 mmol) en diyodometano (102 µl) a 60°C se le añadió lentamente nitrito de isoamilo (27.4 µl, 0.203 mmol). La mezcla de reacción se agitó a 60°C durante 5 h. Después de la refrigeración a la ta, la mezcla de reacción se diluyó con diclorometano. Se añadió bicarbonato sódico acuoso saturado y la fase acuosa se extrajo con diclorometano (3 x). Los extractos orgánicos combinados se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. El residuo en bruto se puso en la bomba durante 16 h para retirar cualquier diyodometano adicional. El análisis por CLEM determinó que era lo suficientemente puro para llevarse a la siguiente etapa en bruto. El producto se usó inmediatamente en la siguiente reacción.

MS (ESI) m/z 450.1 (M+H)

73 Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(1,5-dimetil-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

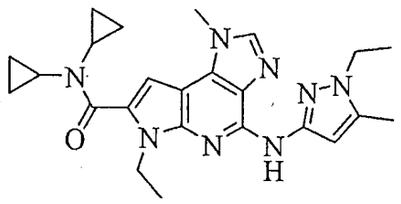
A un vial con 1,5-dimetil-1*H*-pirazol-3-amina (13.60 mg, 0.122 mmol), $Pd_2(dba)_3$ (4.67 mg, 5.10 µmol), Xantphos (5.90 mg, 10.20 µmol) y carbonato de cesio (100 mg, 0.306 mmol) se le añadió *N,N-diciclo*propil-6-etil-4-yodo-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (45.8 mg, 0.102 mmol) en DME (1020 µl). La mezcla de reacción

se roció con argón durante 5 min, el vial se tapó y la mezcla de reacción se calentó a 90°C durante 1 h. La mezcla de reacción se diluyó con diclorometano y se filtró al vacío a través de Celite. El filtrado se concentró al vacío. El residuo en bruto se purificó por cromatografía en columna ultrarrápida usando una columna ISCO de 12 g eluyendo con MeOH al 1-10%/CH_2Cl_2). Se aisló *N,N*-diciclopropil-4-(1,5-dimetil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (14 mg, rendimiento del 31.7%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 433.2 (M+H).

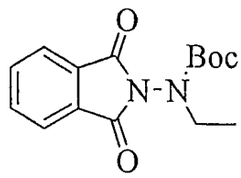
RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 7.63 (s, 1H), 6.94 (s, 1H), 6.85 (s, 1H), 4.65 (c, *J* = 7.0 Hz, 2H), 3.99 (s, 3H), 3.71 (s, 3H), 2.79-2.85 (m, 2H), 2.33 (s, 3H), 1.49 (t, *J* = 7.2 Hz, 3H), 0.82-0.87 (m, 4H), 0.72-0.78 (m, 4H).

Ejemplo 74



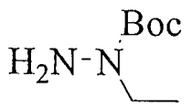
***N,N*-Diciclopropil-6-etil-4-(1-etil-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

74A Preparación de 1,3-dioxoisoindolin-2-il(etil)carbamato de *terc*-butilo



Se añadió azodicarboxilato de diisopropilo (2.92 ml, 15.00 mmol) en una porción a una solución de 1,3-dioxoisoindolin-2-ilcarbamato de *terc*-butilo (2.62 g, 10 mmol, preparado siguiendo el procedimiento descrito por Nicolas Brosse y col. en *Eur. J. Org. Chem.* 4757-4764, **2003**), trifenilfosfina (3.93 g, 15.00 mmol) y etanol (0.691 g, 15.00 mmol) en THF (20 ml) a 0°C y la solución de reacción se agitó a la temperatura ambiente durante 1 h (controlada por TLC hasta que se completó). El solvente se evaporó y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO automatizado (columna de 80 g, eluyendo con acetato de etilo al 5-35%/hexanos), proporcionando 1,3-dioxoisoindolin-2-il(etil)carbamato de *terc*-butilo (2.6 g, rendimiento del 90%) en forma de un sólido de color blanco que se usó tal cual en la siguiente etapa.

74B Preparación de 1-etilhidrazinacarboxilato de *terc*-butilo



Se añadió metilhidrazina (1.415 ml, 26.9 mmol) a

una solución de 1,3-dioxoisoindolin-2-il(etil)carbamato de *terc*-butilo (ejemplo **74A**, 5.2 g, 17.91 mmol) en THF (40 ml) a 0°C y la mezcla de reacción se agitó a la temperatura ambiente durante una noche. Se formó un precipitado de color blanco y se retiró por filtración a través de una capa de Celite. El filtrado se concentró al vacío. El residuo se disolvió en acetato de etilo (50 ml) y se extrajo con HCl 1 N (3 x 30 ml), la fase ácida se lavó con acetato de etilo (50 ml) y se basificó a un valor de pH de 10 mediante la adición de NaOH al 20%. Después, la solución básica se extrajo con acetato de etilo (3 x 50 ml) y las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron al vacío, dando 1-etilhidrazinacarboxilato de *terc*-butilo (2.5 g, rendimiento del 87%) en forma de un aceite incoloro.

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 3.90 (s a, 2H), 3.35 (c, J = 7.0 Hz, 2H), 1.42 (s, 9H), 1.07 (t, J = 7.0 Hz, 3H).

74 Preparación de *N,N*-diciclopropil-6-etil-4-(1-etil-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

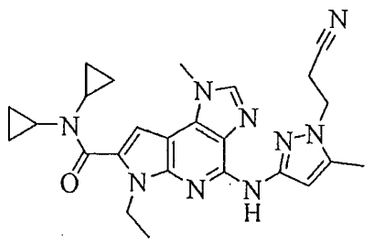
Una mezcla de (*Z*)-*N,N*-diciclopropil-6-etil-1-metil-4-(1-(metiltio)-3-oxobut-1-enilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **74B**, 70 mg, 0.155 mmol) y 1-etilhidrazinacarboxilato de *terc*-butilo (49.6 mg, 0.309 mmol) en ácido acético (1 ml) se agitó a 35°C

durante 4 h (controlada por análisis LC/MS hasta que no quedó material de partida). Se añadió ácido fórmico (1 ml) y la mezcla de reacción se agitó a 60°C durante 6 h. El solvente se evaporó y el producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO automatizado (columna de 12 g, eluyendo con metanol al 2-10%/diclorometano). El material se purificó adicionalmente por HPLC preparativa, proporcionando *N,N*-diciclopropil-6-etil-4-(1-etil-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (38 mg, rendimiento del 53.4%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 447.3 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.61 (s, 1H), 6.93 (s, 1H), 6.84 (s, 1H), 4.66 (c, *J* = 7.1 Hz, 2H), 4.02 (c, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 2.79-2.85 (m, 2H), 2.34 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 0.82-0.87 (m, 4H), 0.72-0.78 (m, 4H).

Ejemplo 75



4-(1-(2-Cianoetil)-5-metil-1*H*-pirazol-3-ilamino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-

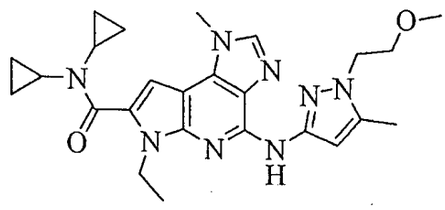
d]pirrolo[2,3-b]piridin-7-carboxamida

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **74**.

MS (ESI) m/z 472.2 (M+H).

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 8.05 (s, 1H), 7.64 (s, 1H), 6.99 (s, 1H), 6.85 (s, 1H), 4.65 (c, *J* = 7.0 Hz, 2H), 4.25 (t, *J* = 6.8 Hz, 2H), 4.01 (s, 3H), 2.92 (t, *J* = 6.7 Hz, 2H), 2.79-2.86 (m, 2H), 2.41 (s, 3H), 1.49 (t, *J* = 7.2 Hz, 3H), 0.82-0.88 (m, 4H), 0.72-0.80 (m, 4H).

Ejemplo 76



***N,N*-Diciclopropil-6-etil-4-(1-(2-metoxietil)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

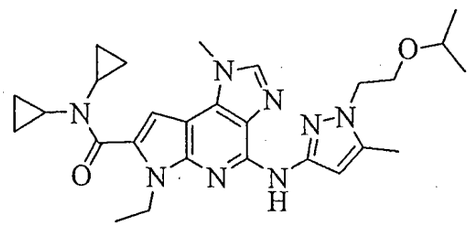
El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **74**.

MS (ESI) m/z 477.2 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.61 (s, 1H), 6.94 (s, 1H), 6.84 (s, 1H), 4.66 (c, *J* = 6.8 Hz, 2H), 4.12 (t, *J* = 5.5 Hz, 2H), 3.98 (s, 3H), 3.74 (t, *J* = 5.8 Hz,

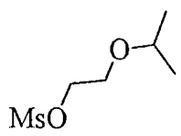
2H), 3.32 (s, 3H), 2.78-2.86 (m, 2H), 2.36 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H), 0.81-0.89 (m, 4H), 0.71-0.80 (m, 4H).

Ejemplo 77



***N,N*-Diciclopropil-6-etil-4-(1-(2-isopropoxietil)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

77A Preparación de metanosulfonato de 2-isopropoxietilo

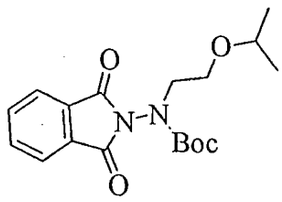


Un matraz de fondo redondo se cargó con 2-isopropoxietanol (0.5 ml, 4.34 mmol) y diclorometano (21.68 ml) y se enfrió a 0°C. Se añadió trietilamina (1.208 ml, 8.67 mmol) junto con una punta de espátula de DMAP. Se añadió gota a gota cloruro de metanosulfonilo (0.338 ml, 4.34 mmol). La mezcla de reacción se calentó lentamente a la ta durante 2 h. La mezcla de reacción se inactivó con cloruro de amonio acuoso saturado y se transfirió a un embudo decantación. La fase acuosa se extrajo con diclorometano (2 x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron

al vacío. Se aisló metanosulfonato de 2-isopropoxietilo (1 g) en forma de un aceite transparente y se usó inmediatamente en la siguiente reacción.

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 4.34-4.40 (m, 2H), 3.67-3.71 (m, 2H), 3.60-3.67 (m, 1H), 3.07 (s, 3H), 1.18 (d, 6H, J = 8.0 Hz).

77B Preparación de 1,3-dioxoisoindolin-2-il(2-isopropoxietil)carbamato de *terc*-butilo



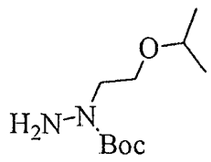
Un matraz de fondo redondo se cargó con metanosulfonato de 2-isopropoxietilo (ejemplo **77A**, 0.791 g, 4.34 mmol) en acetonitrilo (21.70 ml) y se agitó en una atmósfera de nitrógeno. Se añadió 1,3-dioxoisoindolin-2-ilcarbamato de *terc*-butilo (1.138 g, 4.34 mmol) junto con carbonato potásico (2.399 g, 17.36 mmol) y cloruro de benciltrietilamonio (0.198 g, 0.868 mmol). La mezcla de reacción se calentó a 50°C durante 24 h y se enfrió a la ta durante el fin de semana. La mezcla de reacción se diluyó con acetato de etilo y agua. La fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron al vacío a través de un lecho de gel de

sílice y se concentraron al vacío. El aceite en bruto se usó sin purificación adicional (1.26 g, rendimiento del 83%).

MS (ESI) m/z 249.2 ($M-C_4H_9CO_2$)

RMN ^1H (400 MHz, CLOROFORMO-d) en forma de una mezcla de rotómeros δ ppm RMN ^1H (400 MHz, CLOROFORMO-d) δ ppm 7.86-7.94 (m, 2H), 7.73-7.82 (m, 2H), 3.79-3.90 (m, 2H), 3.58-3.66 (m, 2H), 3.41-3.55 (m, 1H), 1.31-1.56 (m, 9H), 0.87-1.05 (m, 6H).

77C Preparación de 1-(2-isopropoxietil)hidrazinacarboxilato de *terc*-butilo



A una solución de 1,3-dioxoisoindolin-2-il(2-isopropoxietil)carbamato de *terc*-butilo (ejemplo **77B**, 1.262 g, 3.62 mmol) en tetrahidrofurano (24.15 ml) a 0°C se le añadió lentamente metilhidrazina (0.289 ml, 5.43 mmol). La mezcla de reacción se agitó a 0°C durante 3 h. La mezcla de reacción se filtró, retirando el precipitado de color blanco y el filtrado se concentró al vacío. El semisólido se trituró con acetato de etilo (2 x) y el triturado se concentró al vacío. Este proceso se repitió, proporcionando al final 1-(2-isopropoxietil)hidrazinacarboxilato de *terc*-butilo (0.665 g, rendimiento del 84%) en forma de un aceite de color amarillo.

RMN ^1H (400 MHz, CLOROFORMO-d) δ ppm 3.52-3.65 (m, 5

H), 1.48 (s, 9H), 1.15 (d, 6H, *J* = 6.27 Hz).

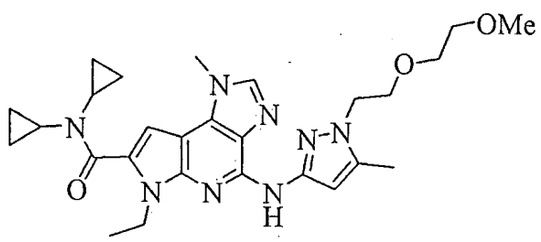
77 Preparación de *N,N*-diciclopropil-6-etil-4-(1-(2-isopropoxietil)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo **73** usando 1-(2-isopropoxietil)hidrazinacarboxilato de *terc*-butilo (ejemplo **77C**, 29.8 mg, 0.137 mmol), proporcionando *N,N*-diciclopropil-6-etil-4-(1-(2-isopropoxietil)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (16.72 mg, rendimiento del 48.7%) en forma de un sólido de color blanco.

MS (ESI) m/z 505.4 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.89 (s, 1H), 6.99 (s, 1H), 6.88 (s, 1H), 4.65 (c, 2H, *J* = 7.03 Hz), 4.22 (t, 2H, *J* = 5.27 Hz), 4.06 (s, 3H), 3.78 (t, 2H, *J* = 5.27 Hz), 3.52 (dt, 1H, *J* = 12.11, 6.12 Hz), 2.79-2.88 (m, 2H), 2.41 (s, 3H), 1.50 (t, 3H, *J* = 7.03 Hz), 1.09 (d, 6H, *J* = 6.27 Hz), 0.82-0.91 (m, 4H), 0.71-0.81 (m, 4H).

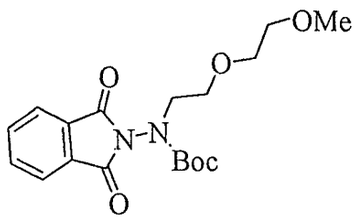
Ejemplo 78



***N,N*-Diciclopropil-6-etil-4-(1-(2-(2-metoxietoxi)etil)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-**

dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

78A Preparación de 1,3-dioxoisoindolin-2-il(2-(2-metoxietoxi)etil)carbamato de *terc*-butilo

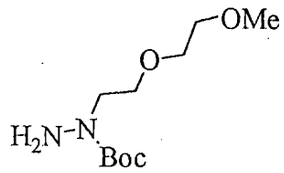


El compuesto se preparó de acuerdo con el Ejemplo **77B** usando 1-bromo-2-(2-metoxietoxi)etano (0.259 ml, 1.906 mmol), proporcionando 1,3-dioxoisoindolin-2-il(2-(2-metoxietoxi)etil)carbamato de *terc*-butilo (0.583 g, rendimiento del 84%) en forma de un aceite de color amarillo claro.

MS (ESI) m/z 265.2 ($M-C_4H_9CO_2$)

RMN ^1H (400 MHz, CLOROFORMO-d) en forma de una mezcla de rotómeros δ ppm 7.85-7.94 (m, 2H), 7.73-7.82 (m, 2H), 3.83-3.93 (m, 2H), 3.67-3.74 (m, 2H), 3.48-3.59 (m, 2H), 3.30-3.43 (m, 2H), 3.16-3.28 (m, 3H), 1.29-1.55 (m, 9H).

78B Preparación de 1-(2-(2-etoxietoxi)etil)hidrazinacarboxilato de *terc*-butilo



El compuesto se preparó de acuerdo con el ejemplo **77C** usando 1,3-dioxoisoindolin-2-il(2-(2-

metoxietoxi)etil)carbamato de *terc*-butilo (0.583 g, 1.600 mmol), proporcionando 1-(2-(2-metoxietoxi)etil)hidrazinacarboxilato de *terc*-butilo (0.4 g, rendimiento del 107%) en forma de un aceite de color amarillo.

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 3.51-3.70 (m, 8H), 3.39 (s, 3H), 1.48 (s, 9H).

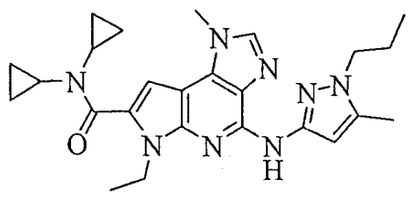
78 Preparación de *N,N*-diciclopropil-6-etil-4-(1-(2-(2-metoxietoxi)etil)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo **74** usando 1-(2-(2-metoxietoxi)etil)hidrazinacarboxilato de *terc*-butilo (ejemplo **78B**, 43.2 mg, 0.184 mmol), proporcionando *N,N*-diciclopropil-6-etil-4-(1-(2-(2-metoxietoxi)etil)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (17.34 mg, rendimiento del 36%) en forma de un sólido de color blanco.

MS (ESI) m/z 521.4 (M+H)

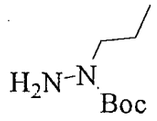
RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.85 (s a, 1H), 6.91 (s, 1H), 6.87 (s, 1H), 4.65 (c, 2H, *J* = 7.03 Hz), 4.20 (t, 2H, *J* = 5.27 Hz), 4.05 (s, 3H), 3.87 (t, 2H, *J* = 5.65 Hz), 3.53-3.59 (m, 2H), 3.50 (ddd, 2H, *J* = 5.40, 2.89, 2.76 Hz), 2.77-2.87 (m, 2H), 2.38 (s, 3H), 1.50 (t, 3H, *J* = 7.03 Hz), 0.82-0.91 (m, 4H), 0.71-0.79 (m, 4H).

Ejemplo 79



Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(5-metil-1-propil-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

79A Preparación de 1-propilhidrazinacarboxilato de *terc*-butilo



A una solución de propilhidrazina, sal del ácido oxálico (0.5 g, 3.05 mmol) en etanol (3 ml) en un matraz de fondo redondo en una atmósfera de nitrógeno se le añadió trietilamina (0.425 ml, 3.05 mmol). La mezcla de reacción se enfrió a 0°C y se añadió gota a gota BOC_2O (0.707 ml, 3.05 mmol) disuelto en etanol (1 ml) durante 10 min. La mezcla de reacción se dejó calentar a la temperatura ambiente durante 16 h. El etanol se retiró mediante concentración al vacío. El residuo se recogió en agua y acetato de etilo. La fase acuosa se extrajo con acetato de etilo (3 x). Los extractos orgánicos combinados se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. El producto en bruto se usó tal cual en la siguiente reacción.

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 3.30-3.36 (m, 2H), 1.59 (dc, 3H, *J* = 14.40, 7.33 Hz), 1.48 (s, 9H), 0.88 (t, 3H, *J* = 7.40 Hz).

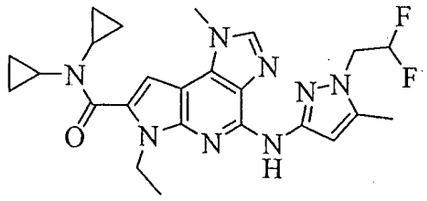
79 Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(5-metil-1-propil-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Este compuesto se preparó de acuerdo con el ejemplo **74** usando 1-propilhidrazinacarboxilato de *terc*-butilo (ejemplo **79A**, 19.87 mg, 0.114 mmol), proporcionando *N,N*-diciclopropil-6-etil-1-metil-4-(5-metil-1-propil-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (15.6 mg, rendimiento del 59%) en forma de un sólido de color blanco.

MS (ESI) m/z 461.4 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7.74 (s a, 1H), 6.92 (s, 1H), 6.86 (s, 1H), 4.66 (c, 2H, *J* = 7.11 Hz), 4.03 (s, 3H), 3.95 (t, 2H, *J* = 7.15 Hz), 2.78-2.87 (m, 2H), 2.34 (s, 3H), 1.87 (dc, 3H, *J* = 14.49, 7.30 Hz), 1.50 (t, 3H, *J* = 7.15 Hz), 0.96 (t, 3H, *J* = 7.40 Hz), 0.83-0.89 (m, 4H), 0.72-0.79 (m, 4H).

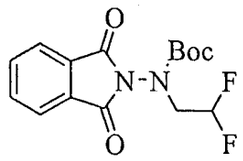
Ejemplo 80



***N,N*-Diciclopropil-4-(1-(2,2-difluoroetil)-5-metil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-**

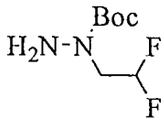
d]pirrolo[2,3-b]piridin-7-carboxamida

80A Preparación de 2,2-difluoroetil(1,3-dioxoisoindolin-2-il)carbamato de *terc*-butilo



El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **77A**.

80B Preparación de 1-(2,2-difluoroetil)hidrazinacarboxilato de *terc*-butilo



El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **77B**.

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ: 5.94 (tt, *J* = 56.3, 4.4 Hz, 1H), 3.74 (td, *J* = 13.8, 4.4 Hz, 2H), 1.48 (s, 9H).

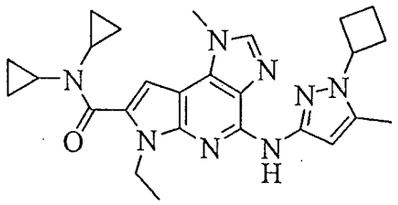
80 Preparación de *N,N*-diciclopropil-4-(1-(2,2-difluoroetil)-5-metil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **73**.

MS (ESI) m/z 483.3 (M+H).

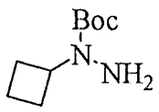
RMN ^{1}H 500 MHz, (CLOROFORMO-d) δ: 8.17 (s a, 1H), 7.66 (s, 1H), 7.01 (s, 1H), 6.85 (s, 1H), 6.05 (tt, *J* = 56.0, 4.4 Hz, 1H), 4.65 (c, *J* = 6.9 Hz, 2H), 4.30 (td, *J* = 13.2, 4.3 Hz, 2H), 3.99 (s, 3H), 2.79-2.86 (m, 2H), 2.36 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H), 0.81-0.88 (m, 4H), 0.72-0.79 (m, 4H).

Ejemplo 81



4-(1-Ciclobutil-5-metil-1*H*-pirazol-3-ilamino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

81A Preparación de 1-ciclobutilhidrazinacarboxilato de *terc*-butilo



El compuesto del título se preparó siguiendo el procedimiento descrito por So Ok Park et al., en *J. Comb. Chem.* 11, 315-326, **2009**.

81 Preparación de 4-(1-ciclobutil-5-metil-1*H*-pirazol-3-ilamino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

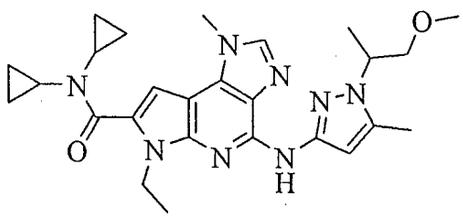
El compuesto del título se preparó usando un

procedimiento análogo al que se ha usado para preparar el ejemplo **73**.

MS (ESI) m/z 473.4 (M+H).

RMN ^{1}H (500 MHz, CLOROFORMO-d) δ: 8.05 (s, 1H), 6.91 (s, 1H), 6.79 (s, 1H), 4.68 (quint., *J* = 8.4 Hz, 1H), 4.61 (c, *J* = 7.1 Hz, 2H), 4.07 (s, 3H), 2.80-2.87 (m, 2H), 2.69-2.79 (m, 2H), 2.37-2.47 (m, 2H), 2.32 (s, 3H), 1.78-1.98 (m, 2H), 1.47 (t, *J* = 7.1 Hz, 3H), 0.82-0.91 (m, 4H), 0.72-0.80 (m, 4H).

Ejemplo 82



***N,N*-Diciclopropil-6-etil-4-(1-(1-metoxipropan-2-il)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

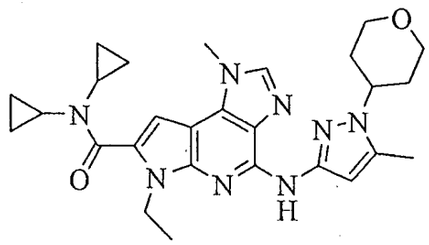
Preparado como se ha descrito en el ejemplo **77**.

MS (ESI) m/z 491 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 8.18 (s a, 1H) 7.63 (s, 1 H) 6.93 (s, 1H) 6.85 (s, 1H) 4.66 (c, *J* = 7.04 Hz, 2H) 4.29-4.48 (m, *J* = 13.31, 6.82, 6.82, 6.71 Hz, 1H) 4.00 (s, 3H) 3.55-3.79 (m, 2H) 3.29 (s, 3H) 2.72-2.92 (m, 2H) 2.36 (s, 3H) 1.49 (t, *J* = 7.04 Hz, 3H) 1.46 (d, *J* = 6.82 Hz, 2H) 0.68-0.93 (m, 8H).

000347

Ejemplo 83



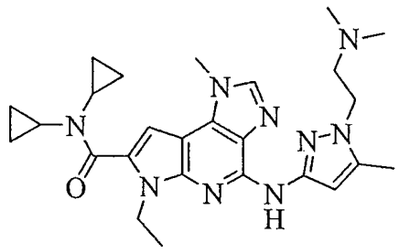
***N,N*-Diciclopropil-6-etil-1-metil-4-(5-metil-1-(tetrahidro-2*H*-piran-4-il)-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Preparado usando un procedimiento similar al del ejemplo **77**.

MS (ESI) m/z 503 (M+H).

RMN ^{1}H (500 MHz, CLOROFORMO-*d*) δ ppm 8.12 (s, 1H) 7.64 (s, 1H) 6.95 (s, 1H) 6.86 (s, 1H) 4.66 (c, *J* = 7.21 Hz, 2H) 4.09-4.23 (m, 3H) 4.01 (s, 3H) 3.55 (td, *J* = 12.00, 1.80 Hz, 2H) 2.73-2.89 (m, 2H) 2.37 (s, 3H) 2.25-2.36 (m, 2H) 1.84 (dd, *J* = 12.76, 2.22 Hz, 2H) 1.50 (t, *J* = 7.07 Hz, 3H) 0.71-0.91 (m, 8H).

Ejemplo 84



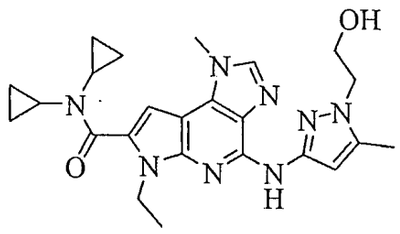
***N,N*-Diciclopropil-4-(1-(2-(dimetilamino)etil)-5-metil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Preparado usando un procedimiento similar al del ejemplo **77**.

MS (ESI) m/z 490 (M+H).

RMN ^{1}H (500 MHz, CLOROFORMO-*d*) δ ppm 8.08 (s, 1H) 7.64 (s, 1H) 6.96 (s, 1H) 6.86 (s, 1H) 4.65 (c, *J* = 7.21 Hz, 2H) 4.24 (s a, 2H) 4.01 (s, 3H) 3.01-3.22 (m, 2H) 2.70-2.89 (m, 2H) 2.50 (s a, 6H) 2.37 (s, 3H) 1.49 (t, *J* = 7.07 Hz, 3H) 0.71-0.91 (m, 8H).

Ejemplo 85



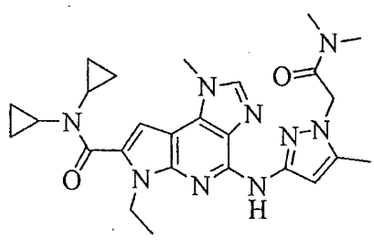
***N,N*-Diciclopropil-6-etil-4-(1-(2-hidroxietil)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Preparado usando un procedimiento similar al del ejemplo **77**.

MS (ESI) m/z 463 (M+H).

RMN ^{1}H (500 MHz, MeOD) δ ppm 7.93 (s, 1H) 7.16 (s, 1H) 6.88 (s, 1H) 4.60 (c, *J* = 7.21 Hz, 2H) 4.09 (t, *J* = 5.55 Hz, 2H) 4.05 (s, 3H) 3.88 (t, *J* = 5.55 Hz 2H) 2.88-3.00 (m, 2H) 2.37 (s, 3H) 1.43 (t, *J* = 7.07 Hz, 3H) 0.62-0.98 (m, 8H).

Ejemplo 86



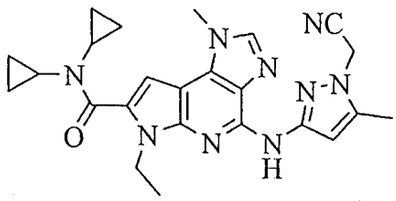
***N,N*-Diciclopropil-4-(1-(2-(dimetilamino)-2-oxoetil)-5-metil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Preparado usando un procedimiento similar al del ejemplo 77.

MS (ESI) m/z 504 (M+H).

RMN ^{1}H (500 MHz, MeOD) δ ppm 7.93 (s, 1H) 7.16 (s, 1H) 6.99 (s, 1H) 4.97 (s, 2H) 4.61 (c, *J* = 6.94 Hz, 2H) 4.05 (s, 3H) 3.15 (s, 3H) 2.98 (s, 3H) 2.79-2.97 (m, 2H) 2.29 (s, 3H) 1.44 (t, *J* = 7.07 Hz, 3H) 0.72-0.91 (m, 8H).

Ejemplo 87



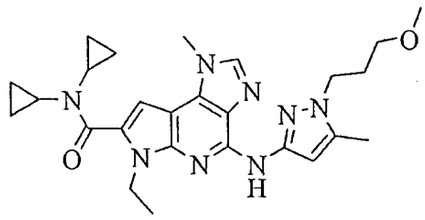
4-(1-(Cianometil)-5-metil-1*H*-pirazol-3-ilamino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Preparado usando un procedimiento similar al del ejemplo **77**.

MS (ESI) m/z 458 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*)™ ppm 8.17 (s, 1H) 7.67 (s, 1H) 7.10 (s, 1H) 6.87 (s, 1H) 4.93 (s, 2H) 4.65 (c, *J* = 7.04 Hz, 2H) 4.01 (s, 3H) 2.76-2.92 (m, 2H) 2.43 (s, 3H) 1.50 (t, *J* = 7.04 Hz, 3H) 0.68-0.93 (m, 8H).

Ejemplo 88



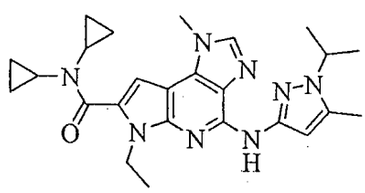
N,N-Diciclopropil-6-etil-4-(1-(3-metoxipropil)-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Preparado usando un procedimiento similar al del ejemplo **77**.

MS (ESI) m/z 491 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-*d*)™ ppm 8.11 (s, 1H) 7.62 (s, 1H) 6.92 (s, 1H) 6.78-6.89 (m, 1H) 4.66 (c, *J* = 7.04 Hz, 2H) 4.06 (t, *J* = 6.60 Hz, 2H) 3.98 (s, 3H) 3.29-3.39 (m, 4H) 2.75-2.91 (m, 2H) 2.34 (s, 3H) 2.08 (dc, *J* = 6.38, 6.16 Hz, 2H) 1.50 (t, *J* = 7.04 Hz, 3H) 0.70-0.94 (m, 8H).

Ejemplo 89



N,N-Diciclopropil-6-etil-4-(1-isopropil-5-

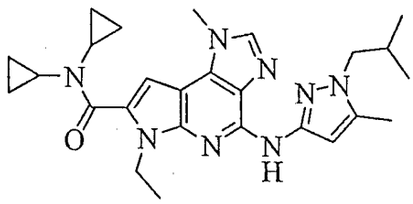
metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Preparado usando un procedimiento similar al del ejemplo **77**.

MS (ESI) m/z 461 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 8.15 (s, 1H) 7.62 (s, 1H) 6.91 (s, 1H) 6.85 (s, 1H) 4.66 (c, *J* = 7.19 Hz, 2H) 4.25-4.48 (m, 1H) 3.99 (s, 3H) 2.66-2.90 (m, *J* = 7.13, 7.13, 3.85, 3.47 Hz, 2H) 2.34 (s, 3H) 1.38-1.58 (m, 9H) 0.68-0.91 (m, 8H).

Ejemplo 90



***N,N*-Diciclopropil-6-etil-4-(1-isobutil-5-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

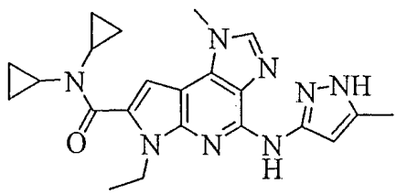
Preparado usando un procedimiento similar al del ejemplo **77**.

MS (ESI) m/z 475 (M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 8.11 (s, 1H) 7.62 (s, 1H) 6.93 (s, 1H) 6.85 (s, 1H) 4.66 (c, *J* = 7.04 Hz, 2H) 3.99 (s, 3H) 3.74 (d, *J* = 7.48 Hz, 2H) 2.74-2.89 (m, 2H) 2.33 (s, 3H) 2.18-2.29 (m, 1H) 1.50 (t, *J* = 7.04 Hz, 3H) 0.94

(d, J = 6.60 Hz, 6H) 0.72-0.88 (m, 8H).

Ejemplo 91



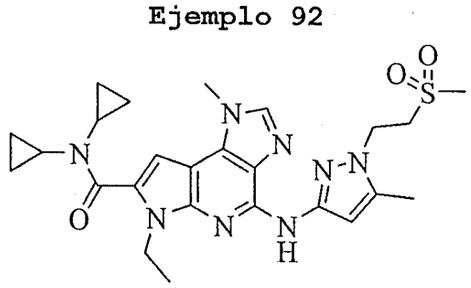
Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(5-metil-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

Preparado usando un protocolo similar al del ejemplo **72** a partir de hidrazina.

MS (ESI) m/z 419.3 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 8.70 (s a, 1H), 7.91 (s a, 1H), 6.87 (s, 1H), 6.09 (s a, 1H), 4.64 (c, 2H, J = 7.03 Hz), 4.08 (s, 3H), 2.74-2.95 (m, 2H), 2.41 (s, 3H), 1.51 (t, 3H, J = 7.15 Hz), 0.81-0.95 (m, 4H), 0.70-0.81 (m, 4H).

Ejemplo 92



***N,N*-Diciclopropil-6-etil-1-metil-4-((5-metil-1-(2-(metilsulfonil)etil)-1*H*-pirazol-3-il)amino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

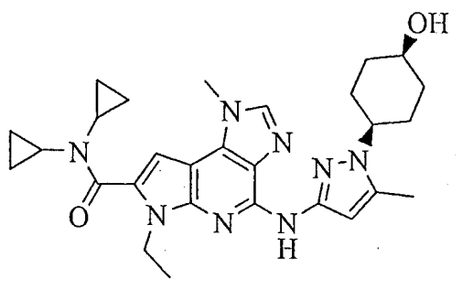
Preparado usando el mismo procedimiento que se ha

usado para el ejemplo **77**.

MS (ESI) m/z 525.3 (M+H)

RMN ^{1}H (CDCl3) δ ppm 8.25 (s a, 1H), 7.75 (s, 1H), 6.86 (s, 1H), 6.77 (s, 1H), 4.54 (c, 2H, *J* = 8 Hz), 4.36 (t, 2H, *J* = 8 Hz), 3.97 (s, 3H), 3.58 (t, 2H, *J* = 8 Hz), 2.71-2.77 (m, 2H), 2.44 (s, 3H), 2.34 (s, 3H), 1.41 (t, 3H, *J* = 8 Hz), 0.75-0.78 (m, 4H), 0.67-0.71 (m, 4H).

Ejemplo 93



***N,N*-Diciclopropil-6-etil-4-((1-(cis-4-hidroxiciclohexil)-5-metil-1*H*-pirazol-3-il)amino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Preparado usando el mismo procedimiento que se ha usado para el ejemplo **77**.

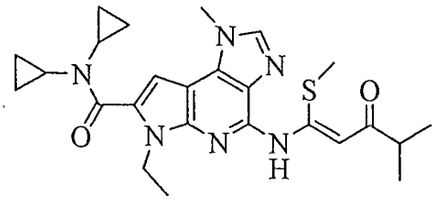
MS (ESI) m/z 517.4 (M+H)

RMN ^{1}H (CDCl3) δ ppm 8.14 (s a, 1H), 7.56 (s, 1H), 6.83 (s, 1H), 6.76 (s, 1H), 4.59 (c, 2H, *J* = 8 Hz), 4.01-4.02 (m, 1H), 3.93 (s, 3H), 3.88-3.93 (m, 1H), 2.73-2.77 (m, 2H), 2.28 (s, 3H), 2.25-2.33 (m, 2H), 1.93-1.96 (m, 2H), 1.59-1.73 (m, 4H), 1.42 (t, 3H, *J* = 8 Hz), 0.73-0.78 (m, 4H), 0.66-0.70 (m, 4H).

procedimiento análogo al que se ha usado para preparar el ejemplo **70A**.

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 6.08 (s, 1H), 2.47 (s, 3H), 2.46 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H).

95B Preparación de *(Z)*-*N*,*N*-diciclopropil-6-etil-1-metil-4-(4-metil-1-(metiltio)-3-oxopent-1-enilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **70B**.

MS (ESI) m/z 481.4 (M+H).

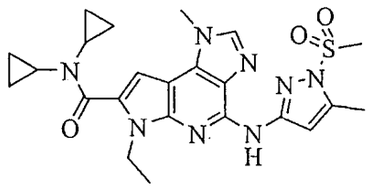
95 Preparación de *N*,*N*-diciclopropil-6-etil-4-(5-isopropil-1-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **73**.

MS (ESI) m/z 461.4 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 7.80 (s, 1H), 7.07

Ejemplo 94



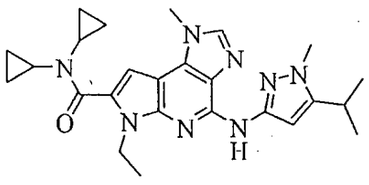
***N,N*-Diciclopropil-6-etil-1-metil-4-((5-metil-1-(metilsulfonil)-1*H*-pirazol-3-il)amino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Preparado usando el mismo procedimiento que se ha usado para el ejemplo **77**.

MS (ESI) m/z 497.3 (M+H)

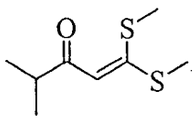
RMN ^{1}H (CDCl3) δ ppm 8.46 (s a, 1H), 7.75 (s, 1H), 7.16 (s, 1H), 6.78 (s, 1H), 4.54 (c, 2H, *J* = 8 Hz), 3.97 (s, 3H), 3.19 (s, 3H), 2.72-2.76 (m, 2H), 2.51 (s, 3H), 1.41 (t, 3H, *J* = 8 Hz), 0.72-0.78 (m, 4H), 0.66-0.69 (m, 4H).

Ejemplo 95



***N,N*-Diciclopropil-6-etil-4-(5-isopropil-1-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

95A Preparación de 4-metil-1,1-bis(metiltio)pent-1-en-3-ona

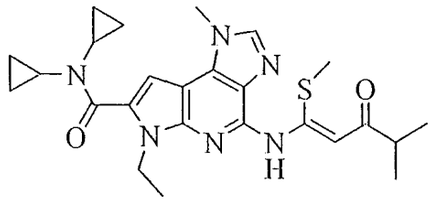


El compuesto del título se preparó usando un

procedimiento análogo al que se ha usado para preparar el ejemplo **70A**.

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 6.08 (s, 1H), 2.47 (s, 3H), 2.46 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H).

95B Preparación de *(Z)-N,N*-diciclopropil-6-etil-1-metil-4-(4-metil-1-(metiltio)-3-oxopent-1-enilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **70B**.

MS (ESI) m/z 481.4 (M+H).

95 Preparación de *N,N*-diciclopropil-6-etil-4-(5-isopropil-1-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

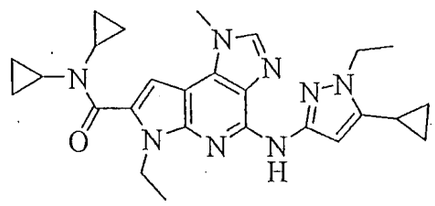
El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **73**.

MS (ESI) m/z 461.4 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 7.80 (s, 1H), 7.07

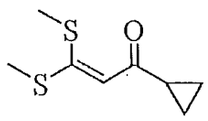
(s, 1H), 6.86 (s, 1H), 4.60 (c, J = 6.9 Hz, 2H), 4.02 (s, 3H), 3.79 (s, 3H), 2.93-3.01 (m, 1H), 2.79-2.86 (m, 2H), 1.52 (t, J = 7.1 Hz, 3H), 1.35 (d, J = 6.9 Hz, 6H), 0.82-0.89 (m, 4H), 0.72-0.78 (m, 4H).

Ejemplo 96



***N,N*-Diciclopropil-4-(5-ciclopropil-1-etil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

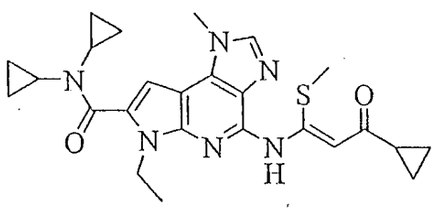
96A Preparación de 1-ciclopropil-3,3-bis(metiltio)prop-2-en-1-ona



El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **72A**.

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 6.23 (s, 1H), 2.50 (s, 3H), 2.48 (s, 3H), 1.86-1.94 (m, 1H), 1.09 (quint., J = 3.7 Hz, 2H), 0.82-0.88 (m, 2H).

96B Preparación de *(Z)*-*N*,*N*-diciclopropil-4-(3-ciclopropil-1-(metiltio)-3-oxoprop-1-enilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **72B**.

MS (ESI) m/z 479.3 (M+H).

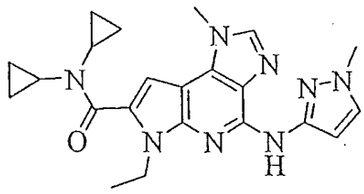
RMN ^{1}H (400 MHz, $CDCl_3$) δ: 14.81 (s, 1H), 7.75 (s, 1H), 6.85 (s, 1H), 5.58 (s, 1H), 4.62 (c, *J* = 7.0 Hz, 2H), 4.00 (s, 3H), 2.75-2.85 (m, 2H), 2.45 (s, 3H), 1.76-1.86 (m, 1H), 1.46 (t, *J* = 7.0 Hz, 3H), 1.17-1.28 (m, 2H), 0.69-0.91 (m, 10H).

96 Preparación de *N*,*N*-diciclopropil-4-(5-ciclopropil-1-etil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **73**.

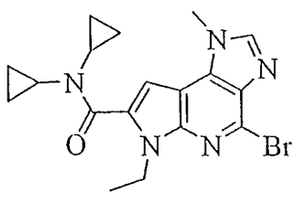
MS (ESI) m/z 473.3 (M+H).

Ejemplo 97



N,N-Diciclopropil-6-etil-1-metil-4-(1-metil-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

97A Preparación de 4-bromo-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



Un matraz de fondo redondo cargado con 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (134.4 mg, 0.397 mmol) en una atmósfera de nitrógeno se trató con dibromometano (397 µl). Se añadió nitrato de isoamilo (107 µl, 0.794 mmol) y la mezcla de reacción se calentó a 60°C durante 3.5 h y se enfrió a la ta. La mezcla de reacción se diluyó con acetato de etilo y se lavó con bicarbonato sódico acuoso saturado. Los productos orgánicos se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. Se aisló 4-bromo-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-

000359

carboxamida (0.156 g, 0.388 mmol, rendimiento del 98%) en forma de un sólido vidrioso de color pardo. El producto se usó inmediatamente en la siguiente reacción.

MS (ESI) m/z 404.2 (M+H)

97 Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(1-metil-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

A un vial con 1-metil-1*H*-pirazol-3-amina (11.89 mg, 0.122 mmol), $Pd_2(dba)_3$ (4.67 mg, 5.10 µmol), Xantphos (5.90 mg, 10.20 µmol) y carbonato de cesio (100 mg, 0.306 mmol) se le añadió 4-bromo-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **97A**, 41.0 mg, 0.102 mmol) en DME (1020 µl). La mezcla de reacción se roció con argón durante 5 min, el vial se tapó y la mezcla de reacción se calentó a 60°C durante 4 h y a 80°C durante 16 h. La mezcla de reacción se concentró al vacío. El residuo en bruto se purificó por cromatografía ultrarrápida en columna usando una columna Isco de 40 g eluyendo con MeOH al 0-5%/CH_2Cl_2 seguido de purificación adicional con HPLC preparativa. Se aisló *N,N*-diciclopropil-6-etil-1-metil-4-(1-metil-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (13 mg, 0.030 mmol, rendimiento del 29.5%) en forma de un sólido de color blanco.

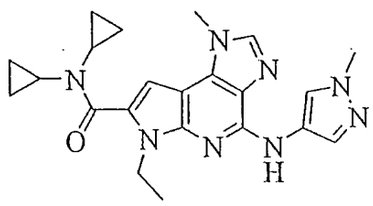
MS (ESI) m/z 419.3 (M+H)

RMN ^1H (400 MHz, CLOROFORMO-d) δ ppm 8.17 (s, 1H), 7.64

000360

(s, 1H), 7.31 (d, 1H, *J* = 2.26 Hz), 7.16 (d, 1H, *J* = 2.26 Hz), 6.86 (s, 1H), 4.65 (c, 2H, *J* = 7.03 Hz), 4.01 (s, 3H), 3.85 (s, 3H), 2.78-2.87 (m, 2H), 1.49 (t, 3H, *J* = 7.15 Hz), 0.81-0.89 (m, 4H), 0.71-0.80 (m, 4H).

Ejemplo 98

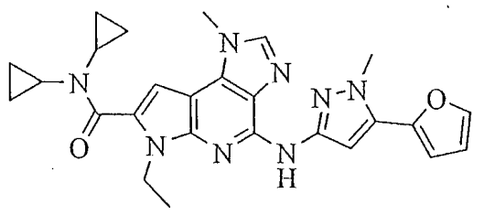


***N,N*-Diciclopropil-6-etil-1-metil-4-(1-metil-1*H*-pirazol-4-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Se preparó usando un procedimiento similar al que se ha usado para el ejemplo **97**.

RMN ^{1}H (500 MHz, CLOROFORMO-d) δ: 8.15 (s, 1H), 7.72 (s, 1H), 7.67 (s, 1H), 7.66 (s a, 1H), 6.85 (s, 1H), 4.65 (c, *J* = 7.2 Hz, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 2.79-2.86 (m, 2H), 1.50 (t, *J* = 7.1 Hz, 3H), 0.81-0.89 (m, 4H), 0.73-0.79 (m, 4H).

Ejemplo 99



***N,N*-Diciclopropil-6-etil-4-((5-(2-furil)-1-metil-1*H*-pirazol-3-il)amino)-1-metil-1,6-dihidroimidazo[4,5-**

000361

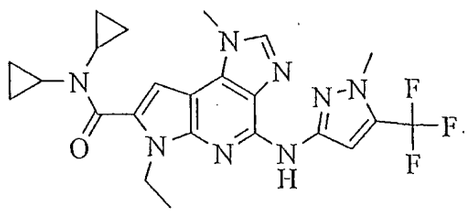
d]pirrolo[2,3-b]piridin-7-carboxamida

Se preparó por un procedimiento similar al usado para el ejemplo **73**.

MS (ESI) m/z 485.4 (M+H)

RMN ^{1}H (CDCl3) δ ppm 8.03 (s a, 1H), 7.58 (s, 1H), 7.48 (m, 1H), 7.35 (s, 1H), 6.79 (s, 1H), 6.54 (d, 1H, *J* = 3.3 Hz), 6.47 (m, 1H), 4.58 (c, 2H, *J* = 7.04 Hz), 3.94 (s, 3H), 3.93 (s, 3H), 2.74 (m, 2H), 1.44 (t, 3H), 0.69-0.79 (m, 8H).

Ejemplo 100



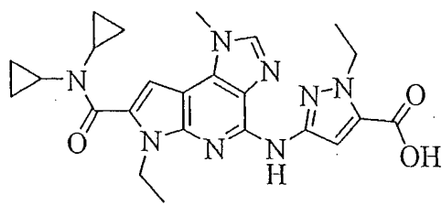
***N,N*-Diciclopropil-6-etil-1-metil-4-((1-metil-5-(trifluorometil)-1*H*-pirazol-3-il)amino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Se preparó por un procedimiento similar al usado para el ejemplo **73**.

MS (ESI) m/z 487.3 (M+H)

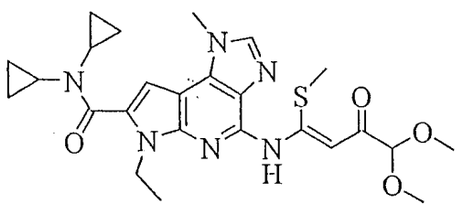
RMN ^{1}H (CDCl3) δ ppm 7.41 (s, 1H), 7.12 (s, 1H), 6.78 (s, 1H), 4.52 (c, 2H, *J* = 7.04 Hz), 4.11 (s, 3H), 3.86 (s, 3H), 2.74 (m, 2H), 1.42 (t, 3H, *J* = 7.15 Hz), 0.67-0.80 (m, 8H).

Ejemplo 101



Ácido 3-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-1-etil-1*H*-pirazol-5-carboxílico

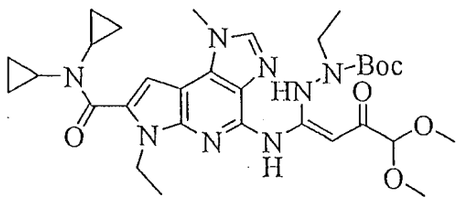
101A Preparación de (*Z*)-*N*,*N*-diciclopropil-4-(4,4-dimetoxi-1-(metiltio)-3-oxobut-1-enilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



Se añadió hidruro sódico (142 mg, 3.55 mmol) a 4-amino-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 400 mg, 1.182 mmol) en DMF (7 ml) a la temperatura ambiente y la mezcla se agitó durante 30 min, se añadió 1,1-dimetoxi-4,4-bis(metiltio)but-3-en-2-ona (394 mg, 1.773 mmol) y la agitación se continuó durante una noche. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua, cloruro de litio al 10% y agua. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al

vacío. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO automatizado (columna de 80 g, eluyendo con metanol/diclorometano al 2-5%). Se obtuvo (*Z*)-*N*,*N*-diciclopropil-4-(4,4-dimetoxi-1-(metiltio)-3-oxobut-1-enilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (484 mg, 0.944 mmol, rendimiento del 80%) en forma de un sólido de color amarillo.

101B Preparación de 2-(1-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4,4-dimetoxi-3-oxobut-1-enil)-1-etilhidrazinacarboxilato de *(Z)*-*terc*-butilo

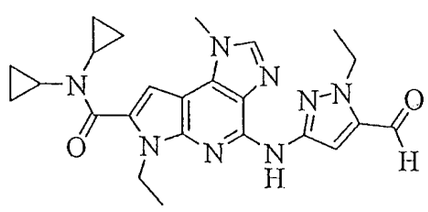


Una mezcla de (Z)-*N*,*N*-diciclopropil-4-(4,4-dimetoxi-1-(metiltio)-3-oxobut-1-enilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **101A**, 160 mg, 0.312 mmol) y 1-etilhidrazinacarboxilato de *terc*-butilo (125 mg, 0.780 mmol) en ácido acético (2 ml) se agitó a 35°C durante una noche. El solvente se evaporó y el producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO automatizado (columna de 40 g, eluyendo con

metanol al 2-8%/diclorometano). Se obtuvo 2-(1-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4,4-dimetoxi-3-oxobut-1-enil)-1-etilhidrazinacarboxilato de *(Z)*-*terc*-butilo (195 mg, 0.312 mmol, rendimiento del 100%) en forma de un sólido de color amarillo.

MS (ESI) m/z 625.5 (M+H).

101C Preparación de *N,N*-diciclopropil-6-etil-4-(1-etil-5-formil-1-*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



Una mezcla de 2-(1-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4,4-dimetoxi-3-oxobut-1-enil)-1-etilhidrazinacarboxilato de *(Z)*-*terc*-butilo (187 mg, 0.299 mmol) y TFA (al 25% en dicloroetano, 1.0 ml, 2.99 mmol) se calentó a 60°C durante 0.5 h y el análisis por LC/MS mostró que la reacción se había completado. El solvente se evaporó y el residuo se repartió entre bicarbonato sódico saturado y diclorometano. Las fases se separaron y la fase acuosa se extrajo con diclorometano dos veces más. La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se

000365

concentró al vacío. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO automatizado (columna de 24 g, eluyendo con metanol al 1-5%/diclorometano). Se obtuvo *N,N*-diciclopropil-6-etil-4-(1-etil-5-formil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (80 mg, 0.174 mmol, rendimiento del 58.0%) en forma de un sólido de color amarillo.

MS (ESI) m/z 461.4 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 9.88 (s, 1H), 8.25 (s, 1H), 7.76 (s, 1H), 7.67 (s, 1H), 6.87 (s, 1H), 4.67 (d, *J* = 7.2 Hz, 2H), 4.52 (c, *J* = 7.1 Hz, 2H), 4.02 (s, 3H), 2.80-2.86 (m, 2H), 1.52 (t, *J* = 7.1 Hz, 3H), 1.44 (t, *J* = 7.2 Hz, 3H), 0.83-0.89 (m, 4H), 0.73-0.79 (m, 4H).

101 Preparación de ácido 3-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-1-etil-1*H*-pirazol-5-carboxílico

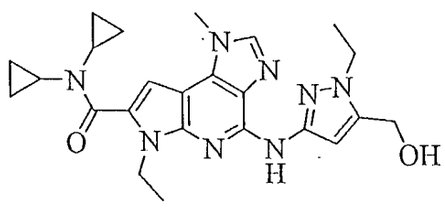
Una mezcla de *N,N*-diciclopropil-6-etil-4-(1-etil-5-formil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **101C**, 27 mg, 0.059 mmol) y OXONE (79 mg, 0.129 mmol) en DMF se agitó a la temperatura ambiente durante 20 h. Se añadió agua y la mezcla se extrajo 3 veces con diclorometano. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto se purificó con HPLC preparativa,

dando ácido 3-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-1-etil-1*H*-pirazol-5-carboxílico (20 mg, rendimiento del 98%)

MS (ESI) m/z 477.4 (M+H).

RMN ^{1}H (500 MHz, METANOL-d_4) δ: 7.96 (s, 1H), 7.48 (s, 1H), 7.18 (s, 1H), 4.70 (c, *J* = 6.9 Hz, 2H), 4.60 (c, *J* = 7.2 Hz, 2H), 4.09 (s, 3H), 2.94-3.00 (m, 2H), 1.45 (t, *J* = 6.94 Hz, 3H), 1.44 (t, *J* = 7.21 Hz, 3H), 0.85-0.92 (m, 4H), 0.77-0.82 (m, 4H).

Ejemplo 102



***N,N*-Diciclopropil-6-etil-4-(1-etil-5-(hidroximetil)-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

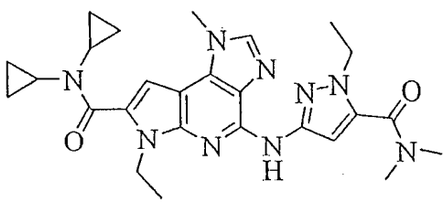
Se añadió bromuro sódico (al 10% en peso en alúmina, 13.14 mg, 0.035 mmol) a *N,N*-diciclopropil-6-etil-4-(1-etil-5-formil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **101C**, 16 mg, 0.035 mmol) en metanol (1 ml) a la temperatura ambiente y la mezcla de reacción se agitó durante 0.5 h. La alúmina sólida se retiró por filtración y el filtrado se concentró al vacío. El producto en bruto se purificó por cromatografía ultrarrápida

sobre gel de sílice usando un sistema ISCO automatizado (columna de 4 g, eluyendo con metanol al 2-10%/diclorometano). Se obtuvo *N,N*-diciclopropil-6-etil-4-(1-etil-5-(hidroximetil)-1-*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (14 mg, rendimiento del 86%) en forma de un sólido de color blanco.

MS (ESI) m/z 563.4 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.59 (s, 1H), 7.08 (s, 1H), 6.81 (s, 1H), 4.72 (d, *J* = 4.7 Hz, 2H), 4.57 (c, *J* = 7.2 Hz, 2H), 4.15 (c, *J* = 7.3 Hz, 2H), 3.97 (s, 3H), 2.76-2.84 (m, 3H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 0.81-0.87 (m, 4H), 0.71-0.76 (m, 4H).

Ejemplo 103



***N,N*-Diciclopropil-4-(5-(dimetilcarbamoil)-1-etil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

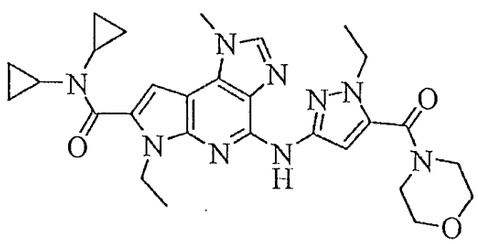
Una mezcla de ácido 3-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-1-etil-1*H*-pirazol-5-carboxílico (ejemplo **101**, 28 mg, 0.059 mmol), HATU (26.8 mg, 0.071 mmol) y dimetilamina (2 M en THF, 59 µl, 0.118 mmol) en DMF (1 ml) se agitó a la temperatura ambiente durante 2 h. Se añadió agua y la mezcla de reacción se

extrajo 3 veces con acetato de etilo. Las fases orgánicas combinadas se lavaron dos veces con cloruro de litio al 10%, se secaron sobre sulfato de magnesio, se filtraron y se concentraron al vacío. El producto en bruto se purificó por HPLC preparativa (columna Phenomenex Luna 5u C18, columna de 21.2 x 250 mm, tiempo de retención de 15.317 min, gradiente del 30-100% de metanol acuoso durante 20 minutos que contenía acetato de amonio 10 mM, caudal 20 ml/min y controlando a 254 nm). Se obtuvo *N,N*-diciclopropil-4-(5-(dimetilcarbamoil)-1-etil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (20 mg, rendimiento del 66.9%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 504.5 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.38 (s a, 1H), 7.75 (s, 1H), 7.28 (s, 1H), 6.86 (s, 1H), 4.61 (c, *J* = 7.2 Hz, 2H), 4.27 (c, *J* = 7.0 Hz, 5H), 4.03 (s, 3H), 3.27 (s, 3H), 3.17 (s, 3H), 2.79-2.86 (m, 2H), 1.47 (t, *J* = 7.14 Hz, 3H), 1.46 (t, *J* = 7.14 Hz, 3H), 0.83-0.89 (m, 4H), 0.73-0.78 (m, 4H).

Ejemplo 104



***N,N*-Diciclopropil-6-etil-4-(1-etil-5-(morfolin-4-carbonil)-1*H*-pirazol-3-ilamino)-1-metil-1,6-**

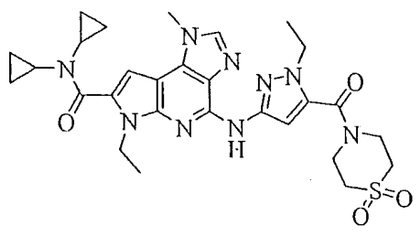
dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **103**.

MS (ESI) m/z 546.5 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.19 (s, 1H), 6.87 (s, 1H), 4.60 (c, *J* = 6.9 Hz, 2H), 4.28 (c, *J* = 7.2 Hz, 5H), 4.07 (s, 3H), 3.82 (s a, 5H), 3.76 (s a, 3H), 2.74-2.93 (m, 4H), 1.48 (t, *J* = 7.14 Hz, 3H), 1.47 (t, *J* = 7.14 Hz, 3H), 0.84-0.90 (m, 4H), 0.74-0.78 (m, 4H).

Ejemplo 105



***N,N*-Diciclopropil-6-etil-4-(1-etil-5-(tiomorfolina 1,1-dioxido-4-carbonil)-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

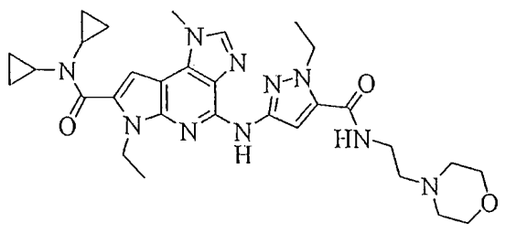
El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **103**.

MS (ESI) m/z 594.5 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.19 (s, 1H), 6.83 (s, 1H), 4.55 (c, *J* = 7.03 Hz, 2H), 4.20-4.34 (m, 6H), 4.06 (s, 3H), 3.13 (s a, 4H), 2.77-2.89 (m, 2H), 1.46 (t, *J* = 7.21 Hz, 3H), 1.43 (t, *J* = 7.21 Hz, 3H), 0.82-0.88

(m, 4H), 0.72-0.77(m, 4H).

Ejemplo 106



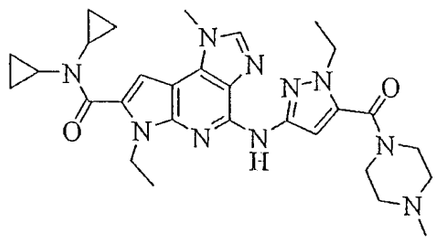
***N,N*-Diciclopropil-6-etil-4-(1-etil-5-(2-morfolinoetilcarbamoil)-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **103**.

MS (ESI) m/z 589.6 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.68 (s, 1H), 7.45 (s, 1H), 6.87 (s, 1H), 4.64 (c, *J* = 6.9 Hz, 2H), 4.54 (c, *J* = 7.2 Hz, 2H), 4.03 (s, 3H), 3.77 (s a, 4H), 3.61 (s a, 2H), 2.80-2.87 (m, 2H), 2.67 (s a, 2H), 2.57 (s a, 3H), 1.71 (s a, 3H), 1.53 (t, *J* = 7.1 Hz, 3H), 1.46 (t, *J* = 7.1 Hz, 3H), 0.84-0.90 (m, 4H), 0.74-0.79 (m, 4H).

Ejemplo 107



***N,N*-Diciclopropil-6-etil-4-(1-etil-5-(4-**

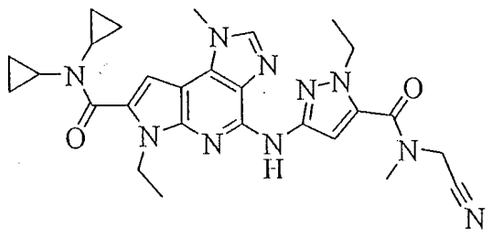
metilpiperazina-1-carbonil)-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **103**.

MS (ESI) m/z 559.5 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 7.66 (s, 1H), 7.26 (s, 1H), 6.87 (s, 1H), 4.63 (c, *J* = 6.9 Hz, 2H), 4.26 (c, *J* = 7.2 Hz, 2H), 4.02 (s, 3H), 3.88(s a, 4H), 2.80-2.86 (m, 2H), 2.54 (s a, 4H), 2.40 (s a, 3H), 1.48 (t, *J* = 7.1 Hz, 3H), 1.47 (t, *J* = 7.1 Hz, 3H), 0.82-0.90 (m, 4H), 0.73-0.79 (m, 4H).

Ejemplo 108



4-(5-((Cianometil)(metil)carbamoil)-1-etil-1*H*-pirazol-3-ilamino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

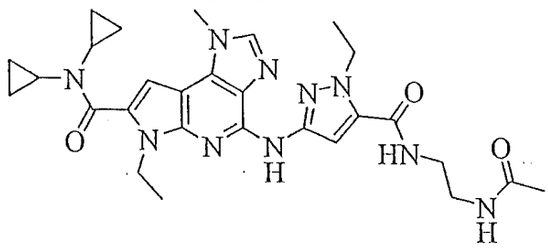
El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **103**.

MS (ESI) m/z 529.3 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.37 (s a, 1H), 7.77 (s, 1H), 7.39 (s, 1H), 6.86 (s, 1H), 4.62 (c, *J* = 7.2 Hz, 2H), 4.54 (s a, 2H), 4.27-4.34 (m, 1H), 4.04 (s, 3H), 3.41 (s a,

3H), 2.79-2.86 (m, 2H), 1.47 (t, *J* = 7.2 Hz, 6H), 0.83-0.89 (m, 4H), 0.73-0.78 (m, 4H).

Ejemplo 109



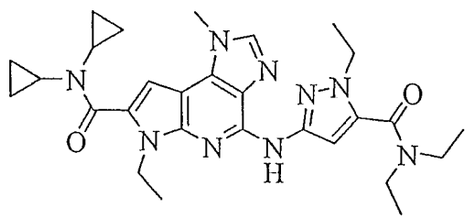
4-((5-((2-Acetamidoetil)carbamoil)-1-etil-1*H*-pirazol-3-il)amino)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **103**.

MS (ESI) m/z 561.5 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 7.77 (s a, 2H), 7.40 (s, 1H), 6.72 (s, 1H), 4.48-4.56 (m, 4H), 3.99 (s, 3H), 3.61-3.66 (m, 2H), 3.52-3.58 (m, 2H), 2.81 (m, 2H), 2.02 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 6.9 Hz, 3H), 1.26 (s, 1H), 0.82-0.90 (m, 4H), 0.70-0.77 (m, 4H).

Ejemplo 110



***N*,*N*-Diciclopropil-4-((5-(dietilcarbamoil)-1-etil-**

000373

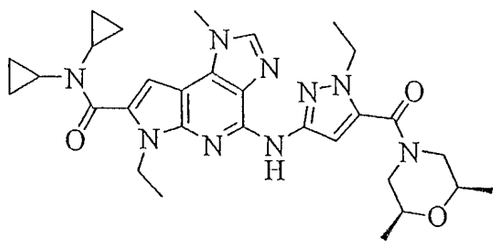
1*H*-pirazol-3-il)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **103**.

MS (ESI) m/z 532.4 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.29 (s a, 1H), 7.70 (s, 1H), 7.23 (s, 1H), 6.85 (s, 1H), 4.62 (c, *J* = 6.9 Hz, 2H), 4.20 (c, *J* = 7.2 Hz, 2H), 4.00 (s, 3H), 3.51-3.62 (m, 4H), 2.77-2.85 (m, 2H), 1.40-1.47 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 6H), 0.80-0.88 (m, 4H), 0.72-0.77 (m, 4H).

Ejemplo 111



***N*,*N*-Diciclopropil-4-((5-(((2R,6S)-2,6-dimetil-4-morfolinil)carbonil)-1-etil-1*H*-pirazol-3-il)amino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

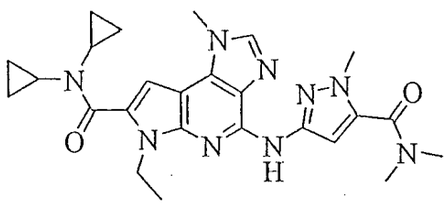
El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **103**.

MS (ESI) m/z 574.4 (M+H).

RMN ^{1}H (500 MHz, $CDCl_3$) δ: 8.30 (s a, 1H), 7.72 (s,

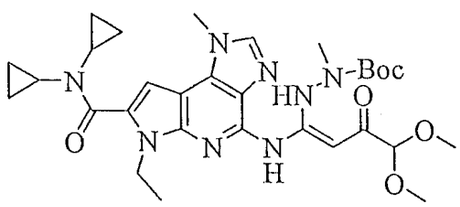
1H), 7.21 (s, 1H), 6.86 (s, 1H), 4.62 (c, *J* = 6.9 Hz, 2H), 4.21-4.28 (m, 2H), 4.07-4.20 (m, 2H), 4.01 (s, 3H), 3.61 (s a, 2H), 2.91 (s a, 1H), 2.79-2.85 (m, 2H), 2.60 (s a 1H), 1.47 (t, *J* = 7.2 Hz, 3H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.07-1.36 (m, 6H), 0.81-0.88 (m, 4H), 0.72-0.78 (m, 4H).

Ejemplo 112



***N,N*-Diciclopropil-4-(5-(dimetilcarbamoil)-1-metil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

112A Preparación de 2-(1-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-4,4-dimetoxi-3-oxobut-1-enil)-1-metilhidrazinacarboxilato de *(Z)*-*terc*-butilo

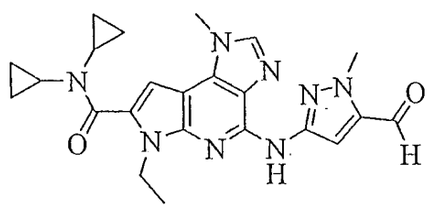


El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **101B**.

000375

MS (ESI) m/z 611.7 (M+H).

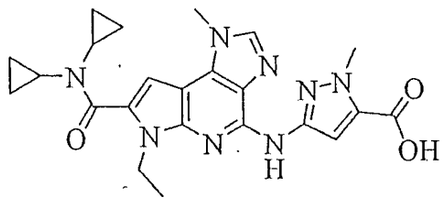
112B Preparación de *N,N*-diciclopropil-6-etil-4-(5-formil-1-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el Ejemplo **101C**.

MS (ESI) m/z 447.3 (M+H).

112C Preparación de ácido 3-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-1-metil-1*H*-pirazol-5-carboxílico



El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **101**.

MS (ESI) m/z 463.3 (M+H).

000376

112 Preparación de *N,N*-diciclopropil-4-(5-(dimetilcarbamoil)-1-metil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

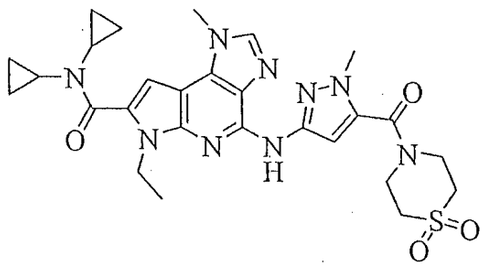
Una mezcla de ácido 3-(7-(diciclopropilcarbamoil)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-4-ilamino)-1-metil-1*H*-pirazol-5-carboxílico (39.8 mg, 0.086 mmol), HATU (49.0 mg, 0.129 mmol) y dimetilamina 2 M en THF (0.086 ml, 0.172 mmol) en DMF (2 ml) se agitó a la temperatura ambiente durante 2 h. Se añadió agua y la mezcla de reacción se extrajo 3 veces con acetato de etilo. Las fases orgánicas combinadas se lavaron dos veces con cloruro de litio al 10%, se secaron sobre sulfato de magnesio, se filtraron y se concentraron al vacío. El producto en bruto se purificó por HPLC preparativa, dando *N,N*-diciclopropil-4-(5-(dimetilcarbamoil)-1-metil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (23 mg, rendimiento del 54.1%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 490.2 (M+H).

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.67 (s, 1H), 7.34 (s, 1H), 6.86 (s, 1H), 4.61 (c, *J* = 7.0 Hz, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 3.29 (s, 3H), 3.16 (s, 3H), 2.79-2.86 (m, 2H), 1.47 (t, *J* = 7.0 Hz, 3H), 0.82-0.89 (m, 4H), 0.72-0.79 (m, 4H).

000377

Ejemplo 113



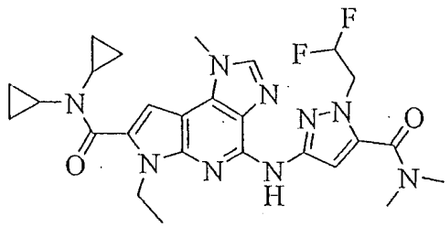
N,N-Diciclopropil-6-etil-4-(1-metil-5-(tiomorfolina 1,1-dioxido-4-carbonil)-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para el ejemplo **112**.

MS (ESI) m/z 580.3 (M+H).

RMN ^{1}H (400 MHz, $CDCl_3$) δ: 8.29 (s., 1H), 7.69 (s, 1H), 7.30 (s, 1H), 6.83 (s, 1H), 4.57 (c, *J* = 6.8 Hz, 2H), 4.31 (s a, 4H), 4.00 (s, 3H), 3.93 (s, 3H), 3.15 (s a, 4H), 2.77-2.88 (m, 2H), 1.45 (t, *J* = 7.0 Hz, 3H), 0.80-0.91 (m, 4H), 0.69-0.80 (m, 4H).

Ejemplo 114



N,N-Diciclopropil-4-(1-(2,2-difluoroetil)-5-(dimetilcarbamoil)-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

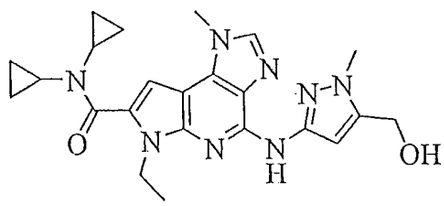
009378

El compuesto del título se preparó usando un procedimiento análogo al que se ha usado para preparar el Ejemplo **112**; con la excepción de que se utilizó el ejemplo **80A**.

MS (ESI) m/z 540.4(M+H).

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ: 8.41 (s a, 1H), 7.73 (s, 1H), 7.43 (s, 1H), 6.86 (s, 1H), 6.17 (tt, *J* = 55.9, 4.2 Hz, 1H), 4.57-4.72 (m, 4H), 4.01 (s, 3H), 3.30 (s, 3H), 3.16 (s, 3H), 2.78-2.86 (m, 2H), 1.47 (t, *J* = 7.0 Hz, 3H), 0.80-0.89 (m, 4H), 0.71-0.80 (m, 4H).

Ejemplo 115



***N,N*-Diciclopropil-6-etil-4-(5-(hidroximetil)-1-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

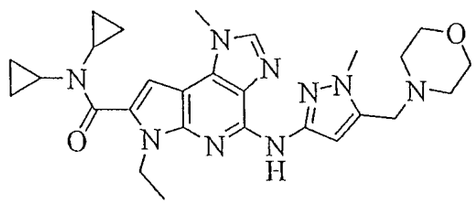
El compuesto del título se preparó por un procedimiento similar al que se ha usado para el ejemplo **102**.

MS (ESI) m/z 449.3 (M+H)

RMN ^{1}H (CDCl3) δ ppm 8.11 (s a, 1H), 7.67 (s, 1H), 7.16 (s, 1H), 6.88 (s, 1H), 4.75 (d, 2H, *J* = 5.94 Hz), 4.67 (c, 2H, *J* = 7.26 Hz), 4.03 (s, 3H), 3.89 (s, 3H), 2.84 (m, 2H), 1.68 (t, 3H, *J* = 6.16 Hz), 1.50 (t, 3H, *J* = 7.15 Hz), 0.75-0.89 (m, 8H).

000379

Ejemplo 116



***N,N*-Diciclopropil-6-etil-1-metil-4-(1-metil-5-(morfolinometil)-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

A una solución agitada de *N,N*-diciclopropil-6-etil-4-(5-formil-1-metil-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **112B**, 22 mg, 0.049 mmol) y tamices moleculares 4 Å (30 mg) en MeOH (2 ml) se le añadió morfolina (0.017 ml, 0.197 mmol). Después de que la solución se agitara a la temperatura ambiente durante 12 h, se añadió borohidruro sódico (7.46 mg, 0.197 mmol) y se agitó durante 3 h. La solución se llevó a un valor de pH = 4 con HCl 1 N, se neutralizó con bicarbonato sódico acuoso saturado y después se extrajo con CH_2Cl_2. La fase orgánica se secó sobre sulfato de magnesio anhidro y se concentró al vacío. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice usando una columna Isco de 40 g eluyendo en MeOH al 0-10%/CH_2Cl_2, produciendo *N,N*-diciclopropil-6-etil-1-metil-4-(1-metil-5-(morfolinometil)-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

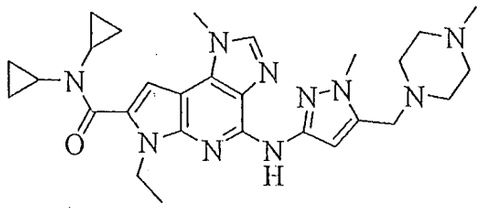
000380

(14.3 mg, 0.027 mmol, rendimiento del 54.9%) en forma de un sólido de color blanco.

MS (ESI) m/z 518.3 (M+H)

RMN ^{1}H (CDCl3) δ ppm 7.99 (s a, 1H), 7.57 (s, 1H), 6.99 (s, 1H), 6.78 (s, 1H), 4.56 (c, 2H *J* = 7.04 Hz), 3.93 (s, 3H), 3.77 (s, 3H), 3.64 (m, 4H), 3.48 (s, 2H), 2.75 (m, 2H), 2.45 (m, 4H), 1.42 (t, 3H *J* = 7.02 Hz), 0.66-0.80 (m, 8H).

Ejemplo 117



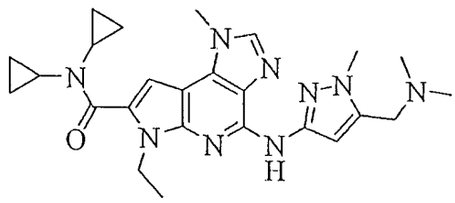
***N,N*-Diciclopropil-6-etil-1-metil-4-(1-metil-5-((4-metilpiperazin-1-il)metil)-1*H*-pirazol-3-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Se sintetizó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **116**.

MS (ESI) m/z 531.4 (M+H)

RMN ^{1}H (CDCl3) δ ppm 8.05 (s a, 1H), 7.60 (s, 1H), 7.01 (s, 1H), 6.78 (s, 1H), 4.56 (c, 2H *J* = 6.75 Hz), 3.95 (s, 3H), 3.72 (s, 3H), 3.61 (s, 2H), 2.96 (m, 4H), 2.76 (m, 4H), 2.74 (m, 2H), 2.71 (s, 3H), 1.42 (t, 3H, *J* = 7.04 Hz), 0.67-0.80 (m, 8H).

Ejemplo 118



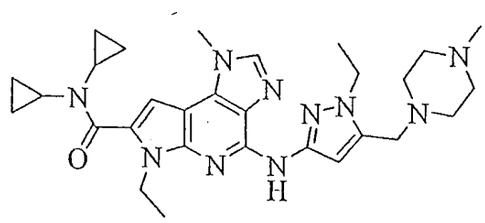
***N,N*-Diciclopropil-4-(5-((dimetilamino)metil)-1-metil-1*H*-pirazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Se sintetizó usando un procedimiento análogo al que se ha usado para preparar el ejemplo **116**.

MS (ESI) m/z 476.4 (M+H)

RMN ^{1}H (CDCl3) δ ppm 7.45 (s, 1H), 7.33 (s, 1H), 6.84 (s, 1H), 4.52 (c, 2H, *J* = 7.04 Hz), 4.25 (s, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 2.80 (s, 6H), 2.77 (m, 2H), 1.37 (t, 3H, *J* = 6.82 Hz), 0.64-0.87 (m, 8H).

Ejemplo 119



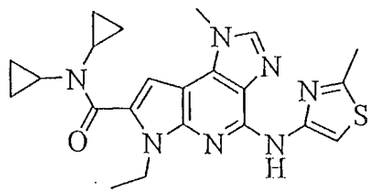
***N,N*-Diciclopropil-6-etil-4-(1-etil-5-((4-metilpiperazin-1-il)metil)-1*H*-pirazol-3-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

Se preparó usando el intermediario **101B** y el procedimiento que se ha usado para el ejemplo **116**.

MS (ESI) m/z 545.4 (M+H)

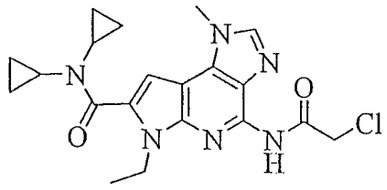
RMN ^{1}H (CDCl3) δ ppm 8.03 (s, 1H), 7.57 (s, 1H), 7.00 (s, 1H), 6.78 (s,1 H), 4.55 (c, 2H, *J* = 7.04 Hz), 4.03 (c, 2H, *J* = 5.72 Hz), 3.94 (s, 3H), 3.60 (s, 2H), 2.93 (s a, 3H), 2.63-2.84 (m a, 10H), 1.42 (t, 3H, *J* = 7.04 Hz), 1.35 (t. 3H, *J* = 7.26 Hz), 0.69-0.79 (m, 8H).

Ejemplo 120



N,N-Diciclopropil-6-etil-1-metil-4-(2-metiltiazol-4-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

120A Preparación de 4-(2-cloroacetamido)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



A un matraz de fondo redondo cargado con 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 47.2 mg, 0.139 mmol) se le añadieron diclorometano (697 µl) y

trietilamina (35.0 µl, 0.251 mmol). Se añadió gota a gota cloruro de cloroacetilo (12.20 µl, 0.153 mmol). La mezcla de reacción se agitó a la ta durante 16 h. Se añadió más cloruro de cloroacetilo (12.20 µl, 0.153 mmol). La mezcla de reacción se diluyó con diclorometano. Los extractos orgánicos se lavaron con agua, se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. Se aisló 4-(2-cloroacetamido)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (58.5 mg, rendimiento del 101%) en forma de una pasta de color naranja. El material se usó en las siguientes reacciones sin purificación adicional.

MS (ESI) m/z 415.0 (M+H)

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 8.04 (s a, 1H), 6.90 (s, 1H), 5.31 (s, 2H), 4.62 (c, 2H, *J* = 7.11 Hz), 4.24 (s, 3H), 2.77-2.88 (m, 2H), 1.47 (t, 3H, *J* = 7.03 Hz), 0.83-0.92 (m, 4H), 0.71-0.80 (m, 4H).

120 Preparación de *N,N-dicicl*opropil-6-etil-1-metil-4-(2-metiltiazol-4-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

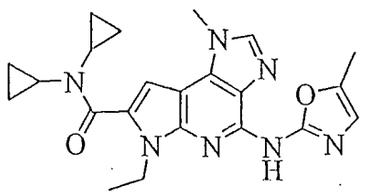
A una solución de 4-(2-cloroacetamido)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (58.5 mg, 0.141 mmol) en DMF (176 µl) se le añadió tioacetamida (12.71 mg, 0.169 mmol). El vial se tapó y la mezcla de reacción se calentó a

80°C durante 3 h. La mezcla de reacción se concentró al vacío. El residuo en bruto se recogió en MeOH y se purificó mediante HPLC preparativa. Se aisló *N,N*-diciclopropil-6-etil-1-metil-4-(2-metiltiazol-4-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (4.05 mg, rendimiento del 6.6%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 436.0 (M+H)

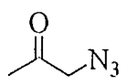
RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.78 (s, 1H), 8.08 (s, 1H), 7.74 (s, 1H), 7.20 (s, 1H), 4.55 (c, 2H, *J* = 7.19 Hz), 4.03 (s, 3H), 2.87-2.98 (m, 2H), 2.65 (s, 3H), 1.34 (t, 3H, *J* = 7.03 Hz), 0.73-0.81 (m, 4H), 0.62-0.69 (m, 4H).

Ejemplo 121



***N,N*-Diciclopropil-6-etil-1-metil-4-(5-metiloxazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

121A Preparación de 1-azidopropan-2-ona

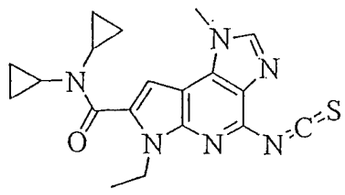


A una solución de cloroacetona (0.680 ml, 8.53 mmol) en acetona (10 ml) y agua (5.00 ml) se le añadió azida sódica (0.555 g, 8.53 mmol). La mezcla de reacción se agitó a la ta durante 3.5 h. La mezcla de reacción se concentró a

presión reducida. La solución acuosa restante se extrajo con diclorometano (2 x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío, produciendo 1-azidopropan-2-ona (0.641 g, 6.47 mmol, rendimiento del 76%) en forma de un aceite de color pardo. Este material se usó sin ninguna purificación adicional.

RMN ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 3.96 (s, 2H), 2.21 (s, 3H).

121B Preparación de *N,N*-diciclopropil-6-etil-4-isotiocianato-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



A una mezcla de 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **1J**, 194.5 mg, 0.575 mmol) en diclorometano (2874 µl) en un matraz de fondo redondo en una atmósfera de nitrógeno se le añadió 1.1'-tiocarbonildi-2(1*H*)-piridona (133 mg, 0.575 mmol). La mezcla de reacción se agitó a la ta durante 16 h. La mezcla de reacción se concentró a presión reducida. Se aisló *N,N*-diciclopropil-6-etil-4-isotiocianato-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (180 mg, rendimiento del 94%) en

forma de un sólido pegajoso de color amarillo. El material se usó tal cual en las siguientes reacciones.

MS (ESI) m/z 381.1 (M+H).

121 Preparación de *N,N*-diciclopropil-6-etil-1-metil-4-(5-metiloxazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

A una solución de *N,N*-diciclopropil-6-etil-4-isotiocianato-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **121B**, 45.7 mg, 0.120 mmol) en dioxano (343 µl) se le añadieron 1-azidopropan-2-ona (14.28 mg, 0.144 mmol) y trifenilfosfina (37.8 mg, 0.144 mmol). Los contenidos del matraz se sumergieron en un baño de aceite precalentado durante 35 min y se enfriaron a la temperatura ambiente. El residuo se diluyó con acetato de etilo y se inactivó con bicarbonato sódico acuoso saturado. La fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron al vacío. El residuo en bruto se purificó por cromatografía ultrarrápida en una columna Isco de 12 g eluyendo con MeOH al 1-10%/CH_2Cl_2. El sólido de color amarillo claro se recogió en MeOH y se purificó adicionalmente por HPLC preparativa. Se aisló *N,N*-diciclopropil-6-etil-1-metil-4-(5-metiloxazol-2-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (10 mg, rendimiento del 25%) en forma de un

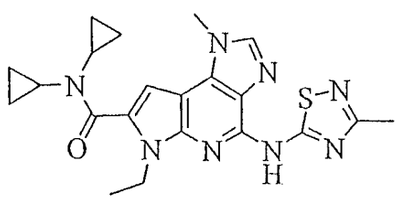
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sólido de color blanco.

MS (ESI) m/z 420.0 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 9.86 (s, 1H), 8.05 (s, 1H), 7.18 (s, 1H), 6.66 (d, 1H, *J* = 1.51 Hz), 4.41 (c, 2H, *J* = 7.28 Hz), 4.02 (s, 3H), 2.85-2.98 (m, 2H), 2.21-2.29 (m, 3H), 1.27 (t, 3H, *J* = 7.15 Hz), 0.71-0.80 (m, 4H), 0.60-0.70 (m, 4H).

Ejemplo 122



***N,N*-Diciclopropil-6-etil-1-metil-4-(3-metil-1,2,4-tiadiazol-5-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida**

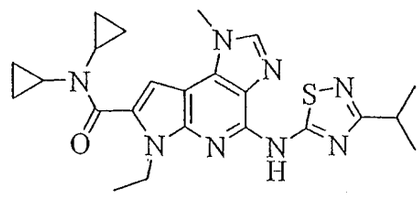
Una mezcla de *N,N*-diciclopropil-6-etil-4-isotiocianato-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **121B**, 0.042 g, 0.111 mmol), clorhidrato de acetamidina (10.49 mg, 0.111 mmol) y base de Hünig (0.058 ml, 0.333 mmol) en DMF (0.617 ml) se agitó a la ta durante una noche. Se añadió azodicarboxilato de dietilo (0.088 ml, 0.222 mmol) y la agitación se continuó a la temperatura ambiente durante 16 h. La mezcla de reacción se concentró. El residuo se recogió en MeOH y se purificó por HPLC preparativa. Se aisló *N,N*-diciclopropil-6-etil-1-metil-

4-(3-metil-1,2,4-tiadiazol-5-ilamino)-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (4.32 mg, rendimiento del 9%) en forma de un sólido de color amarillo claro.

MS (ESI) m/z 437.1 (M+H)

RMN ^{1}H (400 MHz, MeOD) δ ppm 8.10 (s, 1H), 7.28 (s, 1H), 4.73 (c, 2H, *J* = 7.19 Hz), 4.13 (s, 3H), 2.93-3.01 (m, 2H), 2.53 (s, 3H), 1.53 (t, 3H, *J* = 7.03 Hz), 0.83-0.92 (m, 4H), 0.76-0.83 (m, 4H).

Ejemplo 123



Preparación de *N,N*-diciclopropil-6-etil-4-(3-isopropil-1,2,4-tiadiazol-5-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

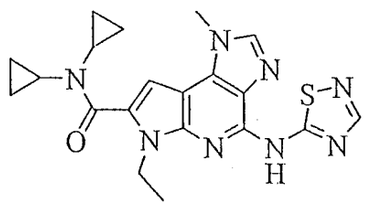
Este compuesto se preparó de acuerdo con el ejemplo **122** usando clorhidrato de isobutirimidamida (15.08 mg, 0.123 mmol) y azodicarboxilato de disopropilo (47.8 µl, 0.246 mmol). Se aisló *N,N*-diciclopropil-6-etil-4-(3-isopropil-1,2,4-tiadiazol-5-ilamino)-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (21 mg, rendimiento del 34.9%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 465.3 (M+H)

RMN ^{1}H (400 MHz, DMSO-d_6) δ ppm 12.24 (s, 1H), 8.18

(s, 1H), 7.28 (s, 1H), 4.64 (c, 2H, *J* = 6.94 Hz), 4.06 (s, 3H), 3.10 (ddd, 1H, *J* = 13.93, 6.90, 6.78 Hz), 2.86-3.00 (m, 2H), 1.42 (t, 3H, *J* = 7.03 Hz), 1.32 (s, 3H), 1.31 (s, 3H), 0.72-0.81 (m, 4H), 0.63-0.71 (m, 4H).

Ejemplo 124



4-(1,2,4-Tiadiazol-5-ilamino)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

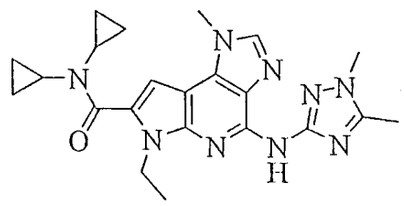
Se calentó una mezcla de *N,N*-diciclopropil-6-etil-1-metil-4-tioureido-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (**ejemplo 2B**, 30 mg, 0.075 mmol) y 1,1-dimetoxi-*N,N*-dimetilmetanamina (1 g, 8.39 mmol) a 50°C durante 2 h. El exceso de 1,1-dimetoxi-*N,N*-dimetilmetanamina se evaporó al vacío, el producto en bruto del ejemplo se disolvió en diclorometano (1 ml) y se añadió *O*-(mesitilsulfonil)hidroxilamina (24.4 mg, 0.113 mmol). La mezcla de reacción se agitó a la temperatura ambiente durante 3 h. Se añadió agua y las fases se separaron. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo en bruto se purificó por HPLC preparativa, dando 4-(1,2,4-tiadiazol-5-ilamino)-*N,N*-

diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (7 mg, rendimiento del 19.20%) en forma de un sólido de color amarillo.

MS (ESI) m/z 423.0 (M+H).

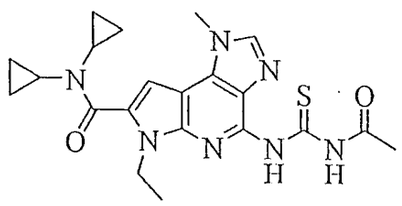
RMN ^{1}H (500 MHz, CD_3OD) δ: 8.32 (s, 1H), 8.27 (s, 1H), 7.38 (d, *J* = 4.4 Hz, 1H), 7.28 (s, 1H), 4.74 (c, *J* = 7.0 Hz, 2H), 4.15 (s, 3H), 2.94-3.00 (m, 2H), 1.53 (t, *J* = 7.0 Hz, 3H), 0.82-0.89 (m, 4H), 0.75-0.82 (m, 4H).

Ejemplo 125



_N,N_-Diciclopropil-4-(1,5-dimetil-1_H_-1,2,4-triazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

125A Preparación de 4-(3-acetiltioureido)-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida



A una solución de 4-amino-*N,N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-

carboxamida (ejemplo **1J**, 60 mg, 0.177 mmol) en acetona (1.182 ml) se le añadió isotiocianato de acetilo (0.020 ml, 0.230 mmol). La mezcla de reacción se agitó a la temperatura ambiente durante 6 h. El análisis por LC/MS mostró que todavía quedaba la mitad del material de partida. Se añadieron otros 0.5 equivalentes de isotiocianato de acetilo y la mezcla de reacción se calentó a 35°C durante una noche. El solvente se evaporó y el producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice usando un sistema ISCO automatizado (columna de 24 g, eluyendo con metanol al 2-8%/diclorometano). Se obtuvo 4-(3-acetiltioureido)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (34 mg, rendimiento del 43.6%) en forma de un sólido de color amarillo.

MS (ESI) m/z 440.1 (M+H).

125 Preparación de *N*,*N*-diciclopropil-4-(1,5-dimetil-1*H*-1,2,4-triazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida

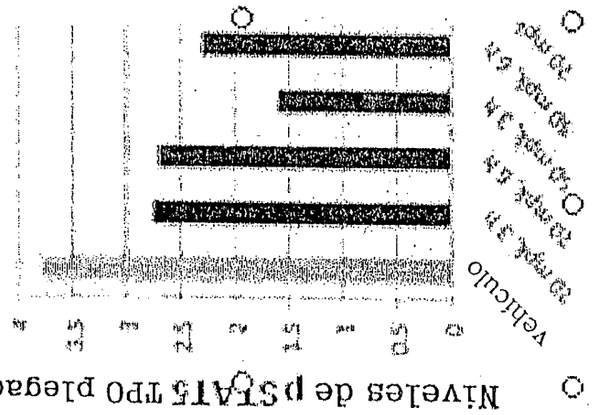
Se calentó una mezcla de 4-(3-acetiltioureido)-*N*,*N*-diciclopropil-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (ejemplo **125A**, 17 mg, 0.039 mmol) y metilhidrazina (2.486 µl, 0.046 mmol) en ácido acético (0.5 ml) a 80°C durante 4 h y el análisis por LC/MS mostró que aún quedaba material de partida. Se añadió más

000392

metilhidrazina (2.486 µl, 0.046 mmol) y el calentamiento se continuó durante 2 h hasta que la reacción se completó. El solvente se evaporó y el producto en bruto se purificó por HPLC preparativa, formando *N,N*-diciclopropil-4-(1,5-dimetil-1*H*-1,2,4-triazol-3-ilamino)-6-etil-1-metil-1,6-dihidroimidazo[4,5-d]pirrolo[2,3-b]piridin-7-carboxamida (5.2 mg, rendimiento del 30.7%) en forma de un sólido de color blanquecino.

MS (ESI) m/z 434.3 (M+H).

RMN ^{1}H ($CDCl_3$) δ: 7.96 (s, 1H), 7.65 (s, 1H), 6.83 (s, 1H), 4.67 (c, *J* = 7.1 Hz, 2H), 4.01 (s, 3H), 3.82 (s, 3H), 2.77-2.84 (m, 2H), 2.43 (s, 3H), 1.48 (t, *J* = 7.2 Hz, 3H), 0.79-0.86 (m, 4H), 0.71-0.77 (m, 4H).



Datos del Ejemplo 26

Datos in vivo para Ejemplo 73

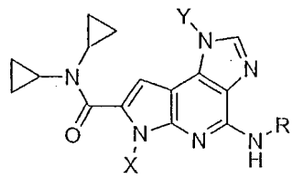
Datos para Ejemplo 74

Datos para Ejemplo 76

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REIVINDICACIONES

1. Un compuesto de fórmula



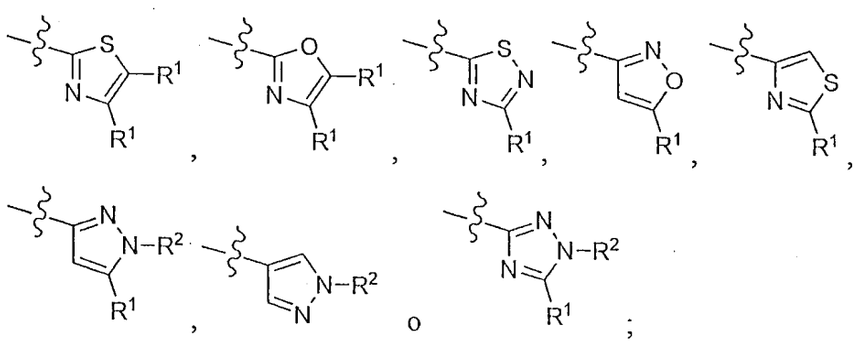
(I)

o su estereoisómero, tautómero o sal del mismo farmacéuticamente aceptable, caracterizadoS porque

X es alquilo C_{1-4};

Y es alquilo C_{1-4};

R es



cualquiera de los cuales que está opcionalmente fusionado con un carbociclo o heterociclo de 5 ó 6 elementos, teniendo el heterociclo un heteroátomo seleccionado entre NR^3 o S, estando el carbociclo o heterociclo fusionado opcionalmente sustituido con 0-3 R^1,

R^1 es H, halo, CN, alquilo C_{1-6} sustituido con 0-3 R^c, CF_3, $CONR^aR^a$, NR^aR^a $COOR^b$, SO_2-alquilo C_{1-4}, $C(O)R^d$,

cicloalquilo sustituido con 0-3 R^e, furanilo, tetrahidropiranilo o piridinilo;

R^2 es H, alquilo C_{1-6} sustituido con 0-3 R^c, C(O)O-alquilo C_{1-4}, SO_2-alquilo C_{1-4}, cicloalquilo sustituido con 0-3 R^e, tetrahidropiranilo o R^2 está ausente;

R^3 es H, C(O)O-alquilo C_{1-4}, o R^3 está ausente;

R^a es H, alquilo C_{1-6} sustituido con 0-3 R^e, cicloalquilo C_{3-6} sustituido con 0-3 R^e, tetrahidropiranilo o dioxotetrahidrotiofenilo;

R^b es H o alquilo C_{1-6};

R^c es H, halo, CN, OH, O-alquilo C_{1-4}, O-alquil C_{1-4}-O-alquilo C_{1-4}, NH_2, N(alquilo C_{1-4})$_2$, C(O)N(alquilo C_{1-4})$_2$, SO_2-alquilo C_{1-4}, o morfolinilo o piperazinilo cualquiera de los cuales está opcionalmente sustituido con 0-1 alquilo C_{1-4};

R^d es alquilo C_{1-6} o azeridinilo, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, dioxidotiomorfolinilo o tetrahidropiranilo, cualquiera de los cuales está sustituido con 0-2 R^e; y

R^e es H, halo, CN, alquilo C_{1-4}, OH, O-alquilo C_{1-4}, SO_2-alquilo C_{1-4}, NHC(O)-alquilo C_{1-4}, morfolinilo, OC(O)-alquilo C_{1-4}, C(O)N(alquilo C_{1-4})$_2$ o O-alquil C_{1-4}-O-alquilo C_{1-4}.

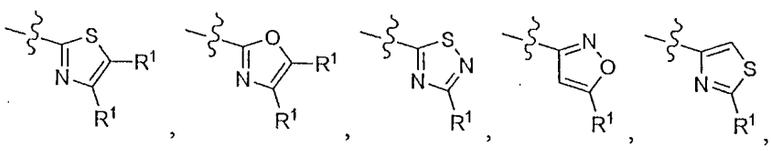
2. Compuesto de conformidad con la reivindicación 1, caracterizado porque

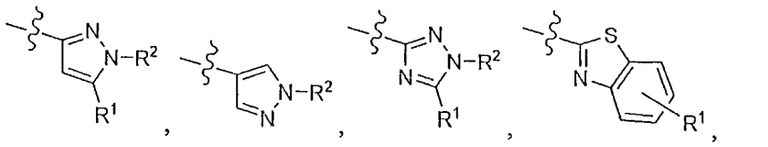
X es etilo;

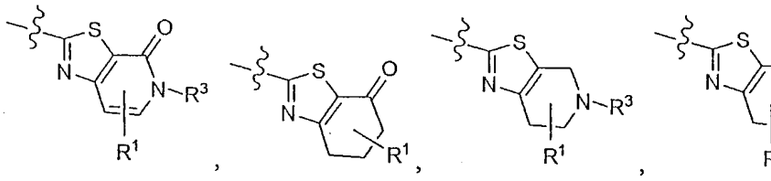
Y es metilo; y

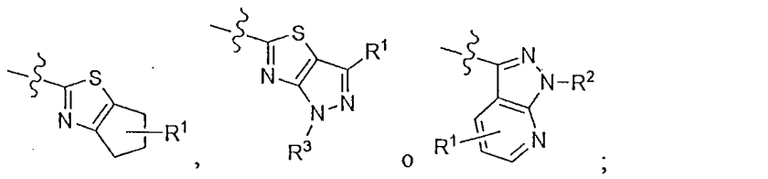
000398

R es







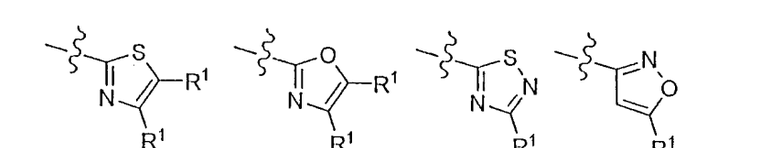


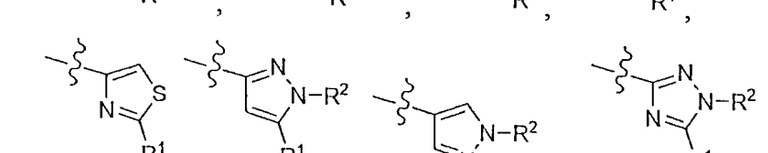
cualquiera de los cuales está opcionalmente sustituido con 0-3 R^1;

o un estereoisómero, tautómero o sal del mismo farmacéuticamente aceptable.

3. Compuesto de conformidad con la reivindicación 2, caracterizado porque

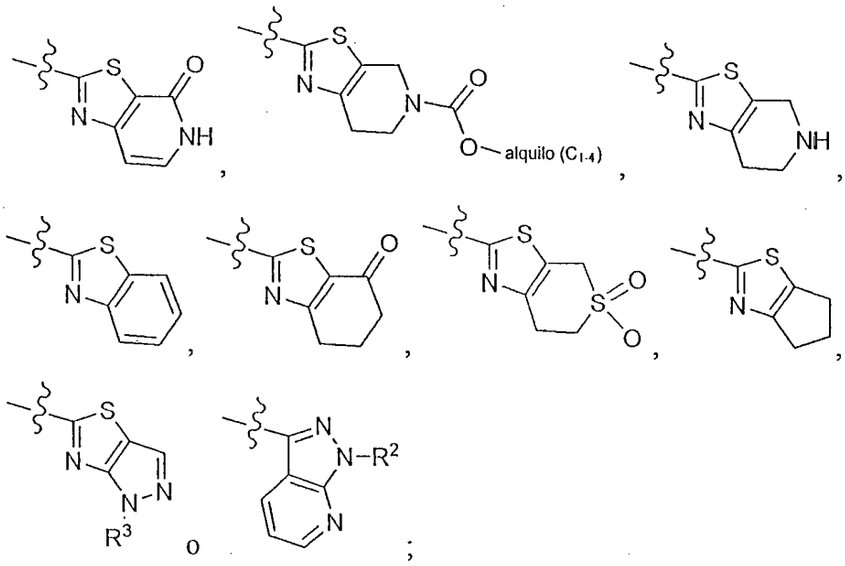
R es





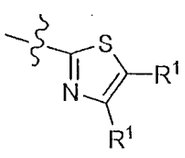
4. Compuesto de conformidad con la reivindicación 2, caracterizado porque

R es



cualquiera de los cuales está opcionalmente sustituido con 0-2 R^1.

5. Compuesto de conformidad con la reivindicación 2, caracterizado porque

R es 

R^1 es H, halo, CN, alquilo C_{1-6} sustituido con 0-3 R^c, CF_3, $CONR^aR^a$, $COOR^b$, SO_2-alquilo C_{1-4}, $C(O)R^d$, cicloalquilo sustituido con 0-3 R^e, o piridinilo;

R^a es H, alquilo C_{1-6} sustituido con 0-3 R^e, cicloalquilo C_{3-6} sustituido con 0-3 R^e, tetrahidropiranilo, o dioxotetrahidrotiofenilo;

R^b es H o alquilo C_{1-6};

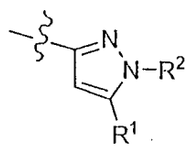
R^c es H, halo, OH, O-alquilo C_{1-4}, SO_2-alquilo C_{1-4} o morfolinilo;

R^d es alquilo C_{1-6}, o azetidinilo, pirrolidinilo, morfolinilo, piperazinilo o dioxidotiomorfolinilo, cualquiera de los cuales está sustituido con 0-2 R^e; y

R^e es H, halo, CN, OH, O-alquilo C_{1-4}, SO_2-alquilo C_{1-4}, NHC(O)-alquilo C_{1-4} o morfolinilo;

o su estereoisómero, tautómero o sal del mismo farmacéuticamente aceptable.

6. Compuesto de conformidad con la reivindicación 2, caracterizado porque

R es  ;

R^1 es H, halo, alquilo C_{1-6} sustituido con 0-3 R^c, CF_3, $CONR^aR^a$, $COOR^b$, $C(O)R^d$, cicloalquilo sustituido con 0-3 R^e, o furanilo;

R^2 es H, alquilo C_{1-6} sustituido con 0-3 R^c, SO_2-alquilo C_{1-4}, cicloalquilo sustituido con 0-3 R^e, o tetrahidropiranilo;

R^a es H, o alquilo C_{1-6} sustituido con 0-3 R^e;

R^b es H o alquilo C_{1-6};

R^c es H, halo, CN, OH, O-alquilo C_{1-4}, O-alquil C_{1-4}-O-alquilo C_{1-4}, NH_2, N(alquilo C_{1-4})$_2$, C(O)N(alquilo C_{1-4})$_2$, SO_2-

000401

alquilo C_{1-4}, o morfolinilo o piperazinilo, cualquiera de los cuales está opcionalmente sustituido con 0-1 alquilo C_{1-4};

R^d es alquilo C_{1-6}, o morfolinilo, piperazinilo o dioxidotiomorfolinilo, cualquiera de los cuales está sustituido con 0-2 R^e;

R^e es H, alquilo C_{1-4}, CN, OH, NHC(O)-alquilo C_{1-4} o morfolinilo;

o su estereoisómero, tautómero o sal del mismo farmacéuticamente aceptable.

7. Compuesto de conformidad con la reivindicación 6, caracterizado porque

R^1 es alquilo C_{1-6} sustituido con 0-3 R^c; y

R^2 es alquilo C_{1-6}.

8. Una composición farmacéutica caracterizada porque comprende un vehículo farmacéuticamente aceptable y uno o más compuestos de conformidad con cualquiera de las reivindicaciones 1-7 o sales, tautómeros o estereoisómeros de los mismos farmacéuticamente aceptables.

9. Un compuesto de conformidad con cualquiera de las reivindicaciones 1-7 o sales, tautómeros o estereoisómeros de los mismos farmacéuticamente aceptables, para uso en terapia.

10. Uso de un compuesto de conformidad con las reivindicaciones 1-7 o sales, tautómeros o estereoisómeros de los mismos farmacéuticamente aceptables, para la manufactura

de un medicamento para el tratamiento de enfermedades mieloproliferativas o cáncer.

11. Uso de un compuesto de conformidad con la reivindicación 10, en donde el cáncer se selecciona de tumores sólidos del páncreas, próstata, pulmón, cabeza y cuello, mama, colon, ovario, cáncer gástrico, mieloma múltiple, melanoma, neuroblastoma, glioblastoma, mastocitosis sistémica y neoplasias malignas hematológicas tales como leucemia mielógena (incluyendo leucemia mieloide aguda refractaria) y leucemia linfoide aguda..

12. Uso de un compuesto de conformidad con la reivindicación 10, en donde la enfermedad mieloproliferativa es policitemia vera, trombocitopenia esencial o mielofibrosis primaria.

13. Uno o más compuestos de conformidad con la reivindicación 1, caracterizados porque son un agente activo para tratar enfermedades mieloproliferativas o cáncer en un mamífero.

14. Uno o más compuestos como un agente activo para tratar cáncer de conformidad con la reivindicación 13, en donde el cáncer se selecciona de tumores sólidos del páncreas, próstata, pulmón, cabeza y cuello, mama, colon, ovario, cáncer gástrico, mieloma múltiple, melanoma, neuroblastoma, glioblastoma, mastocitosis sistémica y neoplasias malignas hematológicas tales como leucemia

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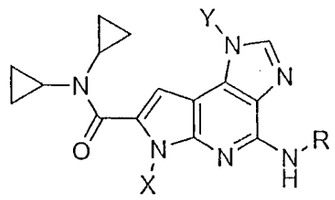
mielógena (incluyendo leucemia mieloide aguda refractaria) y leucemia linfoide aguda.

15. Uno o más compuestos caracterizados porque son un agente activo para tratar enfermedad mieloproliferativa de conformidad con la reivindicación 13, en donde la enfermedad mieloproliferativa es policitemia vera, trombocitopenia esencial o mielofibrosis primaria.

000404

RESUMEN DE LA INVENCIÓN

La presente invención se refiere a compuestos de fórmula I



(I)

y sales farmacéuticamente aceptables de los mismos. Los compuestos de fórmula I inhiben la actividad tirosina cinasa de JAK2, lo que los hace útiles como agentes antiproliferativos en el tratamiento del cáncer y de otras enfermedades.

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN

3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY

4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

ALTERACIÓN DE COPIA DE ORIGINAL
COPIA FIEL DEL ORIGINAL QUE TUVE A LA VISTA
29 FEB 2012
Eduardo Durán Gómez
NOTARIO 33 DE BOGOTA, D.C.

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

AUTENTICACIÓN DE COPIA DE ORIGINAL
CERTIFICO QUE HE TENIDO EL PRESENTE COPIA COTEJADA CON EL ORIGINAL TENIDO A LA VISTA
29 FEB 2012
NOTARIA 38 DE BOGOTÁ D.C.

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

BOGDM5 # 82106

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

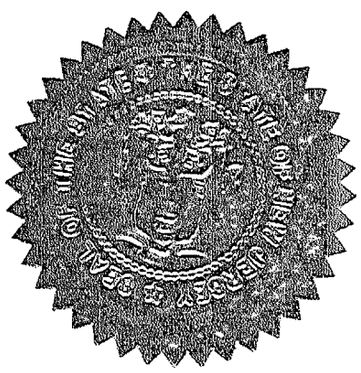
7. BY: Bradley Abelow, NEW JERSEY TREASURER

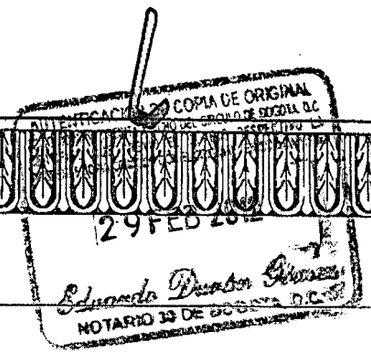
8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow





409

Baker & McKenzie

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.068.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL-MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

on the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL-MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

AUTENTICACION DE COPIA DE ORIGINAL
COMO NOTARIO TREINTA Y OCHO DEL CIRCULO DE BOGOTA D.C.
CERTIFICO QUE PREVIO EL COTEJO RESPECTIVO LA
PRESENTE COPIA COINCIDE CON EL ORIGINAL TENIDO A LA VISTA
29 FEB 2012
NOTARIO 38 DE BOGOTA, D.C.

NOTARIAL CERTIFICATION

On this 30 day of May 2007, the undersigned Notary

CERTIFIES

That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country

set his hand on the foregoing document.

That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

That the grantor has in fact the referred to authority and that his/her representation is legal.

That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public
Sally B. Hansen
SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo de 2007, el suscrito Notario

DA FE

1 Que Anastasia P. Winslow
mayor y domiciliado en Princeton, NJ
Estados Unidos de América

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

está legalmente constituída, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

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CODIGO NOTARIO ... Y OCHO DEL CIRCULO DE BOGOTA, D.C.
CERTIFICO QUE PREVIO EL COTEJO RESPECTIVO LA PRESENTE COPIA CORRESPONDE CON EL ORIGINAL TENIDO A LA VISTA
29 FEB 2012
Eduardo Durán Gómez
NOTARIO 38 DE BOGOTA, D.C.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-036512- -00000-0000

Fecha: 2012-03-01 16:12:28 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 411

Act: 411 PRESENTACION Folios: 410

PATENTE DE INVENCIÓN ☐ MODELO DE

- ☐ 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 INVENCIÓN PCT ☒ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☒ Indicación que se solicita una PCT
- ☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento).

Completa ☒ 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 ☐